



Washington State Health Care Authority
Prescription Drug Program

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UNOFFICIAL TRANSCRIPT*
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING

February 20, 2008
Double Tree Inn Seatac WA
9:00am – 4:00pm

Committee in Attendance:

Angelo Ballasiotes, Pharm D
Robert Bray, MD
Carol Cordy, MD (Vice Chair)
Alvin Goo, Pharm D
Jason Iltz, Pharm D
Janet Kelly, Pharm D
T. Vyn Reese, M.D.
Patti Varley, ARNP
Kenneth Wiscomb, PA-C

Carol Cordy: Did you want to make some announcements first?

Jeff Graham: We have a few announcements for today, and I wanted to say that, and we know this has been done before, this meeting is being recorded so it's important for all of us to speak in the microphone and identify who we are so the record will record who is speaking. The other thing is this is just a reminder. Stakeholders should identify any sponsorship or representation at the beginning of their comments and their comments are limited to three minutes.

This is a new announcement now, we have effective January 17th, the agency director has appointed Dr. Barrack Gaster to a three-year term on the P&T committee and he is replacing Dr. Lessler. Dr. Gaster is an associate professor of medicine at the University of Washington Department of Internal Medicine. There he serves as Chair of the Narcotic Review Committee at the General Internal Medicine Center and is certified by the American Board of Internal Medicine. He is also a member of the Society of General Internal Medicine and the Washington State Medical Association. Unfortunately, we appointed him after he had

* For copies of the official audio taped record of this meeting,
please contact Regina Chacon at (206)521-2027 pdp@hca.wa.gov.

made vacation arrangements with his family to be gone this week. So he will be here at our June 18th meeting.

We also want to make a clarification, we think it's understood, but we are reviewing the fixed dose accommodation drugs for treatment of type 2 diabetes and hyperlipidemia report, but at this meeting today we are only considering the hyperlipidemia drugs contained in that report. If you had submitted a bid for type 2 diabetes drugs, those will be returned to you to any manufacturer.

Today we will be electing a chair to replace Dr. Lessler and we are doing that...the agenda says we're doing that at the beginning of this meeting. We're doing that after noon, after lunchtime.

We also wanted to say we are having a clarification of the TZD motion and that's due, the committees due June 21st meeting, June 21, 2006. The agency selected Avandia as the preferred drug in the TZD class. At the October 17th meeting, this is this year, 2007, the committee moved to defer reconsideration of this class pending a new safety data that will be included in a full update of the class scheduled for review in the October 15th 2008 meeting. In November of 2007, the FDA subsequently asked the manufacturer of Avandia to add additional information to its existing label warning, and we have a question for the P&T committee in light of the November information does the committee want the agencies to make any changes to the existing PDL, Avandia, before the next full review on October, 2008? And that's what our clarification is for the committee. So Carol I think we now have six people here that we can officially begin.

Carol Cordy: Welcome everyone; this is the February 20th P&T committee meeting for the State of Washington. So I think since we moved the first agenda item to the first thing in the afternoon, we'll proceed with answering the question about the TZD decision that was made earlier. Do we want to do the motion again or just...?

Jeff Graham: I think you can just, you can affirm that you, if you want to do that. Whatever you would like to do. Carol, you had mentioned maybe we should, because we have a lot of new people here at the front table, perhaps we should have introductions of this, today.

Carol Cordy: Okay. Do you want to go around the whole table?

Jeff Graham: Sure.

Carol Cordy: Okay, why don't we start here and introduce yourself and who you work for?

Jaymie Mai: I'm Jaymie Mai with Labor and Industry.

Doug Tuman: Doug Tuman of Labor and Industry.

Duane Thurman: Duane Thurman with the Health Care Authority.

Ray Hanley: Ray Hanley with the Health Care Authority.

John Williams: I'm John Williams with the Health Care Authority.

Nancy Fisher: Nancy Fisher with the Health Care Authority.

Janet Kelly: Janet Kelly, member of the P&T Committee.

Patti Varley: Patti Varley, member of P&T Committee.

Ken Wiscomb: Ken Wiscomb, member of the P&T Committee.

Vyn Reese: Vyn Reese, member of the P&T Committee.

Angelo Ballasiotes: Angelo Ballasiotes, member of the P&T Committee.

Alvin Goo: Alvin Goo, member of P&T Committee.

Jeff Graham: Jeff Graham, Health Care Authority.

Jeff Thompson: Jeff Thompson, Washington State Medicaid.

Kaval Flora: Kaval Flora, Medical Director at Eastern State Hospital.

Siri Childs: Pharmacist with HRSA.

Seraya Kanakis: Hi, I'm Seraya Kanakis with Washington Medicaid.

Carol Cordy: Okay, so the question is in light of the November information does the committee want the agencies to make any changes to the existing PDL for Avandia before the next full review in October of 2008? Is there any discussion?

Vyn Reese: Can you read the black box warning, the latest black box warning? Do you have access to that?

Jeff Graham: I do not. Do any of your pharmacists have that? No.

Duane Thurman: The purpose of this is that the last update on this you said let's wait until this full report comes out with everything. There was some subsequent

information and in the interest of keeping everything public, we wanted to come to you. We assumed that what you meant was don't change until we re-review and we just want to confirm that. If that's true we'll just proceed. If you have other issues we can either take whatever steps you'd like to do next. So that's really what we're asking is just to make sure. We didn't feel comfortable polling you individually outside of a public meeting. It's really a simple question, but we want to make it public.

Vyn Reese: This is Dr. Reese. It's a very fluid...I mean according to my Palm, I mean TZD's cause are exacerbate congestive heart failure, observe patients closely after treatment initiation or dose increases, because of excessive rapid weight gain, dyspnea, and/or edema. And that's one of the warnings right now and that's for both TZDs. And there's also a question about excessive cardiac risk with Avandia more than Actos. So it's an area that we do definitely need to look at. As far as I'm aware, the black box warnings are pretty much the same for both and I don't think their first line drugs for certain and we do definitely need to look at that. But the full review is not going to be out; the full review as I understand is not going to be out until October. So I'm sort of just...my view is just to wait and wait for the complete review. This is a very fluid area right now.

Duane Thurman: I guess just to be perfectly clear, what we're assuming is that you leave in effect your previous motion.

Vyn Reese: Correct.

Janet Kelly: Janet Kelly. I just would like to clarify the practicalities of what does it mean having it on there? What is the current processes there an EPA on these or how are they handled?

Siri Childs: This is Siri Childs and for the TZD class, Avandia is the preferred drug, Actos is the non-preferred drug. And so Actos requires PA and Avandia does not. There is no EPA criteria on it.

Janet Kelly: I don't think I'm particularly comfortable with this at this point, having there be no stop at the Avandia to evaluate the congestive heart failure risk, the MI risk and that, so I'm not really comfortable with keeping it on the preferred list as it is.

Carol Cordy: So it sounds like this isn't a simple answer. Did you want to propose, and I'm not sure, I know this isn't what you wanted, but did you want to propose some kind of a change or a motion?

Janet Kelly: Well, Janet Kelly again. I guess that making this practical, I mean I know that there's a lot of people on these medications and we don't want to have this huge problem with how to transition them, but I think that there needs

to be a step in there to stop and evaluate, because I don't know how many of these people I see that come in on the cardiology service on these medications when they clearly should not be. And I think we need to have some sort of an EPA in there, it's like okay do you have these criteria and then to asses whether or not. Because it's for both of them, I have some concerns that there be some, there not be just a preferred drug that you can go ahead and get without evaluating the safety of them.

Duane Thurman: This is Duane Thurman again. I guess the issue is in terms of our process you have an existing motion out there that basically said that the decision should be made on the basis of our cost analysis. In terms of our process, we've not put any additional information before this committee in terms of evidence produced by the DERP project. And so I understand the realities, you still have the dispense as written, you know Avandia, Actos, they're equally available...they're still available. The question is do you have evidence that would change your previous motion that would cause us to change our system while we're waiting for the new update? I know that sounds sort of lawyeristic, but...

Vyn Reese: This is Dr. Reese. I actually was against having Avandia on it last time for these very reasons. And so Janet and I were both...we were outvoted though and the last time that we raised this and that's how these drugs are on the PDL now. But we don't have...I mean there's really not a lot, there's a lot of very...lots of information out there, some of it not real solid. I'm not sure we have any more information to change that. I mean if the committee wants to keep those drugs, take them off the PDL, it'd be fine with me. I mean I didn't want to have them on the PDL in the first place, but there's really not that much difference if there's a change in the majority of the members that want to change that that's fine, but I don't see that we have a lot more information than we did the last time and a lot of these concerns were raised before.

Duane Thurman: This is Duane again. If I could ask Siri, what is the policy at HRSA regarding when someone does try to get an Actos prescription?

Siri Childs: Actually because of all of the information that has been available, if there is any consideration, any hint that the patient or the physician is concerned about safety, we do an automatic approval for Actos.

Ken Wiscomb: This is Ken Wiscomb. In lieu of that and in lieu of the concerns and not having available information until October, would it be reasonable to raise Actos's status to the PDL?

Duane Thurman: From a practical standpoint, no. I mean we've made a decision where we've decided on a preferred drug. It invokes contracts for supplemental rebates. It's been programmed into the system. The question is we're

trying to make it as easy as possible for people who have concerns with Avandia to get access to the non-preferred drug, understanding that this is a difficult situation. But this is one of those examples where if you're looking at it from a purely evidence-based perspective, I think the issue is we don't know. And the question is at this point do we simply wait until October when we hopefully will get more information about this and leave things as they are with the note that we are trying to make it as available as possible? And I guess also the traditional distinction between what we're trying to do as a P&T committee versus letting the individual prescriber have the option to try to do what's best for their particular patients. You can do...you can tell us what you would like us to do and we will do everything we can to implement it. I guess the question is on the basis of the evidence you had at the last meeting was there evidence there that you would reconsider and say we would like to change that decision?

Janet Kelly: This is Janet Kelly. As far as the evidence there's not going to be any new evidence before October. I think the evidence is the same. Having reviewed it, we didn't review it at this committee, but I've reviewed it myself. There's a lot of meta-analysis that show different things depending on how the statistics are done and who did them. Yes there's a difference, no there's not. It is very gray. And so I think that, but October's not going to make that better. It still looks that there's a trend with Avandia. It looks like it has more of a negative affect than Actos has. Having said that though, I'm not particularly comfortable with either of those agents and I think that's I guess where...but I think that if you're saying that if someone says they have a...the provider says they have a safety concern with Avandia and they get Actos, I guess that would take us through until October when we could evaluate the class more thoroughly I guess everyone's comfortable with that.

Vyn Reese: This is Dr. Reese. I'm comfortable with that as long as they can get Actos too, but I agree with you, I don't like either one of them.

Carol Cordy: It seems like there's been enough of a discussion. Maybe we need to make this a little more formal and someone make a motion. It may just be a motion not to change and to wait until October, which is what the original motion was. Does somebody want to do that so we can take a vote?

Man: Carol you do have a copy of the motions that you've made previously?

Carol Cordy: Right.

Duane Thurman: One option would be to reiterate your previous motion and let it stand until the October 15th review becomes available.

Carol Cordy: Okay, it looks like Ken you were the motion.

Ken Wiscomb: So I would move that we defer consideration of this class until such time as new safety data is available and included in the full update of the class.

Carol Cordy: Is there a second?

Janet Kelly: I'm happy with that, can we just add the part about that in light of the safety data that the DSHS and others can, I don't know how we word that so that that's in there, but it would make me feel more comfortable having that actually stated in the motion that we are aware of the safety issues and if the provider feels strongly about the safety they can...I don't know how we...

Carol Cordy: Did you want to complete that?

Janet Kelly: That until the review in October that if a provider has concerns about the safety that Health Care Authority will substitute, will allow them to get Actos. I don't know how to word that. I can't do it without a pencil. I think if we just reiterate the same motion we had, it doesn't sound like we address the safety concerns that we have. So if someone is better at word smithing than I am, I'm happy to let you do that.

Duane Thurman: This is Duane again. What I would suggest is that you reiterate your last motion and direct the agencies to take as many steps as they can to make the non-preferred drug available upon request and at the discretion of the provider.

Ken Wiscomb: Because of the safety issues that have been pointed out in recent FDA data, we would encourage and because of provider concerns, we would encourage an eased access to Actos on the PDL.

Carol Cordy: In the...are we able to type this up? It sounded like you wanted us not to add this to the...

Duane Thurman: No, I think it'd be sufficient if you just say that your previous motion stands. All we need is the understanding that we will not make changes to the current preferred drug list, but we will make all efforts to make the non-preferred agent available. I think if you second Mr. Wiscomb's motion with that clarification I think we'd be fine.

Carol Cordy: Okay. I think it was just the wording of the...

Janet Kelly: Janet Kelly, I'll second it.

Carol Cordy: Okay. And now I'm not really clear if the motion...if we're going to include that in the motion. If we are we probably need to type it in.

Jeff Graham: Jaymie that's in addition to the previous motion. I think the motion is down a ways on that slide. The one from October 2007.

Jaymie Mai: You want to see the October motion?

Carol Cordy: The October 17th motion.

Jeff Graham: Yes. And then would you repeat the words so she can type in those words?

Patti Varley: This is Patti Varley. That's the 2006 one.

Vyn Reese: That's, no it's the seven.

Jaymie Mai: No, right here.

Patti Varley: Okay.

Ken Wiscomb: So we want to add after full update of the class then? So this is all we want to add on?

Duane Thurman: Just say that in light of your previous motion you would attach the following clarification.

Ken Wiscomb: Okay. In light of our previous motion...in light of our previous motion and recent information from the FDA we would recommend no changes to the current PDL with the caveat that agencies take all steps to make all agents available in this class.

Jaymie Mai: In light of our previous motion and recent information from the FDA that...

Ken Wiscomb: That we make no changes to the current PDL at this time with the caveat that agencies take all steps to make all agents available in this class.

Vyn Reese: It's pretty cumbersome.

Ken Wiscomb: Yeah it is.

Vyn Reese: I think we should just delete in light of our previous motion. This is Dr. Reese. We delete that and just...you should say in light of recent information of the FDA we make no changes to the current PDL.

Ken Wiscomb: And take the that out.

Vyn Reese: That in light of our previous motions in light. We will make no changes to the current PDL at this time, but will take all steps and leave out caveat. We will take all steps to make every agent available in this class, or all agents available in this class.

Ken Wiscomb: In this class.

Vyn Reese: I wouldn't just say it would take all steps...will make all agents available in this class. Instead of take all steps, take that out too. Just chop it down to the bare necessities.

Ken Wiscomb: So I would move that in light of recent information from the FDA, we will make no changes to the current PDL at this time, but will make all agents available in this class.

Carol Cordy: Since this is a new...

Vyn Reese: This is Dr. Reese. I'll second that.

Carol Cordy: All in favor?

Group: Aye.

Carol Cordy: Opposed. Okay.

Duane Thurman: Duane Thurman, one more time I apologize for the messiness of this, but I want to make it clear that what this means is that Avandia remains our preferred drug, but that we'll do everything we can to accommodate prescriptions and desires for the non-preferred alternative?

Jeff Graham: Right.

Duane Thurman: Thank you.

Carol Cordy: Okay, thank you. Is Marian available?

Marian McDonagh: Yes I am.

Carol Cordy: Okay. Hi Marian.

Marian McDonagh: Hello.

Carol Cordy: So Marian is going to give us an update on the drugs to treat ADHD.

Marian McDonagh: That's right.

Carol Cordy: If you can wait just a minute until we get the PowerPoint up.

Marian McDonagh: Okay.

Woman: This is a reminder to speak directly into the microphones so that Marian can hear well on the phone.

Carol Cordy: Okay Marian, we have the introductory slide up.

Marian McDonagh: Alright. So as you can see on the slide there, this update was completed in September. It is the second update of this group of drugs.

Carol Cordy: Can I just interrupt you for a minute. Can you speak a little louder?

Marian McDonagh: Sure. Is that better?

Carol Cordy: That's great, thanks.

Marian McDonagh: Okay. So this new update was actually quite large and we added a new question as we were, that participants in DERP were going through. So I will walk through all of those changes here before we get into the results.

If we go to the next slide, we see we used our usual search strategy and we just report here the companies that we did receive dossier information from, so additional information on their products.

The next slide our populations and interventions. Populations were the same. Interventions we added a number of new drugs this time. Lisdexamfetamine, methamphetamine, and the transdermal methylphenidate. All of those were new products added, new drugs added to this report.

On the next slide the outcomes were the same as before except for the final one there. Misuse and diversion. So that was the new question added to this report was looking into the evidence on the risks for misuse or diversion with these products and there are a number of related questions. We will see when we get to that how that splits out.

Looking at the next slide on the results, we had a while...we had quite a lot. There were I think 80 new studies added to this report, but out of all of that only nine of those were head-to-head trials. You'll see when we walk through the evidence there are quite a lot of small crossover studies still being added to this report. Small before and after studies and then a whole host of placebo controlled trials.

On the next slide we have a summary again of our concerns about this body of evidence and the lack of true effectiveness trials. Under efficacy studies I would add that the biggest problem with these studies is the outcome reporting bias where only pieces of the...whatever scale is chosen to be used in the trial only parts of the scale is reported at the end. So that's a big concern for us.

If we move to the next slide, generalized ability is still an issue for this body of evidence. This has not changed from the very beginning first report.

Move on to the next slide. This is a summary of the direct so the head-to-head evidence. And here we do have, as I mentioned, some new studies. We still have the most information on comparing methylphenidate to the other products. We have a few new studies in each of those yellow boxes, so it's not a large number for any of them.

If we move to the next slide, we'll move in to some of the new information. We have...this is kind of a busy slide, I'm sorry about that. The preschool aged children we had some new information. Overall we had six trials in preschool age children that are comparing immediate release methylphenidate to placebo, but four of those are rated poor quality for a variety of reasons, including using outcome measures that are not validated. But the two best trials here have one trial found no difference between methylphenidate and placebo and the other did show a difference, but only with the higher doses. That being the 0.5 mg/kg in children. And then in the other study it was 7.5 to 10 mg three times a day. So mixed results here, not a clear evidence of a benefit.

Adverse events certainly were more frequent with the immediate release and they were the typical adverse events we see with stimulants with appetite problems and sleep problems. Also in young children social withdrawal was seen. In the PATS trial, so this was the larger trial that was four weeks, it had three different phases. The beginning was a crossover phase, which was dose stabilization. So identifying which dose worked for that particular child. Then there was a randomized control trial of four weeks duration, and then there was an open label follow up study. And the information on growth comes from that follow up study. So they were a mean age of four years old. At baseline, and this is typical for a lot of the studies, the children were larger than average at baseline. So they were higher in the percentiles for both height and weight. After using methylphenidate, and I do note there are a mean of over 300 days, it was associated with a mean loss of 6 percentile in height and 14 in weight. So they were still above the 50th percentile, but they had not continued to maintain the 70 plus percentile that they had started out.

In looking at subgroup analyses, these results were not modified by sex, initial height, or methylphenidate dose. And in adolescence we added just one new piece of information here, that for extended release Adderall, the appetite suppression, sleep problems, and stomach upset...similar adverse events were reported in teenagers just as they were in adults and children for that drug. And we'll get back to one other trial of this in adolescents in looking at driving abilities in just a minute.

Now looking at the immediate release methylphenidate compared to various extended release formulations, we have 11 trials now and 4 of those are new. Across the body of evidence here we didn't see clear differences among the products compared to the immediate release. Looking specifically at the OROS formulation versus immediate release methylphenidate, there are four trials looking at efficacy. The two double blind studies did not find a difference between the products and their outcome measures, but the two open label studies did, depending on which outcome measure and which subgroup of the scale they were looking at. We did find that in the overall dose across all four of these studies the mean dose in the OROS group was higher than the mean dose in the immediate release group. When we pooled three of these studies...[end side A]

Marian McDonagh: ...and this study found the two products to be equivalent.

On the next slide, comparing sustained release methylphenidate formulations, we really don't have a lot new here. We added two new crossover studies to the Ritalin LA to MPH SODA versus the methylphenidate OROS. And it was, there was a new, I'm sorry one new crossover study was added, which was conducted to replicate the findings of the first one and indeed it did replicate the findings indicating that the SODA's formulation was superior on some outcome measures, but not all.

Now on the next slide as I mentioned we have some new information, new evidence on the methylphenidate OROS compared to the mixed amphetamine salts extended release. In teenagers looking primarily at driving outcomes. This, it was a small crossover study, and they were looking at driving ability in the evening and nighttime, and not during the daytime. For these teens, did not report a difference in symptoms over this time between the two products, but the methylphenidate OROS was associated with better overall driving performance. So combining the three different time points in the evening. If you look at the specific times of day, the 8:00 pm driving time is when the mixed amphetamine salts scores were actually worse than baseline. So it's probably that 8:00 pm scores that are driving the results. Because the other results looked very similar at 5:00 pm and 11:00 pm, so that's an odd finding. But a reminder

that it is a very small study. And the study did not do a statistical analysis of the impact of the order of randomization, which is a very important component for a crossover study. So a little bit of caution there in interpreting those findings.

Now on the next slide we have dextroamphetamine immediate release compared to methylphenidate immediate release. And this is...we have no new information for this particular comparison. There were nine trials here and differences were not found between those products.

On the next slide looking at mixed amphetamine salts, we do have new information comparing the immediate release compared to the extended release. And again this is just a small crossover study. The study was designed to compare each of the products to placebo and not to each other. So unfortunately, direct comparisons were not undertaken in this study. The 30 mg extended release was clearly superior to placebo. The 10 and 20 mg dose of extended release mixed amphetamine salts were not superior at all time points. 10 mg of the immediate release was, as you might expect, better early in the day, but variable later in the day. And then for adverse events the higher dose of the extended release caused more anorexia, while the immediate release caused more insomnia. Again, it's a small study, and probably not strong evidence.

On our next slide we have the evidence for Lisdexamfetamine, so a new product. We don't have very much in the way of direct evidence for this drug. We found one study in the FDA documents that has not been fully published and we found in this study that Lisdexamfetamine was not different to the mixed amphetamine salts extended release, and both drugs were superior to placebo, which was the intent of the study was to compare Lisdexamfetamine to placebo. Indirect evidence, we found a four-week trial dose ranging study looking at 30, 50, and 70 mg of Lisdexamfetamine compared to placebo and the drug was found to be superior to placebo.

On a variety of outcome measures, subscale measures related to the ADHD-RS-IV. This was found to be a little bit less robust in girls and in non-white populations. So the improvement on the scale was that all of these people did improve, but not as much as the overall population. So you can see there that it goes from being statistically significant in the total population and not significant in girls or non-Caucasians. And of course the caution there would be that the subgroups are small, so it could be that in a larger group we would still see a statistically significant difference.

Adverse events for Lisdexamfetamine look quite similar to the other stimulants. Any adverse event reporting is similar across the doses

however. But definitely higher than placebo. Decreased appetite, insomnia, and irritability were all seen in higher rates than in the placebo group, and weight loss was seen, was more prominent in the higher dose, the 70 mg group compared to placebo, whereas the others were not statistically significantly different.

Moving on to the next slide, we have Dexmethylphenidate. Here we have new information on the extended release formulation. Two placebo controlled trials. One was a smaller crossover study and then one was a parallel design. And in both they were, the new, the product, Dexmethylphenidate extended release was superior to placebo. And in adverse events looking at the two-week crossover trial, 28% versus 22% of patients reported any adverse event. So fairly close, they are not that different. But in the seven-week trial there is more of a difference you can see and also decreased appetite being the most common one that was statistically significantly different to placebo. So not a lot of adverse event reporting from these two trials however. I would say not all that well done in terms of reporting adverse events.

On the next slide, summarizing the information about Modafinil at this point, we do have five trials, placebo-controlled trials of Modafinil. And they are...they present conflicting evidence and they do indicate that possibly the higher dose, so 300 mg a day or more is beneficial compared to placebo. But the lower dose is probably not. And the of course, adverse events are the area where there is the most concern with Modafinil for insomnia and decreased appetite the relative risks compared to placebo are both greater than five. Probably the biggest concern is about the rash-related adverse events and while those are in low numbers here on this slide, there is certainly concern about that for this drug and use for ADHD.

On the next slide we have the information about the methylphenidate transdermal system. Only at the time we did this, we were doing the update there were only one of the three trials submitted to the FDA had been fully published. This was a one-week crossover trial, and the transdermal system was found to be superior to placebo on both symptom subscales and also on math outcomes. So the proportion of math problems attempted during a timed period. Adverse events, here we have 30% versus 22% for the number of people reporting any adverse event during this short-term one-week trial, and then anorexia being the clearly higher rates than placebo and withdrawals were not really reported adequately for us to make an assessment on adverse event withdrawals. We were also asked to look at methamphetamine this time around. The only study we were able to find came out of a PhD dissertation that is several years old. And in this study there were 32 boys and methamphetamine was found to be superior to placebo in a number of outcome measures. They did not measure adverse events in this study unfortunately.

On the next slide, looking at non-stimulants compared to methylphenidate immediate release we were only able to add two new trials here of Atomoxetine versus methylphenidate, but we didn't rate either of these trials as even fair quality, so we didn't think that they added anything to this body of information here.

On the next slide, looking at the maintenance effects, so how well are the effects of these drugs maintained over time? We added two new studies, open label extension studies of Atomoxetine that indicate that over 8 and 24 months the effects are maintained.

Now on the next slide, going in to the update on evidence in adults, we added seven new placebo-controlled trials in update two. We still have only one head-to-head trial. And so you can see on the slide that the additions are spread out across most of the drugs here in this group for adults.

If we move to the next slide, this is the information about the head-to-head trial, so there is nothing new on this slide. If we move to the next slide, looking at the stimulants both short, so the immediate release and extended release in controlling symptoms compared to placebo we found one new trial of the mixed amphetamine salts extended release and this one provided inconclusive evidence and it was low quality.

On the next slide we have information on other outcome measures—quality of life, anxiety, and other types of outcomes. Placebo-controlled trials of Atomoxetine and the mixed amphetamine salts extended release showed that both of the drugs improved quality of life in the short term, but these were uncontrolled studies.

On the next slide looking at the tolerability, the side effects of these drugs, we added some new information on longer acting forms. So Dexmethylphenidate and then two different formulations of methylphenidate extended release. They were again very similar adverse events to those seen with the other stimulants.

And on our next slide we have our indirect comparisons of appetite disturbance and sleep disturbance, and these have been updated with the new information, but really the bottom line has not changed on this slide.

Moving on to the major harms, so looking at major harms across the entire body of evidence. We originally, last time we had 10 studies in this area, now we have 30. So we have quite a few added to this section. And I think most of those are going to be in the area of the abuse and diversion. So we'll move on and get to that. In weight change, as I summarized

earlier the, in the preschool kids there is an impact of methylphenidate immediate release that comes out of the PATS trial. The extension study from PATS, where after a year the children had less weight gain than was expected by their age by a little over a kilogram. In the methylphenidate OROS, a 12-month before and after study also showed the final weight to be less than expected for age, and in this case it was 2.6 pounds.

Looking at the mixed amphetamine salts extended release, we also found some information here. So in children we found a 24-month before after study. Five percent withdrew due to weight loss. And the change in age adjusted weight quartiles was about 15%. So they started out at the 75th percentile on average and ended up at the 60th percentile after 24 months. As we have seen in the past with looking at dextroamphetamine and methylphenidate immediate release, the weight change seems to occur primarily in the first year of treatment, and in the second year the change, any differences are not statistically significant. In a study of adolescents, a six-month open label study, 25% of the teens experienced weight loss as an adverse event. The mean weight decreased by 2.4 kilos and it was noted that in those that had not received mixed amphetamine salts prior to this study, the weight loss was greater, so 9.2 pounds.

Looking on the next slide at height change. Very similar results. So coming out of the PATS trial in the preschool age children, a reduced growth, reduced height increase of 1.3 cm per year compared to their cohort. And for methylphenidate OROS in that 12-month before after study again final mean height of 2.3 cm less than was expected.

On the next slide looking at other adverse events that are serious, we have some new information we added to Tics, so treatment emergent Tics for methylphenidate immediate release. We find as we reported before, but can see more clearly now, the rate varies greatly across the studies, and particularly by design. The range that we have is .16% to 20%. We did not find that methylphenidate immediate release has a significantly greater rate of Tics compared to placebo after a year, but for both groups rates were quite high. A meta-analysis of MPH OROS and MPH immediate release compared to placebo indicates rates of 4%, 2.3%, and 3.7%, so not statistically significantly different across those drugs. And we have no new information on Atomoxetine for the outcome of suicide.

In cardiovascular events on the next slide, we have here primarily information coming out of the FDA. Unfortunately, in the trials we don't have a lot of good information on cardiovascular adverse events. We were able to add some new information in adults and also for the mixed amphetamine salts extended release. We do note we...in this update we were abstracting information about blood pressure changes, heart rate changes, and withdrawals due to cardiovascular adverse events across all

of the groups and found that there are small numbers of children who do experience these types of things, an increase in blood pressure or heart rate that requires them to withdraw from the study. The numbers are small, but they are there. We did not find that the QTC interval increases were significant or found to be clinically important in these studies.

Now moving on to the new evidence, we have the risk of misuse or diversion. So the risk of people misusing drugs once they have them in their hands. We find overall that the evidence here is not robust. So we have small numbers of studies and many of these studies are very small in number. We also found that how they control for confounding variables varies a lot in terms of the method, but also what variables are controlled for vary dramatically across the study. So it does not appear that there is a strong agreement as to what is a compounding factor in these, across these studies. We found for example, a couple of small what are called choice studies, one in children and one in adults, and they are very, very small so I don't really want to spend time on their results. But the point here is you give the patient the treatment, so in this case methylphenidate, and then so they know what it feels like to have symptom response, and then after that you give them blinded placebo or methylphenidate and they get to choose did you like condition A or condition B? And that's the choice study. And then there was also looking at diversion. The national survey on drug use and health found that about 35% of those surveyed had misused a stimulant medication. Almost 5% were dependent or abusing a stimulant ADHD. Now these were specifically medications that are prescribed for ADHD and the rates were highest among teens and young adults. And most commonly reported drugs of abuse here were methylphenidate immediate release and dextroamphetamine immediate release. There were reports in this study of mixed amphetamine salts and the ORA formulation of methylphenidate.

Now on the next slide we have the risk of drug misuse following treatment for ADHD. So here this is the risk of misusing drugs in general has been found to be higher among children who were diagnosed with ADHD compared to the general population. And then in follow up studies there were four studies in teens. They did not find a clear association between treatment for ADHD as children and substance abuse or dependence as teens with the exception of one study finding an association with tobacco use when they were teenagers. Now in adults we found three studies with conflicting results. So two studies found stimulant use in childhood was actually protective, and one study found the opposite, that it increased the risk of abuse later in adulthood. And again I think you can see from the slide that it does depend somewhat on which drugs you are looking at as drugs of abuse. And there was an increased risk, for example in that second study of use of tobacco and cocaine. And cocaine combined with amphetamine dependence. In the other study they were looking at cocaine

or hallucinogen abuse so combining two different categories of drugs. And then also looking at alcohol abuse. So very different.

On the next slide we are looking at the risk of misuse or diversion in a sub population of patients who have both ADHD and substance abuse disorder. So we have here a couple of studies and one in teens who were being treated for substance abuse, they were inpatients. And they reported, 23% reported using methylphenidate or dextroamphetamine as a drug of abuse, 6% were current users of one of those drugs as a drug of abuse. I think interestingly, the second bullet point not significantly associated with the ADHD diagnosis, but more significantly associated with not being in school and the patient also having an eating disorder.

In adults, there were a couple of studies. Two with methylphenidate immediate release and then another two with extended release methylphenidate compared to placebo. These studies found that the measures of recovery from substance use disorder were not affected by stimulant use for ADHD and, but they did find that they ADHD symptoms showed a lower response compared to non-abusers. So less of an affect on ADHD symptoms.

Now moving on to our subpopulations, key question three. We do have some new information to add to this this time. A lot of this information comes from the Lisdexamfetamine trials. In the one-week crossover study that also compared the drug to mixed amphetamine salts extended release or placebo, there was no difference in response by race. And in the four-week parallel trial, the difference in the symptom scale, the ADHD-RS mean change score compared to placebo, it was statistically significant at the 50 and 70 mg doses in the subpopulation of non-Caucasians, but the 30 mg dose did not show a difference there. So that's...you can see there that it's not statistically significant in the non-Caucasians. But I think the important point again is that it's a subgroup. So we would need to see if in a larger study that would hold out.

On the next slide we have, looking at gender, very similar results in that in the crossover study the gender for Lisdexamfetamine gender did not alter the results. In the parallel design, again for the 30 mg dose the results were less robust in girls and not statistically significantly different to placebo. In a study of...looking at the mixed amphetamine salts compared to Atomoxetine, gender did not alter the results in that the mixed amphetamine salts were still superior to Atomoxetine in the subgroup of girls.

On the next slide, looking again at subpopulations. Now we have some information on ADHD subtypes. Previously we had no information at all on differences in response based on ADHD subtypes. So now this is

looking at methylphenidate immediate release and methylphenidate OROS and there is placebo-controlled trials for each. Indicates that higher doses were more effective in the combined subtype for both of those products or with ADD with hyperactivity while those with an inattentive subtype respond better to lower doses. So not comparative studies, but at least some new information. Now also we were looking more carefully at anxiety in this update. And in children we found that methylphenidate immediate release compared to dextroamphetamine, mixed amphetamine salts, methylphenidate sustained release and OROS, or Atomoxetine, there were no differences in treatment emergent anxiety during the course of six trials. Looking at those who had comorbid anxiety disorder there was one study, which found Atomoxetine superior to placebo and in both ADHD symptoms but also in the anxiety rating scale. So it improved the anxiety in those patients. Methylphenidate immediate release compared to placebo, in all of those trials the evidence is conflicting. So with some reporting an increase in anxiety and others reporting no difference. Looking at Atomoxetine or Modafinil versus placebo, there were similar rates of anxiety compared to placebo in those two studies.

Now in adults, we have evidence, two studies on adults with anxiety in methylphenidate immediate release resulted in improved anxiety symptoms. With OROS higher rates of anxiety were reported compared to placebo in two trials however.

Now this next slide, our final slide, has the list of the comorbidities that are included in this report. We have several that were here before and some new ones. So for oppositional defiant disorder we have some new information. A mixed amphetamine salt extended release placebo controlled trial. With learning disabilities we have one immediate release methylphenidate trial that is again compared to placebo. And then for tic disorders we have some new studies as well with methylphenidate and dextroamphetamine immediate release and Atomoxetine. And those are...that summarizes the report if anyone has any questions I would be happy to answer them.

Carol Cordy: We have four stakeholders, can you stay through that and then we'll have questions and discussion?

Marian McDonagh: Sure.

Carol Cordy: From the committee. And the stakeholders I will read your names and please limit your comments to three minutes and let us know who you're representing or who you are associated with. First Mr. Stephen Cheng.

Stephen Cheng:

Good morning. My name is Stephen Cheng and I am a representative from the medical division of Eli Lilly. I would like to provide comments supporting the availability of Strattera for the patients in Washington.

First, not all ADHD medications are the same. Strattera is unique in that it is the only non-stimulant FDA indicated and approved for the treatment of ADHD. Second, not all ADHD patients are the same and comorbidities are common. Studies have shown that 65% of children with ADHD have at least one comorbidity, specifically comorbid anxiety disorders are present in up to 39% of children and 47% of adults with ADHD. Comorbid tic disorders are present in up to 10% of children and adolescents with ADHD and comorbid substance use disorders are present in up to 15% of adults with ADHD. The Academy of Adolescent and Child Psychiatry practice parameters for the assessment and treatment of children and adolescents with ADHD in 2007 stated that while stimulants are considered first line therapy when no comorbidities are present, Atomoxetine or Strattera may be considered as a first medication for ADHD in persons with an active substance abuse problem, comorbid anxiety, or tics.

Third, the diversion of stimulant medications and their subsequent abuse by individuals without ADHD is a growing problem in the U.S. According to the 2006 national survey on drug use and health, an estimated 1.2 million people age 12 and older use prescription stimulants or methamphetamine illicitly in the past year. Unlike stimulants, Strattera does not have any potential for abuse due to its different mechanism of action. Prescription diversion and abuse can generate several concerns for example, when prescriptions are diverted, a portion of the medication that pairs or is paid for is not being used by the intended patients and thus patients with ADHD may remain untreated. The lack of abuse potential makes Strattera an ideal ADHD treatment in patients with a history of substance abuse.

Overall safety and tolerability of Strattera has been demonstrated in clinical trials, however the Strattera package insert includes a box warning regarding increased risks of suicidal ideation with no completed suicides. Warnings regarding risk of severe liver injury, two out of more than two million patients were found to have a severe liver injury reported in the post marketing reports. Warnings regarding allergic skin conditions, treatment emergent psychotic or manic symptoms in children, adolescents, and emergent agitation, aggression, and hostility. Warnings regarding sudden death, stroke, and myocardial infarction in adults warning regarding sudden death in children and adolescents with structural cardiac abnormalities or other serious heart problems. Also Strattera should not be taken within two weeks of an MAOI. Full prescribing and safety information is available in the Strattera package insert, which I can

provide at your request. Thank you for your time and I hope you consider keeping Strattera available for your patients in Washington. Thank you.

Carol Cordy: Thank you. Dr. Carl Plonsky.

Carl Plonsky: I'm Dr. Carl Plonsky and I'd like to thank you for letting me speak today. I represent the children and I'm not a stakeholder. I have a full three minutes of information that I would like to read to you and that's why I would like to read you my statement. I am a board certified pediatrician. I have been practicing and teaching pediatrics for a long time. I have been on the teaching faculty of two medical schools, I have been board certified in pediatrics. I have had two one-year long fellowships, one in developmental pediatrics and one in behavioral medicine. I was the director of the developmental behavioral fellowship for three years, except for my time at the University of Washington and Children's Hospital in Seattle. I have been involved in the day-to-day care on the front lines. So today I am asking you to please consider open access for medicine for the ADHD population.

Because I am on the front lines I am helping kids to stay healthy, helping parents to understand development, helping families to not need the services of our overloaded mental health system through anticipatory guidance and education. However, ADD does exist. I do run a developmental disorder clinic, behavioral clinic in Tacoma, which is open to all patients. We have more than 1,000 patients there whom we serve in this subspecialty area. Of the 1,000 patients, many on Medicaid, Healthy Options, and DSHS as their primary insurance we have an important role in their management. However, no medicine is a silver bullet. I am speaking for the kids who we serve on the front lines, and not for any one drug company. All medicines, because they are long acting, no matter what studies you quote are not created equal. Some have long acting...some of the long acting medications we have act too short. Some of the long acting medications we have act too long. These don't come across in our meta-analysis or in our studies. As new medicines come to the market, they often improve the lives of those who have been using older generation medications.

Point in fact, both of the diabetes and asthma have seen their lives improved with improved medications as they have developed over the years. Neural pathways of attention are complex and varied. Attention is multi-dimensional. We're not talking about the pathways of the hindbrain involved with survival, fear, high interest and one-on-one, which permits kids to watch television, have fun, and seek instantaneous gratification. We instead are really talking about the attentional pathways involved in using executive function better. This attention span lets people consider consequences before they act. This is the way medicine works, the

reduction of impulsivity. And we need to use that throughout all waking hours. The pharmacokinetics of medicines have a very great variability. And for some patients, for example Adderall extended release, which you've been quoting today, has a T-max of two hours. For those children it may last until three or four in the afternoon. What happens to the adolescent driving late in the afternoon next to you, when this medicine wears off? For other medicine, for the same medication the T-max may be ten hours and as a result, they have difficulty getting to sleep. And therefore compliance is a real issue. Most studies do not address the issue of compliance. On a real world, we have that problem. Other medicines have varying impacts on appetites and/or tics. For example, some children with tics are worse with stimulant medicines and have anxiety as a comorbid feature. In some cases Strattera can be of help. While appetite suppression is especially prohibitive, we have found a number of times where [inaudible] has less appetite suppression and is better tolerated. There is no silver bullet. Other children have difficulty with taking short acting medicine after school because they forget and they are unsupervised. One then needs to look for a medicine that can be used longer than 3:00 to 4:00 pm and the study of the literature shows that many don't.

Carol Cordy: Dr. Plonsky can you wrap up your comments please?

Dr. Carl Plonsky: In summation I would like to say that I've had two children, two adolescents in the past 12 months and they had sustained massive head trauma.

Tracy Durgin: Thank you. Can you hear me okay? My name is Tracy Durgin and I work within medical affairs at Novartis Pharmaceuticals and I would like to just make a few salient points regarding the use of stimulants for the treatment of ADHD and then just point out a few key characteristics of Focalin XR in particular. To echo what was just mentioned, one size does not fit all for ADHD treatment. Recently published consensus statements, practice parameters highlight the need to individualize treatment. Patients' responses to therapy can vary greatly depending on the drug, the dosage form, and the extended release mechanism employed. Some key points that differentiate Focalin XR include the following.

It's an extended release formulation of Dexmethylphenidate, which is the active racemic isomer of methylphenidate. It therefore provides efficacy at half the dose. It's extended release technology results in 50% of the drug being released immediately upon ingestion and then 50% approximately four hours later. It is the first and only methylphenidate preparation that is FDA approved for children, adolescents, and adults. And of note and potential interest to the committee is the fact that the recently published DERP report does not include the adult indication,

which has actually been in place since 2005. So I just wanted to make the committee aware of that.

Focalin XR has a rapid onset of action, taking effect as quickly as one hour and lasts up to 12 hours of the day. It was well tolerated in clinical trials and the pivotal study that was mentioned this morning in children and adolescents. No subjects discontinued due to adverse events and overall discontinuation rates in the adult study that was published were comparable to placebo.

Lastly, Focalin XR's extended release technology provides the option to sprinkle it on to food, which is beneficial for patients who cannot swallow pills.

In closing, effective treatment of ADHD requires individualization of therapy for a particular patient. Focalin XR given the aforementioned characteristics offers a valuable treatment option for patients burdened by the symptoms of ADHD. Novartis respectfully requests that this committee consider adding Focalin XR to the preferred drug list. Thank you for your time.

Carol Cordy: Thank you. Dr. Thomas Charbonnel.

Tom Charbonnel: Yes, my name is Tom Charbonnel and I'm a pediatrician, I work with Dr. Plonsky at Union Avenue Pediatric in Tacoma and we do have a large population of ADHD children we take care of in a special area in our office. I'm a board certified pediatrician, also I've taken a fellowship in adolescent medicine, so I'm familiar with adolescent problems. The thing I was asked to come talk about Vyvanse by Shire. But I really want to use Shire's product as an example of what Dr. Plonsky was talking about. About the fact that the population we take care of is not what we see when they do the studies. Studies are done with certain limitations as far as inclusion, exclusion factors and those are not what we see in our everyday practice. We see kids who are very complex. And I just want to give you an example of a patient that I had the name of...well I don't want to mention, name names, but the child was born in August of '97 and this child started getting help in 2002 from a child psychiatrist, Dr. John Rose and he took care of him until the last year, when I took care of...started taking care of him. This patient has a single mother who also has another child with very similar problems. In fact I was taking care of that child while Dr. Rose was taking care of this child. We sort of exchanged the two at the beginning of 2007.

But this child had been on many, many medicines. Dr. Rose was working on him to try to get mom to do better parenting, because she had very limited parenting skills. And the time I started trying to put him on

Vyvanse, which was in September of last year, he was on Concerta, Strattera, Tenex, and Clonidine as combination drugs and I put him, decided to try him on Vyvanse and I did the free trials that the company gave. And I finally reached the dose of two 50 mg dosages, 100 mg a day of Vyvanse and the result was amazing in the sense that this child, mom said this was the best behavior this child's ever had. What happened after that was that I said, "Okay, let's do this," and of course he was a DSHS patient and DSHS said, "No, we can't approve that dosage." And I had to go through review and I did the review and it was denied. After that the child was kicked out of school, had horrible problems, and then finally it was approved after the second and third review in January. But by this time the child's life had been really fallen apart. So this is the kind of patient we're talking about. When we want different drugs available to be able to treat in these situations, without having to go through a number of reviews like we did. It took four months in order to get this done.

I just wanted to let you know that Vyvanse, I've put a lot of kids on Vyvanse. Switched over to that. And this is the only drug that I've tried that was new that I actually had results...I said, "Wow, this is amazing." This is the first drug I ever had that, it met the expectations for a new drug. And that's the only thing I can tell you. And the report comes from teachers, from parents, and adults who are given it to. They said one of the smoothest drugs, it doesn't have the jolt that you feel when it goes up, it doesn't have the downside when it comes down. So it's been a very good drug. I just want to...I'm not trying to sell Vyvanse. I'm just trying to tell you that we like to have access to a lot of drugs that we can use.

Carol Cordy: Thank you very much. Were there any other stakeholders? Marian are you still there?

Marian McDonagh: Yes I am.

Carol Cordy: We can open up for discussion. Questions?

Angelo Ballasiotes: Angelo Ballasiotes from the committee. Can you expand your comment on Modafinil with respect to the rash? Does this rash issue a recent report from the FDA?

Marian McDonagh: This was the reason, when the product was brought to the FDA for review there, they had sent it back to say they wanted more studies on safety. And their concern in particular was the rash.

Angelo Ballasiotes: Is this a Stevens Johnson type rash?

Marian McDonagh: Yes, there were, there was at least one patient reported in trials, but there may have been more reported to the FDA with Stevens Johnson and then

the others were just severe rash. So it's a little unclear what the N is on the Stevens Johnson versus rash.

Patti Varley: This is Patti Varley and my understanding is the drug company, when asked by the FDA to go back and repeat studies for safety based on the Stevens Johnson type rash, they declined to do that. So as a result, Provigil is not actually FDA approved for ADHD. Correct?

Marian McDonagh: As far as I know, yes.

Alvin Goo: Hi Marian it's Alvin. Regarding Atomoxetine, are you...I couldn't find any studies in patients with a history of substance abuse. Is that correct? Have there been any studies with Atomoxetine in patients with ADHD with a history of substance abuse?

Marian McDonagh: I am trying to think, I think there was one in adults. And if you'll let me flip through here. We may have taken that slide out of this particular presentation. Let's see...yea I guess not. I guess it's not really a substance use disorder.

Alvin Goo: Correct, and are you aware of any studies comparing Atomoxetine with stimulants in that same population?

Marian McDonagh: No.

Alvin Goo: Okay, thanks.

Marian McDonagh: Unfortunately a lot of the studies that we see in this, in that population but in a lot of the subpopulations that we're interested in are compared to placebo.

Alvin Goo: Okay, thanks.

Angelo Ballasiotes: Angelo Ballasiotes, the committee again. With regards to diversion studies, is there any study or implication with regards to parents or guardians using the children's medication?

Marian McDonagh: It's such a great question and we were looking for lots of information like that, but what we found was a lot of studies that are really unclear. For instance, the national survey on drug use and health, it's unclear who was abusing those, when the people who responded, it's unclear if the drug had been prescribed for themselves or for a child, for their child. So it's really...I would say I don't have, we didn't find evidence on that that was clear.

Patti Varley: This is Patti Varley and not evidence based, but a comment would be in my 26 years, the notorious abusers of the medications I've prescribed are not my patients, but their families and relatives. It's the adults, it tends not to be the patients themselves who are in treatment.

Marian McDonagh: And we were hoping to find studies that could uncover the rate of that, and really we did not. And I think we were surprised at the quality of the studies we found, they were kind of epidemiologic studies, but not the higher, the better quality ones.

Carol Cordy: Any other questions or comments? Do you want to...is the previous motion...

Jeff Graham: Carol, this is Jeff Graham. I'm wondering if we can let Marian go for probably the next 20 minutes or so.

Carol Cordy: Okay, Marian it looks like you're up for...do you think we'll be on time?

Jeff Graham: I think so.

Carol Cordy: So we'll vote and let you go until 10:45.

Marian McDonagh: Okay. I'll be back.

Carol Cordy: Okay thank you.

Patti Varley: This is Patti Varley, and I'll go ahead and read the previous motion. After considering the evidence of safety, efficacy, and special populations for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), I move that methylphenidate based and amphetamine based agents of both long and short acting formulations were safe and efficacious. Now, we did review the dexamphetamines and we did review the lys dex...so I'm wondering, do we need to add those in there?

Jeff Graham: If you look at the proposed motion, they are, the interventions are listed so you could go ahead and just include the interventions that you want to have there in your motion.

Patti Varley: So I think...

Vyn Reese: This is Dr. Reese. It says methylphenidate based. I don't know if you'd include an isomer as methylphenidate based. It's like, it's sort of a matter of...

Patti Varley: So it's implied.

Vyn Reese: It's semantics, yea. It's in the same drug class, it's an isomer of methylphenidate.

Pattie Varley: Okay. As long as it is all inclusive. Are safe and efficacious. A long and short acting formulation of each stimulant should be preferred drugs on the Washington State Preferred Drug List. No single stimulant medication is associated with fewer adverse events in special populations. The stimulants listed above shall not be subject to therapeutic interchange on the Washington Preferred Drug List.

Carol Cordy: Do we have a second?

Man: I'll second that.

Carol Cordy: All in favor?

Group: Aye.

Carol Cordy: Opposed. So the motion passes.

Patti Varley: And then we had a second motion regarding the non-stimulant.

Alvin Goo: Hi this is Alvin. I still have some concerns with Strattera as far as how it's being utilized. I think it's being promoted for adults with a history, or if you're concerned about abuse potential. And I just don't think there's sufficient evidence to support that, although it makes sense, but there's a lot of things that make theoretical sense that we've been...found out decades later that that's wrong. So that's my only concern about having Strattera or the last motion. And I think that it would be nice if we could also include in a review interventions no longer included the Bupropion, Clonidine, things like that. Because I think there are other alternatives besides Strattera, but that's just my thoughts.

Patti Varley: This is Patti Varley. It's not that I disagree in context with what you're saying Alvin, but when you look at the approved drugs for ADHD right now, Atomoxetine is a non-stimulant alternative that is approved with at least some evidence based and safety data. The other meds you are referring to are mainly used off-label and so I'm not sure that they could be considered in the same review process.

Angelo Ballasiotes: This is Angelo Ballasiotes. I think we do need...I think it's imperative that we have a FDA approved non-stimulant. My work is mostly in substance abusers and that's the only drug I really feel safe in using with regards to these people relapsing. A lot of them do use methamphetamine because they do have some relief from their ADHD. So it's unfortunate

that we don't have the studies, but it's in my opinion empirically I see it as a real necessity.

Jeff Graham: Carol, this is Jeff Graham. I want to just point out that the participating organizations in DERP made the decision regarding the interventions not to be included in that this study would have been so huge that we would have never gotten it completed. So that was one of the main reasons. And I think those drugs are available for folks to use in general. So it just decided not to go and make the study real large.

Alvin Goo: Right, correct. This is Alvin. I can understand that, but it just seems that if it's on my Washington State Preferred Drug List, that in itself says I should be used first. And I guess that's where I have issues.

Patti Varley: This is Patti Varley. So Alvin could you walk me through in your mind when you were not using stimulants and you were using a non-stimulant what your logistical order would be?

Alvin Goo: Well, that's I guess if we look at who's prescribing most of these agents, I would surmise that they are primary care. Is that correct Siri?

Siri Childs: Yes.

Alvin Goo: Probably, right. And I think that is the problem. Is that we do not have great guidance as to what we should be starting with first. And so right now if you look at non-stimulants when you compare those with the stimulants, I have not found any great evidence that they are superior or that they're the same. So in that case, I don't see why I should be using a drug if it's not superior than my stimulants. I don't see any difference. And then they're telling me, well you should be using this in your substance abuse patients, but yet I don't have any studies in that population. So I guess that's where my dilemma comes in.

Patti Varley: This is Patti Varley again. I don't disagree with you on that, except my understanding is that we are not implying that Atomoxetine be used as a first line drug of choice in place of stimulants. It just is an alternative non-stimulant that exists with the FDA approval for this.

Alvin Goo: Correct, but I think the underlying premise is that if you're on the PDL that gives a lot of clout and power to marketing.

Patti Varley: Well, unless some other drug comes out with FDA...I mean Provigil could have done it, and they chose not to. And if Provigil had done it I would probably be changing my statement here, but at this point in time I'm limited by the studies and the data and the evidence that's in front of me.

Alvin Goo: I understand. I can understand the difficulty, but I think Modafinil was denied.

Ken Wiscomb: This is Ken Wiscomb. I think...to me backing up historically a little bit, we've always tried to include if there was something, an alternative we've always tried to make one of each class available so that we weren't limiting. And I actually, sort of think we have that obligation here as well.

Carol Cordy: Any more discussion? Does somebody want to...I guess my question is would something...if there's only one drug in a category as in this case, could it be a non-preferred drug? Is that an option?

Siri Childs: This is Siri Childs, and if you are suggesting that it be used for a special population, we could always put it on EPA for that population. If that's what you're suggesting.

Carol Cordy: Alvin is that, would that be a reasonable option for you?

Alvin Goo: I just don't want to put more blocks on drugs and I don't think having it on EPA is going to resolve the issue. I think it's a bigger problem that we're facing. So I just wanted to bring up that point. I think we can move on.

Patti Varley: This is Patti Varley. My issue would be that in this particular specific case, although there are risks of side effects, they are less serious and less dangerous than some others and so I would hate to put that stumbling block in front of something that from a clinical safety point of view really doesn't need that level of protection.

Alvin Goo: Correct, I agree.

Angelo Ballasiotes: This is Angelo Ballasiotes again. I've run into situations where the guardians or parents don't want their children started on stimulants. And that brings up another dilemma also.

Patti Varley: And I would say that we had a child at Children's Hospital who didn't want the blood transfusion. I mean there are families who get to choose and have a say in their care on all levels. And that is something as clinicians, I think we all deal with in regard to patient education and patient relationships and I wish I could control the world in a positive way and make that better, but I'm not sure that's our mission here.

Carol Cordy: Any other discussion, comments? Does somebody want to...I'm noticing in reading this it says Atomoxetine is efficacious. We've usually put safe and efficacious or, is that just something missing there?

Patti Varley: This is Patti Varley. My recollection actually had to do with the issue of the liver toxicity, which has actually been reviewed and actually now taken away as much of a concern after the new data. So I think we can add it back in at this point based on the new data.

Vyn Reese: This is Dr. Reese. But it also now carries the warning of suicidal ideation. So it's like it sort of exchanged one for the other. I don't know if methylphenidate has the same warning.

Patti Varley: No. It's because Atomoxetine is within the same realm as the antidepressants because it's a norepinephrine reuptake inhibitor. So it got the labeling with all of the antidepressant meds.

Carol Cordy: Does somebody want to take, make an attempt to make a motion?

Patti Varley: This is Patti, I'll go ahead. After considering the evidence of safety and efficacy in special populations for the treatment of Attention Deficit Hyperactivity Disorder, I move that the non-stimulant Atomoxetine is safe and efficacious and should be included as a preferred drug on the Washington State Preferred Drug List.

Carol Cordy: All in favor? Oh second, sorry.

Ken Wiscomb: I'll second.

Patti Varley: Ken.

Carol Cordy: Ken, Wiscomb. Okay, all in favor?

Group: Aye.

Carol Cordy: Opposed?

Alvin Goo: Aye.

Patti Varley: May I make a statement of clarification? Within the first motion the fact of having both long and short acting, I just want to always remind people that whatever ends up on the PDL, if clinicians have failed things and they are endorsing prescribers the PDL does not limit access and the ultimate goal is again safety. Looking at trying the safest things first. And cost effective so we can treat more patients.

Carol Cordy: Thank you all. We'll take a break. We'll take a ten minute break?

Jeff Graham: Yea, let's start at 10:50.

Carol Cordy: Start, back at 10:50. A little bit louder for me?

Marian McDonagh: Okay. Let me know if I'm...if you still can't hear me.

Carol Cordy: That's fine.

Marian McDonagh: Okay. Now on the second slide is an example of one of the analytic frameworks in this report. And I'm sorry, this is actually, I meant to put the lipids one in here and I put the diabetes one in, but they are very similar and the point of this is to show you the walk through what it means. And we have nine key questions for this report, so it was quite different than some of the other reports. And each number on the analytic framework corresponds to one of the key questions. So we were asking a variety of questions about is there direct evidence between the combination product and long term health outcomes. So that would be the arrow that goes from the combination product box to the big box on the right with the long term health outcomes. We were also looking however, at the intermediate steps. So improvement in this case in lipids and then also the question of does improved adherence also result in improved lipids or long term outcomes? And then of course adverse events there. And then on the bottom half is the individual product, so either given as monotherapy or as the two drugs given together, which is referred to co-administration. So that's what our analytic frameworks will look like, and on the next slide we can ignore that third slide, it's really just the same thing, but not as detailed.

So on that, the fourth slide inclusion criteria we included any adult patient with hyperlipidemia. We included the two products that are available as fixed dose combinations, that's Vytorin, which is Lovastatin and Niacin. Oh, sorry, I've got those reversed. Vytorin, which is ezetimibe and Simvastatin and Advicor, which is Lovastatin and niacin. And then we, as monotherapy we included any of the drugs that are included in those products as well as any statin. Included study designs are summarized in that table.

Now on the next slide, again as usual we were focusing on long term health outcomes as well as other effectiveness outcomes like hospitalization, quality of life, things like that. But we were also as I showed on the analytic framework including short term outcomes. So the serum lipid, changes in LDL and HDL reading NCEP, ATP3 goals, things like that. We were also interested in adherence, or persistence. So the ability of patients to take the drug as directed, but also with persistence looking at long term ability of a patient to continue taking the drug over long periods of time. And then of course looking at harms, both overall adverse events, major adverse events, and then general.

On the next slide we have our search strategy, which was typical. We received one dossier from the manufacturer of Vytorin. We had public comment in August of '07 and ultimately we included 13 studies. Eight trials and six non-randomized studies.

So starting with Advicor, we did find no studies that were comparing Advicor to co-administration and no studies reporting long term health outcomes. We found three trials that were comparing Advicor to monotherapy and then three uncontrolled studies. And all of those were looking at short term outcomes, but we did find a study of Advicor looking specifically at adherence outcomes.

On the next slide we have the outcomes for LDL lowering comparing Advicor to monotherapy. So we have a study comparing Advicor to Lovastatin 20-40 mg and in this study the combination, so adding a second drug to the statin resulted in 10-24% additional lowering of LDL. In the similar study comparing Advicor to Simvastatin 40 mg, the reduction was smaller, 0-3% additional lowering. Compared to Atorvastatin 40 mg it was 7-10%. So all of those were statistically significant differences, additional lowering with the second, the combination product so two drugs compared to the single statin. In the bottom part of the slide there is commenting on triglyceride, effects on triglycerides. Adding niacin, so the combination product in two trials did result in additional triglyceride reduction compared to monotherapy with a statin. HDLC the increase was greater with Advicor compared to statin monotherapy. About 20% when looking at the higher dose of Advicor compared to Atorvastatin, Simvastatin, or Lovastatin, all at the 40 mg dose. The differences however were not always statistically significant, even though they were numerically higher.

On the next slide looking at withdrawal rates. The overall withdrawals comparing Advicor to niacin extended release as monotherapy or Lovastatin as monotherapy. Advicor had 18 and 19% compared to 20% and 23% with niacin and 9% and 10% with Lovastatin. So the regimens that included niacin had higher rates of withdrawal discontinuation from study. Now withdrawals due specifically to adverse events similar results. The Advicor groups had higher rates from the statin monotherapy groups and flushing was the most common cause of withdrawal in the niacin containing regimens. Looking at withdrawals due to myopathy or elevated liver enzymes, they were very, very low rates of withdrawal in these studies due to those two outcome measures.

Now on the next slide, looking at the actual rates of adverse events and not withdrawals flushing was reported in much higher rates with the niacin containing regimens. AST or ALT elevations were very small in these trials, similar to what you'd see in statin trials, so not high but still

important. Dizziness and flushing were reported more often with Advicor than compared to the statins. Looking at subgroups we have very little information in the subgroups and again caution because the subgroups themselves are quite small.

The only good evidence we found on adherence and this was a study of prescription claims data. Looking at a one-year period and they were looking at both adherence looking at the medication possession rate and also persistence. And the results here, they were comparing Advicor to co-administration, so the two products given separately or to monotherapy. And so for adherence the medication possession rate score was .88 for Advicor and .90 for co-administration. So no statistical difference there. For persistence compared to co-administration with logistic regression to control for confounding factors, an odds ratio of 1.31, but not statistically significant. So again no difference in the persistence rates between co-administration and the combination product. Overall I think again that we point out in other reports as well as here that less than 20% of patients were persistent over this one-year time period.

Now in the trials themselves a few of them reported adherence rates and so one of three trials reported 90% adherence in all groups, or greater than 90% I should say. So very, very high adherence to the treatment regimens during the trial time period at least. Two open label studies also reported adherence. 77 and 94%. And again it's considered generally that if you have at least an 80% adherence rate that that's considered good. So these were both even in open label some much broader types of studies that they were still very high rates of adherence.

In moving on to the evidence for Vytorin, we found no studies comparing Vytorin to co-administration and no studies reporting long-term health outcomes. We found five trials of Vytorin compared to monotherapy and these were all compared to statin monotherapy. So three trials compared to Atorvastatin, one versus Rosuvastatin and one versus the components of Vytorin, Simvastatin, and ezetimibe. And then we also had one before and after study. And all of these were reported serum lipid outcomes and adverse events in the short term.

So on the next slide looking at the change in LDL-c compared to Simvastatin, now this is a study that averaged the results over the dosing range, so 10 to 80 mg. For Vytorin the mean change in LDL-c was 14% greater when averaged across the doses. Compared to Atorvastatin, similarly the Vytorin had a lowering of LDL, 8% greater than Atorvastatin averaged across 10 to 80 mg. When you look at the individual rates you do see somewhat dose dependent results with the difference being 11% at 10 mg, but almost 6% at 80 mg. In the second study the Vytorin had 12.5% greater LDL reduction at a dose of 20 mg of Atorvastatin. And in

the third study with diabetics only it was a 9% difference at 20 mg and 7% at 40. Looking at Rosuvastatin, this is averaged across the dosage range of 10 to 40 mg. Vytorin resulted in a 4% additional lowering of LDL-c. Those were all statistically significantly different, regardless of the 4% difference being much smaller than the 14% difference seen compared to Simvastatin.

Now on the next slide, looking at the achievement of the NCEP ATP 3 goal. In the first comparison there, Vytorin versus Atorvastatin, here we see that Vytorin does result in more patients meeting goals. So 80, almost 90% versus 81% and that results in a number needed to treat of 12. In the next Atorvastatin study it was not reported in the way that we could calculate a number needed to treat, but the number of patients achieving the lower goal of 70 mg/dL was greater with the Vytorin group compared to the combined statin Atorvastatin groups across all doses. For those who were trying to meet a goal of 100 mg/dL, again across the dosage groups Vytorin was able to...patients were able to meet goal more often or a higher number of patients were, but not with the 40 mg dose of Atorvastatin. There was no statistically significant difference at that dose, just with the lower doses. In the Vytorin versus Rosuvastatin comparison again Vytorin was superior, 96% of patients met goal compared to 93% with Rosuvastatin. So here the difference is much smaller, a 3% difference. And the number needed to treat is higher, 35.

On the next slide looking at triglycerides and HDL we find that significantly, there's a significantly greater improvement in triglycerides with Vytorin compared to the monotherapy of Simvastatin or ezetimibe. No significant improvement over Atorvastatin reduction in three trials however and compared to Rosuvastatin at the lower doses, Vytorin does result in better triglyceride reduction, but not at the 40 mg dose. For HDL-c we did not see a statistically significant difference compared to Simvastatin, Rosuvastatin, or ezetimibe monotherapy. But, compared to Atorvastatin there was a significant difference in the rate of improvement. So 1.4 to 4% additional increase in HDL with the combination products compared to Atorvastatin.

Now on the next slide, looking at adverse events, first looking at discontinuation from the study due to adverse events. Vytorin, the combination product was very similar to Simvastatin. Ezetimibe monotherapy was found to be very similar to placebo in that study. Adverse events, significant differences were not found across the product here, the three drugs that were studied.

In the next slide, we have looking at the same adverse events Vytorin compared to Atorvastatin. And again the adverse event rates were not significantly different across the groups looking at myopathy, serum

transaminases, other outcome measures commonly associated primarily with the statins. Vytorin versus Rosuvastatin again discontinuation rates and adverse event rates were not different between the groups here.

Now looking at both subgroups and adherence evidence for Vytorin. We have really limited evidence here. So we have one study that was an observational study looking at two groups of patients. Patients with either CHD or in a separate group type 2 diabetes. Looking at patients who were switching from a low to moderate dose of any statin, monotherapy to combination product. And here we did see an additional reduction in LDL-c of 27-28% and this compares very well to the Barrios trial, which was also converting patients over from randomizing them from their current therapy, which was a low to moderate dose statin into the trial where the reduction was 32.8%. So a little bit lower. We found no evidence on adherence for Vytorin.

Now on the next slide we have in the analytic framework that we looked at at the very beginning we had that little box that looked at what is the length between adherence and long term outcomes? So this is looking at that evidence to see what kind of evidence here is due to, linked adherence improvement to long term outcomes. We found an observational study, kind of medium sized, 600 patients. The link between adherence and statin therapy and the attainment of LDL goals, specifically in diabetics. Here the medication possession ratio was also used and the mean MPR over a nine-month period was 70%, so pretty good. Adherence threshold for achieving the LDL goal was found to be 82% and the choice of statin had a significant impact on the ability of the patient to achieve their LDL goal. And specifically they found here that the choice of Atorvastatin in particular meant that the patients would meet goal more often, and it did not have a significant relationship with adherence. Importantly, the study did not examine some other things that we were interested in, such as the other aspects of a patient's drug regimen, how complicated it was for example and did not stratify the data by gender or for other confounding factors.

So that summarizes the information, there's a lot less information here in this particular review than we just saw in the ADHD review, so that's the summary.

Carol Cordy: Thank you Marian. We have two stakeholders if you could stay and then we'll have some discussion, some questions.

Marian McDonagh: Okay.

Carol Cordy: Dr. Pham.

An Pham:

Good morning, I'm Dr. An Pham, medical assigned liaison in cardiovascular with Schering Plough. I would like to thank the P&T committee for the opportunity to provide public comment on the clinical benefit of Vytorin for the treatment of elevated LDL cholesterol for many high risk patients in Washington. As you know, LDL cholesterol comes from three sources, their food, the liver, and the [inaudible]. So the question is how it's important and clinically relevant to treat these three sources of cholesterol, especially in high risk patients, including patients with diabetes and CHD [inaudible].

As an analogy, if your office is in a high risk, tough neighborhood and your office has three doors, is it enough to lock just one door? Or all three doors together at the end of the day? Vytorin, a powerful lipid lowering therapy is available in a once daily tablet. Vytorin containing ezetimibe and Simvastatin is the first and only first line lipid lowering agent approved to simultaneously treat the primary sources of hypercholesterolemia. First by inhibiting the production of cholesterol in the liver through [inaudible] statin and secondly by uniquely blocking the absorption of cholesterol from [inaudible] and dietary in the small intestine. The complimenting mechanism of Vytorin reduced LDL-c by 52% of its usual 10, 20 starting dose. Furthermore, Vytorin is indicated to increased HDL and lower triglyceride. In the three large head-to-head studies as presented by Dr. McDonagh, Vytorin demonstrates the pure efficacy to both Lipitor and Crestor in achieving mean LDL-c cholesterol across the entire dosing range and superior in the percentage of patients attaining the NCEP lipid goals of less than 70 for LDL cholesterol for high risk patients, including the type 2 diabetic or CHD equivalent.

More importantly, several other large outcome studies are currently underway to assess the additional benefit of Vytorin on cardiovascular morbidity and mortality above and beyond that demonstrated for Simvastatin. Most importantly, Vytorin is generally well tolerated and has not demonstrated an adverse event profile significantly different in quantity or scope than statin alone. Please refer to the full prescribing information for additional information.

In summary, Vytorin in a single tablet offers patients superior lipid lowering efficacy and helps many high risk patients to achieve the new NCEP guideline treatment goal of less than 70 for LDL cholesterol. Thank you very much for the consideration and I would strongly ask the P&T committee to place Vytorin on the preferred status of Washington State Medicaid for the benefit of patient access.

Carol Cordy:

Thank you. Dr. Evans.

Tim Evans:

Good morning, I am Tim Evans. Is this on? I'm Tim Evans from the University of Washington where I'm an internist and endocrinologist and associate professor of medicine. In the University system we see a lot of patients who are Medicaid patients, both at the University and at Harborview and our other sites, so this is a topic of great importance to us. We are fortunately, we have a number of very potent agents for lowering LDL cholesterol primarily, but a couple of other changes have occurred in recent years that have made this an even more timely topic.

Number one, as data has accumulated, we are more and more confident that the lower the LDL the better. And that's true in everyone, but it's especially true in high risk patients. And the other major change has been that we have really quite dramatically expanded the group of people we consider to be at high risk. Now it's not just people who have previously had heart attacks. It includes all diabetics. It includes people who have a risk of having a coronary event of 20% in the next ten years based on the Framingham data, and this has really dramatically enlarged the number of people in whom we are trying most aggressively to lower LDL cholesterol. The advantage of this combination product is first of all that it's the best way we have to lower LDL cholesterol. It is, by blocking as you have heard both cholesterol synthesis and cholesterol absorption from the gut, we have the most effective mechanism by which we can lower LDL cholesterol in those high risk patients.

Secondly, for me personally as a clinician I like getting my patients to goal with the first dose of the drug I try. If I have to start on one dose and then they come back in four to six weeks and I check their cholesterol and it's not there, and I say, "Well it didn't work, let's double the dose. Come back again in another four to six weeks." After that first dose you only get another few percent lowering with each additional titration and pretty soon you've lost the enthusiasm of your patient to stick with this regimen and actually get their LDL lower. So if I can get them there with the starting dose, which I'm much more likely to do with this combination than with a statin alone, I think that has significant benefits in the long term for my patient, because they're likely to stay with that program. Likewise, I am more likely to get them to go with a lower dose of a statin, which is the component of this combined drug that has the side effects. They're low, if I can keep it at a low dose that's a benefit for the patient.

Carol Cordy:

Thank you. Is there anyone else? We'll open up to the committee for questions.

Vyn Reese:

This is Dr. Reese for Marian McDonagh. There is a recent study that was suppressed, apparently about Vytorin and intimal thickness and carotid arteries. Could you comment on that study? Have you had a chance to look at it yet?

Marian McDonagh: You know the only information I have on it is from the press release that the company released and I haven't looked in the last few days to see if something else has been published. Based on that I would say it's probably early to be making any real comments on it. The information in there just shows no statistically significant difference between the drugs in the change from baseline in intimal thickness. And it is in a very, very narrow population of patients. So I would really like to see the full trial to see what other data are reported before I really want to place a lot of emphasis on it.

Vyn Reese: This is Dr. Reese. The interesting thing about that study was that Simvastatin looks like it, in that small study, had an actually better effect on decreasing intimal thickness than the combination product and there were questions raised about whether, even though Vytorin was more effective at lowering LDL, was it any better at preventing the major end points? And we don't know that yet. And there haven't been any studies that have really shown that Vytorin is going to be superior to Simvastatin alone at decreasing hard cardiac events. Is that right?

Marian McDonagh: I think you're right. I think that the issue is probably that we don't have long term data, particularly for ezetimibe. So the combination here. And that is really the issue. And this study unfortunately does not help to answer that question.

Jason Iltz: Marian this is Jason with the committee. Can you go into a little bit more detail potentially in your findings of...with really both of the agents, but I'm more in particular concerned with Advicor in terms of ALT and ASD elevations and then potential Hepatotoxicity. You mentioned it briefly, but was there actual reports that you can refer to and did you compare that to, like for example Niaspan alone without the statin or what was the available data for that area?

Marian McDonagh: That's a great question. And what we have is really one trial that would be making that comparison. They did not find a difference in the trial, but it is a short term trial and a highly selective patient population. So what we did not find is good quality observational studies that would be able to answer that in a broad, a typical treatment situation. So I would say at this point all we have is that the elevations between the three arms, so it was niacin extended release, Advicor, and Lovastatin were not statistically significantly different. But that's maybe not helpful in the long term in a broader population.

Jason Iltz: Thank you. And then one more question for both of the agents in terms of rhabdomyolysis. Was there a difference in that particular assessment compared to monotherapy?

Marian McDonagh: No there wasn't. It was very similar. And the rates were very, very low. Again I think that points to the fact that these are short term trials and they are not really large either, so I think the chance of finding a difference is probably limited there.

Carol Cordy: Are there any additional comments or questions? Can we let Marian leave? Marian, thank you very much.

Jeff Graham: Marian are you coming back on for the statin?

Marian McDonagh: I will do that, yes.

Jeff Graham: I will try to call you right before we think we're ready, okay?

Marian McDonagh: Okay, sounds good.

Carol Cordy: Can I ask, this is Carol Cordy. Are there...on the list are there other combination drugs and can somebody remind me how we've dealt with those if there are?

Jeff Graham: This is the first class that we've done combination.

Carol Cordy: Okay.

Vyn Reese: This is Dr. Reese. I'll just open the discussion. I actually don't see any need for these drugs, to be honest. High potency statin is very effective at lowering LDL. We know that cardiovascular and cerebrovascular events are decreased with statins. Vytorin is a relatively new drug. Zetia has not been out long. We don't have any hard outcome data on Zetia. And it's...I don't see how the combination that's very close to the high potency statins.

Vytorin isn't, its efficacy at lowering HDL cholesterol. So I don't see a reason to add them. I'm not sure that there's a reason to think it's more effective than the statins and I think it's needlessly expensive and complex and basically I...and Advicor I think is another drug and both these drugs, I think niacin is useful as an add on and so I think Zetia is if somebody can't tolerate a statin you can, even though don't have good outcome data you can still make a case for giving Zetia instead of nothing if they can't take statins. Or adding on Zetia to somebody who is already on a maximal dose of a high potency statin would be a reasonable thing if you couldn't get the LDL down.

But as a first line drug I don't see using it and Advicor is like, is a combination niacin, which is a drug that holds a very high side effect

profile. A good drug, but hard to use. Lots of people drop out and it's not a drug that you'd want to use as a first line therapy for lipid lowering. It'd be definitely way down in the list as a drug that you use if somebody couldn't tolerate the statins, you'd think about niacin or something you did if their HDL elevated. So I don't see the need for these drugs.

I mean and you can't say that it improves compliance either, if both drugs are once a day you take two pills instead of one, I don't see the improvement in compliance. It hasn't been shown in any studies I'm aware of. For all these reasons I don't think it makes sense to have fixed dose combinations of these products. Thank you.

Jason Iltz:

This is Jason. I think I agree with most of your comments and I think where really you're going with it is why did we single these agents out to review, because certainly they have a niche area, but we've really only talked about statins so far. And so there's a whole host of other medications that we use that we will add to statin therapy or that we'll use if statins are not tolerable. So I'm wondering if in the future we may be served better to not only look at combination products, but to look at the fibric acid derivatives and look at the...some of the other agents that are out there with omega 3s now available and bile acid sequestrants and things like that. There's a lot of other agents we can use as an add on, and so as Vyn said, I'm having a little trouble trying to figure out where we would put these in relative to the other agents that are also available that could be used in combinations. Because they all have their little niche. If we're looking at mixed cholesterol disorders. I don't know other than Advicor, I'm probably going to choose a statin and a fibrate first if I'm trying to get triglyceride, LDL, and HDL intervention. So I think there are some other things that we need to look at as well and maybe just call this and other cholesterol lowering therapies that are there.

Vyn Reese:

This is Dr. Reese. I'd like to see those presented to the committee as well. The other drugs. The triglyceride lowering drugs and other drugs that lower LDL. I think the combination products here don't really add much, but I would definitely like to see those other drugs, drug classes reviewed.

Jeff Graham:

This is Jeff Graham and I think what I'll say why the DERP decided to do this. It was to compare combination therapy to monotherapy. And this is one that has just been released and come out and we wanted to really look at is there really a difference. Pharmaceutical manufacturers come to you and say, "You should have these drugs on your PDL. Look how good they are." That is you only have to have one drug rather than two and this begins to show that maybe the evidence isn't there. We will be looking at another combination drug class later in the year. Because of the things that the participation organization in DERP saw coming down the line and things that they needed to have evidence saying, "Well it doesn't look like

it's as effective or it is, it's really there's an additive effect here and that they do, are much better than even single dose of each one." So those are the kinds of things we were looking at. And you're right, I think it would be nice to look at the whole class. I think that might be more of DUR type of topic in that all those other classes we probably couldn't get reviewed in DERP because there are so many of them.

Duane Thurman: Excuse me, this is Duane Thurman. Just to elaborate on that. We're not trying to say this is what you have to do. We are deferring to a group of 14 entities that make the decision as to what drug classes that we review. It gives us the transparency and also doesn't allow us to individually as a state sort of try to game the system in terms of what drugs we want to review individually and bring before you. I think we've reached this issue once before, I believe it was the ARB's where we had done the review and the committee declined to put that on the preferred drug list. So that's certainly an option. It's just this is an output from DERP. We bring to you the combined output from DERP and it's in no way an endorsement that we have any opinion whether it should be on the preferred drug list or not, but it was a consensus of the group that Siri and Dr. Graham have been representing us as a state.

Siri Childs: This is Siri Childs and we were really happy when DERP selected this topic because just like Dr. Graham said, we hear a lot of promotions for a combination drug that would replace this monotherapy with the individual ingredients. And so DERP put together a model and these are models for us to use in our own programs to kind of run through what a combination drug would look compared to the monotherapy with the single ingredients and look at outcomes. And so that was really the purpose of this, not to select Vytorin versus Advicor. It was here are two examples of how you would use this model to show the difference between combination therapy and monotherapy.

Ken Wiscomb: Hi, Ken Wiscomb. Siri, is pricing included in that model for that? To me the one question would be in that small niche of people that would benefit, is there, is it less expensive to take the combination product than it is two products individually.

Siri Childs: Again, we always look at safety and efficacy and outcomes first and then after all of that we would price it and see, is there really an advantage? But we only do that if we see that the safety and efficacy would be the same.

Alvin Goo: Hi, it's Alvin. Siri, what do we have an estimation of the utilization of these combination products compared to statins? Do you have any idea?

Siri Childs: We probably should ask our drug manufacturers in the audience. But my sense is that the monotherapy with our preferred statin drugs far exceed what the combination drugs are.

Alvin Goo: I think we're all in agreement that these combination agents should not be first line and used after failure or some odd intolerance to a specific dose of a statin that you used.

Siri Childs: That's the type of recommendation that we're looking for. Here's the evidence, what would be your recommendation regarding this model?

Carol Cordy: It seems like what we need to do, we've had this format for the motions before, but it seems like we need to maybe develop a different format which I can see saying something like if there's no advantage in terms of safety, efficacy, and really compliance that there would be no reason to include a combination drug on the PDL.

Vyn Reese: And we wouldn't even need a motion at all if we don't want to add them. Is that correct?

Duane Thurman: Excuse me, this is Duane Thurman. The templates are just templates. So you can do whatever you'd like. I think that the...it can be very simple. Just basically that having reviewed the report the committee does not believe it should be part of the preferred drug list at this time. Something to that extent.

Carol Cordy: I think it would make sense to have sort of some reason for our decision, but again something really simple.

Jason Iltz: So just to clarify, this is Jason. If the committee says should not be on the PDL, does that mean should not be preferred on the PDL, meaning that it's still been reviewed so that the DAWs or any prior authorization or EPAs would be in place that the agencies would set forth, correct?

Duane Thurman: This is Duane again. If you're saying it is not on the preferred drug list, what you've done is basically said, you've not done an evidence based review and it would be treated as if this program didn't exist. It would be treated like everything else that's not part of our preferred drug list program so each individual agency would treat it according to how their benefit structure works.

Patti Varley: This is Patti Varley. I actually agree, I think that the intent is that we've reviewed it and if I am hearing people correctly, the intent that we want to say, and again this template is only a template, is that we've reviewed this class that we do not want it to be the first line for treatment, but it is safe and efficacious. So I don't have the motion down correctly, but I think the

intent is that we reviewed it, they're safe and efficacious, but we want somehow to state that these should not be first line drugs of choice for the treatment.

Vyn Reese: This is Dr. Reese. I think we can say we reviewed it and we don't want to put them on the preferred drug list. I mean there's no compelling need to do that.

Carol Cordy: And you're meaning the preferred drug list, not a preferred drug on the preferred drug list?

Vyn Reese: That we've reviewed these drugs, we do not want them to be a preferred drug on the preferred drug list period.

Carol Cordy: So can I clarify, they would be on the preferred drug list?

Jeff Graham: No this is the way it would say, it would be likely our would say that these are not to be included in the Washington State Preferred Drug List.

Alvin Goo: But if there's a...this is Alvin. Is there a way that we can not put...

Duane Thurman: And the preferred drug list is not a...we don't use it to tell people what to do in terms of second line therapy. It's either on the preferred drug list and we do that dynamic or it's not. What I'm saying is it would not be a part of this program. Each agency would treat it like it does all the other drug classes that are not on the preferred drug list.

Carol Cordy: Okay and I think I asked for the clarification that from what Patti was saying that it doesn't really have to be on the list. We don't, even though we've reviewed it, we don't have to say it's on the list.

Patti Varley: And I think we have this...this is Patti again. I think we also have to say we reviewed it.

Jason Iltz: This is Jason again. So Duane I know you're trying really hard to explain this procedurally, but are we reviewing this as a whole, separate, potential class for the PDL?

Duane Thurman: Yes.

Jason Iltz: Okay. So for example, if we were just to make a statement that said these drugs are safe and effective, that would mean since it's a separate class, when the next part of the review came in to play of cost and all those things, one would have to be chosen to go on the PDL? Or would the agencies be able to not even choose one of the two?

- Duane Thurman: One or both would be, you'd end up with a preferred drug. We would go ahead with our cost analysis.
- Jeff Thompson: This is Jeff Thompson. I think the general principle the PDL cannot be used to [inaudible] step therapies or guidelines. It really is an all or nothing activity based on safety, efficacy, and special populations.
- Duane Thurman: And that said the agencies could adopt their own step therapies for the benefits. Like Uniform Medical Plan could do that on its own, but once you put it on the preferred drug list, if it's a preferred or non-preferred drug we would, it limits what we're able to do in terms of making it available or making it second line therapy.
- Vyn Reese: This is Dr. Reese. The last time we tried to do this we did it with the TZDs and we said they're second line therapy and then we kind of did this horrible mess later, so I think we should not say second line, I think we should just say we looked at these drugs, we do not wish to add them on the PDL or talk about second line or anything else. I think we should just, we've reviewed them, we're not going to add them to the PDL. That would be my view. I would really like to have us review other lipid lowering agents. And maybe that's not going to be practical. But there are other good drugs out there that we haven't looked at [inaudible] binding agents, they're fibrates, and that we should really and niacin, we should review at some point.
- Carol Cordy: Unless someone else has a different comment, it sounds like we're pretty much in agreement that we don't think that these drugs need to be on the PDL.
- Duane Thurman: And I would say that we will take your comments regarding the kinds of studies that you would like to see and the way you'd like to look at this class back to the DERP to do that. But this is our first foray into the combination drugs and there is no, we don't have an agenda whether it should be on or off. I do think we need to be very careful before this committee gets into recommendations on second line therapy and things that the agencies need to do within the context of their business models. That said, you're free to do what you want with this.
- Jason Iltz: I don't know if this adds anything or not. This is Jason again. So could the committee say, I know at times we've said these medications should not be part of this class or should not be considered as part of this class. Could we in turn do something that said these should really be part of the HMG A co-A reductase inhibitor class and then make the statement or...because then that would be part of the same class and then my understanding would be the agencies wouldn't have to include them as a preferred drug, but they'd be on the preferred drug list.

Duane Thurman: You're testing my knowledge here, but I think the issue is that we define the drug classes based on an external target. The first databank. I don't think we'd be able to let you change the definition of the class.

Carol Cordy: And I would say, since the drugs here, you can get them. And I think one of the points is that we want our patients to be able to get whatever they need, but you can get these by taking two pills instead of one. And since it's available and I'm not convinced that compliance is no better and efficacy is no better. So I guess I wouldn't see an argument for including it in another drug class. This is...I'm trying to move on. We've got a lot of stakeholders for the next round and if there's no more comments if somebody wants to make a motion to move things on that would be great.

Vyn Reese: This is Dr. Reese. I'll make a motion. The committee has reviewed Advicor and Vytorin and has decided not to put them on the Washington State Preferred Drug List.

Carol Cordy: Before I ask for a second, does anybody want to wordsmith this at all? Okay. Do we have a second?

Jason Iltz: Okay, one second. Sorry, I'm a little slow here. Do we need to at least make a statement relative to what we've reviewed and that was safety and efficacy and then say that the committee feels they should not be included in the Washington State Preferred Drug List?

Duane Thurman: This is Duane. I think that that is an option. I frankly think the less said the better. Because I don't think you're making this decision on the basis of safety or efficacy.

Carol Cordy: Do we have a second?

Bob Bray: Second.

Carol Cordy: All in favor?

Group: Aye.

Carol Cordy: Opposed. The motion passes.

Man: I forgot to get Marian on the phone, I'm sorry. I got too involved.

Carol Cordy: Hi, Marian are you there?

Marian McDonagh: Yes I am.

Carol Cordy: We have the first slide up on the drug class review of statins if you want to go ahead.

Marian McDonagh: So this is the scan for the statins and so we have the update scan was completed in December of 2007. The last full update of this report was completed in August of '06. We did do an update scan of the literature last November as well. November of '06 I should say. So for this the key questions an inclusion criteria have remained the same. So pages two and three are the same as the original report. And then on page four we have a summary of our methods used for scanning the literature. We do scan looking for primarily for trials. And additionally looking for new drugs, new FDA indications, and new safety alerts coming out of the FDA.

So in our literature search, electronic literature searches we found this time 178 new citations that were referring to trials. Of those 20 were potentially relevant and those are summarized in the tables. So there were six new trials of statins looking at lipid outcome measures.

The first one there is looking at Atorvastatin 80 mg versus Rosuvastatin 40. And it's looking at a patient population with hyperlipidemia. The outcome measures are all focused on HDL and HDL subtypes.

And then the next study down there in the table is looking at patients of south Asian origin and Atorvastatin versus Rosuvastatin again.

The third trial Atorvastatin ten to 20 mg versus Rosuvastatin ten to 20 mg in African American patients. Then the third trial is the Solar study. That's Atorvastatin ten mg versus Rosuvastatin ten versus Simvastatin 20 in high-risk patient population high risk for CHD.

And then the next trial study Pierson(?) is actually, should not be on the list. It's actually a pooled analysis from three trials. The next one, Pravastatin versus placebo is looking at HIV infected patients. So it's really examining the drug interaction issues with Pravastatin and looking at HIV levels and trying to figure out if Pravastatin is safe in that patient population.

On the next page there are five new trials that do report health outcomes. So the first is looking at Atorvastatin 80 mg compared to placebo in a patient population with recent stroke or TIA and the primary outcome being new stroke. And in this study Atorvastatin was found to be superior to placebo for that outcome.

The next trial Robert Knop(?), the Aspen study is looking at Atorvastatin versus placebo in patients with type II diabetes with a composite endpoint

and this study did not find a statistically significant difference in the composite outcome or in the subgroup analyses that they conducted.

The next trial is [inaudible] Pravastatin versus [inaudible] placebo. This is looking at Japanese patients with hyperlipidemia and in this study Pravastatin was superior to placebo in preventing coronary heart disease.

The next study is looking at heart failure, so specifically looking at Atorvastatin for preventing additional heart failure outcomes. So worsening of left ventricular function in patients with existing heart failure. And Atorvastatin was significantly superior to standard care. That was the comparison group.

The last trial here is a head to head study of Atorvastatin at 80 mg versus Pravastatin 40. So intensive versus moderate dose therapy in older patients with coronary artery disease or prior MI. No differences were found in the primary outcome, which was ischemia. So the duration of ischemia at 12 months.

And we also have nine additional studies that are secondary publications or additional subgroup analyses from trials that were already included in the primary, the previous full report on statins. And it includes things like looking at chronic renal insufficiency, renal transplant patients, peripheral artery disease outcomes. So none of those studies would appear to be anything that would change the statins report in the bottom line.

Now on the next page, page six. We have found no new drugs would have been introduced to the market in the last year and Atorvastatin has a new FDA indication for patients with clinically evident coronary heart disease for Atorvastatin to reduce the risk of a variety of outcome measures. And then Rosuvastatin also has a new indication for slowing the progression of atherosclerosis. We found no new safety alerts.

So that summarizes the scan and then we have attached all the abstracts of the trials that we thought might meet inclusion criteria.

Carol Cordy: Thank you and we have quite a few stakeholders signed up to speak and I want to remind you again. Marian can you stay?

Marian McDonagh: Yea, I can.

Carol Cordy: To limit your comments to three minutes. When you've hit the three-minute mark I will say thank you. And you'll know that means. And then if you also can say who you're representing. First, Dr. Yang.

Eugene Yang:

I'm Eugene Yang, I'm a cardiologist. I am representing myself. I think I just have a few comments I would like to make. First of all, I think as a cardiologist one of the main things that I look for when prescribing drugs is really what are the hard endpoint or hard inpoint data studies that have looked in the kinds of patients that I take care of. So those patients who have had a history of heart disease, heart attacks, heart failure, stroke, etc. And while you show a compendium of different studies that have been released recently, the studies that you've shown there are about five or six of them in which hard endpoints were evaluated whether it was looking at recurrent stroke or heart failure in high risk patients that have diabetes. Typically I take care of patients and I think that using a lot of the generic drugs or how I treat patients because there have been numerous studies in both primary and secondary prevention that have shown favorable outcomes that are statistically significant.

However, in patients in whom we can't achieve cholesterol goals with less potent drugs that are not generic medications, then you have to ask yourself what are the studies that have shown efficacy in looking at the major endpoints. And so when I look at the data, and whether we're talking about a drug, a combination therapy like Vytorin or we're looking at Rosuvastatin or Atorvastatin, I think that from my standpoint there is rather compelling data in terms of clinical trials, specifically looking at the hard outcome studies that I've been alluding to with Atorvastatin. And so if I'm offering patients drugs based on the evidence that have looked specifically at the major endpoints, it's hard for me specifically to justify using drugs like Rosuvastatin where many of the studies have only looked at surrogate markers and not specifically looking at the hard endpoints, which for myself are the really clinically important ones that I think need to be addressed. So I'll just end with that. Thank you.

Carol Cordy:

Thank you very much. Dr. Mike Shannon.

Mike Shannon:

I'm Michael Shannon and I'm a UW and Harborview trained endocrinologist in Olympia, Washington and I'm the only Medicaid accepting endocrinologist in Southwest Washington and probably unique to Olympia, a quarter of our patients have Uniform medical plans. I was informed of the meeting by Pfizer, but came on my own, representing myself. I like to give patients things based on two things, which is improving adherence and outcomes. And I'd agree with what Dr. Yang says, that only Atorvastatin for high potency offers that. I like to give patients a couple of sentences on why they're getting it, and that would be something such as I want you to take ten mg of Atorvastatin because for type II diabetics like you, you had a third less heart attacks and 48% less strokes. I'm asking people to take two to three different medications for their blood pressure, two to three for insulin, their aspirin, and their statin. And I'd struggle to try to tell them why it's important to walk out with a

wheelbarrow full of medications for asymptomatic disease. This is hard to get by in.

When I have the ability to deliver something and put it down into a two-sentence version that says this lowers a third of your heart attacks and 48% of your strokes I can get some buy in. That means a lot, especially when I'm working through a telephone interpreter and where I'll be honest, that I even try and explain to my nurse slowing the progression of atherosclerosis is a pretty abstract concept. And so giving this in a way that patients understand and a way that I can draw it on my butcher paper on my exam table and try to show them why they're taking it. I think it brings cardiovascular benefit to people and improves their adherence. Thank you.

Carol Cordy: Thank you. Dr. Ed Gill.

Ed Gill: Good morning, I'm Edward Gill, a board certified and practicing cardiologist and lipidologist from Harborview Medical Center. As such, many of my patients are affected by the decisions made today by your board. Relevant to this discussion my patients have a very high incidence of multiple disease states, including renal failure, HIV disease, and conditions requiring anticoagulation. I would like to emphasize that multiple disease states. I would like to provide a pharmaceutical industry independent commentary on the statin drugs today. So as such, I represent myself and particularly my patients. First the statins have clearly been a revolutionary class of agents and are arguably the most important class of drugs introduced in the recent era for cardiovascular disease. Second it is evident that not all statins are created equally. Third it is important to note that not all patients can tolerate statins and a corollary is that some patients can tolerate some statins but not others.

Fourth, the evidence regarding the use of statins to lower LDL is impeccable across the board, but having said that it is clear that Rosuvastatin is the best agent to lower LDL from the standpoint of efficacy and potency. The downside however, is that Rosuvastatin has the least amount of outcomes data supporting its use. There are also some minor but significant issues regarding drug interactions with Rosuvastatin. Conversely, Atorvastatin has the most safety and outcomes data regarding its use. It is the only statin with an indication for prevention of stroke. Next to Pravastatin it arguably has the best drug interaction profile and is least affected by renal insufficiency. It is the only major statin that does not require dose adjustment in renal failure. That's an important point.

So that's a major issue, particularly amongst Medicaid patients. Simvastatin has the longest track record amongst high potency statins, hence it is clear that all three of the major statins should be available to my

patients and to physicians in general. Simvastatin is generic. This statin is generally available and not such an issue regarding formularies.

Finally, the combination of Simvastatin and ezetimibe offers LDL lowering in the same range as Rosuvastatin and I wanted to point out since it wasn't pointed out in your studies there has recently been a major press release regarding the results of the enhanced trial using this combination that is the combination of Simva and ezetimibe. The enhanced trial compared the use of Simva alone and the combination of ezetimibe plus Simva using the carotid IMT endpoint there was no difference. Much has been made by the media regarding the trend of more IMT progression in the ezetimibe plus Simvastatin arm compared to Simvastatin alone. It is important that no treatment decisions particularly change in formularies should be made regarding this particular result. Because it is a trend only and it is not significant. Further, it's an IMT trend, not a cardiovascular outcomes result.

So in summary, I wanted to say that our patients could be served best if all three of the major statins, Simva, Atorvo, and Rosuvastatin were available to them on formulary and also ezetimibe in combination. Thank you.

Carol Cordy:

Thank you. Dr. Muczynski. No. Dr. Nathan Ross.

Nathan Ross:

Thank you. I've never been to one of these meetings before, I have to say that I actually agreed with most of what Dr. Reese had said earlier. And also a person whose name I can't see in the corner over there. But I would say with Dr. Shannon, the two of us are responsible for more or less all of the Medicaid patients in the southern part of Puget Sound. We go down to Vancouver, we go up about halfway between Tacoma and Seattle. Thus far we are able to take all comers. What I have been attempting to do over the past several years is to duplicate in my practice or in the practice of our office, I work with a nurse practitioner for this purpose, the results and the practice of the Steno(?) study, initially published about five years ago, updated about two weeks ago in the New England Journal of Medicine, which is a simplified approach to diabetes which looks principally at controlling things that are easy to control. Make sure blood pressure is good, make sure lipids are as well controlled as they can be controlled, make sure blood sugars are reasonably controlled. Tell people not to smoke. That's not terribly effective by the way. And follow up closely.

Typically with lower paid employees we don't hire doctors to call people and tell them to take their medicine. But it's cheap to hire nurses and say, "Have someone call if necessary two or three times a week. Are you taking your medicines?" Because this is our approach, we like to find inexpensive drugs because we would like to do this in the best way possible with the least amount of money expended. We like to find

inexpensive drugs with the fewest side effects. Generally for lipid control we're looking at Simvastatin. Simvastatin I believe is an excellent drug. It's been well shown to be very efficacious in type II diabetes. There are a certain percentage of patients who will not adequately respond to Simvastatin because the lipid profile resulting from treatment for Simvastatin or similar to Simvastatin that is my second choice and I think it's very valid to use that as an exclusive second choice, which we have been doing in our office.

I think Atorvastatin is a very good drug if your initial HDL cholesterol is about 50. It's been proven well. If that's my choice and I can be given patients only with HDL of 50, I'm very happy. The Medicaid population in Washington doesn't generally meet that criteria. I would also say that as part of the general Steno approach, which is the Steno study, it has shown very effective results using this multifactorial intervention. That I would like to have access to all available anti-diabetic agents that can be safely used. For that reason I would like, if possible, for Pioglitazone to be available if I write it and say dispense as written. Thanks very much for listening to me, but I would urge you to read the Steno papers in last week's paper in the New England Journal.

Carol Cordy: Thank you. Dr. Roy Palmer.

Roy Palmer: Good morning. My name is Dr. Roy Palmer. I'm a medical director with Pfizer and I'd like to just say a few words about Atorvastatin or Lipitor. So two years ago when you reviewed the statin drug class you generated a clinical statement at the end of that meeting that stated that Atorvastatin had to be included on the preferred drug list. And in your discussions the rationale behind that was because of the large body of clinical outcomes data that supports the use of Atorvastatin. So I'd like to emphasize that since that time we have even more data that supports the use of Atorvastatin and no successful outcome studies have been presented with any of the other high potency statins. So I just wanted to review very quickly where we are with Lipitor, what we know about it. We've conducted over 400 clinical studies in over 80,000 patients. Now some of those are imaging studies, we have positive imaging studies with IVARS(?) and CIMT techniques. We have LDL studies. But where we put the majority of our effort and our weight is in large long term randomized outcome studies. We've done those in virtually every patient population that could be expected to commonly get a statin in clinical practice. Primary prevention, secondary prevention, patients with diabetes, patients with hypertension, and two very high risk patient populations acute coronary syndromes and patients who have had a stroke already in which the only data with any statin is with Atorvastatin.

So not only does that give us a good understanding of the efficacy of Atorvastatin, but also a great deal of information about the safety data. So in order to characterize safety you want to look at a drug preferably at the highest available dose and over long periods of time in a lot of different patients. We've done that, we've published that data. In fact at 80 mg alone we've published data from over 14,000 patients.

To summarize, in reviewing statins from an evidence based perspective, I really hope that you will consider the wealth of outcomes data that supports Atorvastatin and I'd like to respectfully ask if you would include Atorvastatin on the Washington State PDL once again. Thank you.

Carol Cordy: Thank you. Dr. Hurst.

James Hurst: Good morning. My name is Jamie Hurst. I'm the regional scientific manager with AstraZeneca. It was mentioned this morning Rosuvastatin or Crestor received an indication to slow the progression of atherosclerosis. And this indication is unique among the class of statins because it is not restricted to either a particular vascular bed or to the disease state. The indication was based primarily off of the Meteor trial, which is a double blind, randomized, placebo control trial investigating the effects of 40 mg of Rosuvastatin on the progression of carotid atherosclerosis. Based on the primary endpoint, Rosuvastatin slowed the progression of atherosclerosis relative to the placebo group. The tolerability of Rosuvastatin was very good over the course of the trial 40 mg gave a similar safety profile to that of placebo. There were no cases of rhabdomyolysis, hepatitis, or renal failure.

There have been up to 18 head to head studies that have demonstrated a greater LDL lowering and HDL raising efficacy of Rosuvastatin over Lipitor across the dose range. These studies have been conducted across multiple ethnic groups and have been conducted across a cardiovascular risk profile, specifically for diabetic patients there have been three studies that have demonstrated that the starting dose of Crestor, up to 94% of patients achieved the LDL goal of less than 100. As I mentioned earlier, the safety profile of Rosuvastatin has been demonstrated. Our post marketing data continues to reinforce the clinical data safety profile that we see. The OHSU report identified that there was no safety issue with Rosuvastatin. Rosuvastatin or Crestor is not extensively metabolized. It is not dependent upon the cytochrome P450 3A4 pathway to any clinically meaningful extent, which would reduce the probability there would be any drug/drug interactions. So just had some quick comments. Thank you for your time, I appreciate your attention.

Carol Cordy: Thank you very much. Dr. Fahmy. Not here. Dr. John Luber. Was there anybody I missed? Okay, well thank you all for your coming here and for

your presentations and we'll open it up for questions of Marian or comments. No questions? No comments?

Ken Wiscomb: Just one question. Ken Wiscomb, just one question. Did we not review this class in '07?

Carol Cordy: I think it was '06.

Ken Wiscomb: Is '06 the last time? I mean October of '06.

Man: October, yes, that's correct.

Carol Cordy: Marian thank you.

Marian McDonagh: Okay, sure.

Carol Cordy: For all your great presentations and I guess you can go.

Marian McDonagh: Alright, thank you.

Jason Iltz: This is Jason. I just want to make one comment to clarify a point that Dr. Palmer alluded to during his testimony and that was two years ago when this committee reviewed these medications. Atorvastatin was named under the motion because at the time the committee felt that we needed to have a high potency statin and the other agent, which was Rosuvastatin at that time, the committee was not comfortable including it because there were some safety concerns that had not yet been answered. And so the next time when it was reviewed, those safety concerns were evaluated again and so the statement was changed after the safety and evidence was there from that standpoint to then say a high potency statin needs to be included. So we don't, the committee does not consider Simvastatin a high potency statin. We really classified that as a medium potency statin. So just to clarify the reason why that wording was changed. It wasn't necessarily due to only the reasons that he had mentioned.

Vyn Reese: It is true though that Atorvastatin really has more...

[end side A]

Alvin Goo: Generic Simvastatin is not on the PDL, is that correct?

Siri Childs: Right now it's a non-preferred drug on the PDL. But when we do this evaluation it will have a chance to be selected.

Vyn Reese: I'm confused about this. This is Dr. Reese. The generics are automatically on the PDL if they're safe and efficacious.

Siri Childs: Not for Washington Medicaid. I believe they are for UMP. They're a tier one. But for Washington Medicaid when we go through the evaluation, the cost analysis we do indeed, unless you direct us otherwise, we do indeed take the lowest cost drugs. And at the time that we did it, Simvastatin had just changed. And so it was still about 80% of the brand name price.

Vyn Reese: But you're going to look at it again because it's obviously a very good drug, it's intermediate potency, it's now cheaper.

Duane Thurman: This is Duane. Just to add to that, the Uniform Medical Plan's benefits structure is more flexible in terms of the three tiered structure. So the generics are picked up immediately. When we do our cost analysis we're looking at a set place in time with the supplemental rebates on the Medicaid side and so it leads to results that don't seem to make sense at this level, but as we move forward we begin to take in to account the pricing of the new generics. And then you have the six-month exclusivity period also that affects our calculations.

Carol Cordy: Any more discussion? It sounds like the only question that's come up is whether Atorvastatin should be the only drug on the preferred drug list or the only preferred drug or whether we should just keep it as it was and say one or the other has to be on the...

Duane Thurman: This is Duane. I'll direct you to your previous motion where you simply said that it must include a high potency option, meaning that the results of our cost analysis would determine whether which or both of the high potency statins would be included.

Jason Iltz: This is Jason. I can certainly try to craft this motion again since this was my motion the last time. And I think that's our job.

Duane Thurman: Excuse me Jason, you need to accept the scan first.

Jason Iltz: Oh, well let's do that. I move to accept the scan as an adequate review of the HMG-CoA reductase inhibitors.

Patti Varley: Patti Varley.

Carol Cordy: All in favor.

Group: Aye.

Carol Cordy: Opposed. Okay. Go ahead Jason.

Jason Iltz: After considering the evidence of safety, efficacy, and special populations I move that the following statins are safe and efficacious Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, and Simvastatin and can be subject to therapeutic interchange in the Washington Preferred Drug List. The PDL must include at least one high potency option (Atorvastatin and/or Rosuvastatin) and the PDL must include Pravastatin as an alternative with minimal cytochrome P450 drug interactions.

Janet Kelly: Janet Kelly. I will second that.

Carol Cordy: Last chance. All in favor?

Group: Aye.

Carol Cordy: Opposed. The motion is passed. And unless there are other announcements we break for lunch.

Jeff Graham: And I guess we can say 1:10 we'll be back.

Carol Cordy: Okay, we'll resume the meeting at 1:10.

[tape cuts]

Carol Cordy: I think we have someone who's very interested, but we need to go through the formal process of having a nomination. Does somebody want to nominate a chair?

Bob Bray: This is Bob Bray. I nominate Vyn Reese.

Carol Cordy: Any other?

Man: I'll second that.

Carol Cordy: Okay. All in favor?

Group: Aye.

Carol Cordy: Opposed. So I'm going to turn this microphone over to our new chairperson. No you can have your own microphone.

Vyn Reese: This is Dr. Reese. Is Susan Carson ready to review estrogens?

Man: She should be any, within the next minute calling in.

[tape cuts]

Susan Carson:

On slide eight it shows no new topical products for urogenital symptoms were added this update, and those are the ones that are currently included.

Next slide, slide nine. We searched multiple electronic databases through March 2007 for this update and we used our original search strategies. We received dossiers from one pharmaceutical company for three products this update, but we identified no additional studies that we didn't already have through the dossiers. So 313 new citations were identified, and of those 44 studies were included. There were six new head to head trials with symptom or quality of life outcomes, 36 placebo controlled trials, and two recent systematic reviews.

Next slide. There was a new FDA black box warning added to the label of all estrogen products in February, 2004 and this warning was based on the Women's Health Initiative memory study. The Women's Health Initiative memory study reported an increased risk of probable dementia in women 65 and older and showed that estrogen with progestin failed to prevent mild cognitive impairment.

So we'll move on to the results of the first key question, which addressed comparative effectiveness for symptoms. There were six new head to head studies that addressed symptoms. Four of these were fair quality and two were poor quality. Their results don't change our current conclusions, which are that head to head comparisons do not identify one agent as more effective than another for relief of menopausal symptoms. So in the fair quality studies there were no differences between the products compared.

Next slide. Results of six new fair quality placebo controlled trials were consistent with our previous findings, which they confirmed the efficacy of estrogens versus placebo for reducing the frequency or severity of hot flashes. An exception was in one study of ultra low dose transdermal Estradiol patch. This is the Ultra study and it was 14 µg per day. There was no difference from placebo two years in older women who were asymptomatic at baseline. From these placebo controlled trials we weren't able to add any new information to our existing meta-analysis, which is in the current report. The meta-analysis showed no differences among the estrogens for hot flashes. They were all effective versus placebo, but no differences among them. Because of how the outcomes were reported in these new placebo trials we couldn't add them. So the results of that meta-analysis don't change and it was consistent with the previous Cochran meta-analysis.

Next slide. We're on slide 13 now. Evidence for comparative effectiveness for other symptoms aside from hot flashes is very limited. For this update one new study found no difference in sleep disturbances and night sweats combined with CEE. In one study of transdermal

Estradiol there was no difference from placebo on depression measure. In one study of low dose transdermal estrogen there was no difference from placebo on vaginal dryness and urinary incontinence, although in one study of oral Estradiol acetate there was decreased vaginal dryness. So in summary there is few fair or good quality data on symptoms other than hot flashes. Studies show few positive effects versus placebo and there is very little head to head data. The results are mixed in the placebo-controlled trials for these other outcomes.

Next slide. Three new placebo controlled trials measured quality of life outcomes for this update, and none of the three found a significant effect for the treatment group compared to placebo. One was the low dose transdermal Estradiol caps in the Ultra study that I mentioned earlier. Another was for conjugated equine estrogen, there was no difference from placebo on quality of life or general health. And a study of oral Estradiol found no difference from placebo on the SF 36 measure of quality of life. So in conclusion there is little data and no significant effects on health related quality of life from these studies.

Next slide, slide 15. For the outcome of improving symptoms of vaginal atrophy, we identified a Cochran systematic review that was recent and it compared intravaginal products for symptoms of vaginal atrophy. The reviews concluded that the preparations were similar in efficacy, but they had some differences in side effects. The reviewers found that CEE vaginal cream caused more side effects than Estradiol tablets, vaginal tablets, or the Estradiol ring, but there is no difference between CEE vaginal cream and E2 ring in withdrawals due to adverse events. Symptom improvement was similar for tablet versus cream, but there were fewer withdrawals due to adverse events with the tablets versus cream. So similar efficacy, but some differences in side effects.

Next slide. So this is just a summary of the evidence for the three new drugs that we added this update. The evidence for symptom relief. So oral Estradiol acetate was similar in efficacy to Estradiol and CEE for hot flashes. Oral Estradiol plus Drospirenone, that's the Angeliq product improved hot flashes versus placebo, but this product doesn't have any head to head evidence. And then finally the Estradiol transdermal gel improved total symptoms for depression compared with placebo, but there is no head to head evidence for this product either.

Next slide. So now moving on to key question two, addressing prevention of low bone density and fractures. And for this key question there was no new direct evidence, no new head to head trials. New placebo-controlled trials were consistent with previous evidence, which showed increased bone density or slowed bone loss compared to placebo. In the women's health study of conjugated equine estrogen alone in women who were post

hysterectomy found decreased risk of fracture at follow up of almost seven years, but we identified no other new studies with fracture outcomes this update. Of course the Women's Health Initiative is a placebo-controlled trial.

Next slide, moving on to key question three, which addresses short-term harm, which we defined as less than five years of use. There were six new head to head trials that were designed to measure efficacy that also reported adverse events and these showed few differences in the rates of specific adverse events or in withdrawals due to adverse events. There were a couple of exceptions. More breast tenderness in withdrawals with oral Estradiol versus oral conjugated estrogen, but in the study different progestins were also used in combination with the estrogen. And the other exception was more withdrawals in the first three months with the Estradiol vaginal ring compared with the vaginal tablet when used for urogenital symptoms.

Next slide. We're on slide 19. So consistent with previous evidence placebo controlled trials of estrogen progesterone combinations found increased vaginal spotting and breast tenderness, but these studies don't add comparative evidence to our body of evidence. There was no increased incidence of venous thrombosis found in one study of oral Estradiol and no study reported endometrial hyperplasia, but few studies addressed this outcome.

Next slide. We identified four short-term studies that reported measures of cognitive function. These included the low dose Estradiol patch in the Ultra study, Estradiol patch at a different dose, CEE plus progesterone, oral Estradiol. It is...are you still there? I just heard a beep.

Vyn Reese: We're still here.

Susan Carson: Okay. I thought maybe I got disconnected. Okay, so none of these studies found differences from placebo in cognitive function either improved cognitive function or worsening of cognitive function in these short-term studies.

So moving on to key question four, there's an arrow on the slide. That's key question four about long term harms. The Women's Health Initiative provides the best evidence to address this key question, but since it was a placebo trial of CEE it doesn't provide any comparative evidence. And then the slide describes some characteristics of the two arms of the trial.

Next slide, slide 22. This slide shows an overall summary of the harms found in the Women's Health Initiative for both the estrogen plus progesterone and the estrogen only arm. In the estrogen plus progesterone

arm, there was an increase in cardiovascular disease events in stroke, in invasive breast cancer, venous thromboembolism, and probable dementia, but there was no increase in cardiovascular disease mortality or in mild cognitive impairment at four years. And in the estrogen only arm, which had almost seven years of follow up, there was an increase in stroke and venous thromboembolism, but no increase in cardiovascular disease events or mortality. No increase in invasive breast cancer, mild cognitive impairment, or in probable dementia.

Next slide. This just shows a summary of the benefits from the Women's Health Initiative to help you to weigh the benefits and harms from the study. Vasomotor symptoms and bone outcomes were improved in these studies, but health related quality of life was not significantly different from placebo.

The next slide. This addresses the last key question. Key question five, which looked at comparative efficacy and safety in subgroups. We found little new evidence this update for this key question with no new evidence at all based on race or comorbidities. In the Women's Health Initiative the effect of CEE on symptoms in younger women age 50-54 were similar to the benefits found in older women and in the Women's Health Initiative memory study the increase in probable dementia was related to older age and lower mental status exam at baseline.

And then the last slide, slide 25. In conclusion, new evidence does not change our previous conclusions for short-term benefits and harms. New evidence from the Women's Health Initiative does not provide comparative evidence, and evidence shows the new drugs added this update are effective for reducing menopausal symptoms, but there is no evidence that one is superior to another estrogen preparation. Thanks, I'll take any questions if you have them.

Vyn Reese: Thank you. Are there any questions from the committee?

Carol Cordy: I have a question. This is Carol Cordy. Of the vaginal preparations for atrophy, are there any long-term outcome studies on the use of those?

Susan Carson: No, we didn't identify any longer term studies.

Jeff Graham: I want to ask a question. This is Jeff Graham. So did you do numbers needed to treat the NNTs on some of those studies?

Susan Carson: For the hot flashes?

Jeff Graham: On the poor outcomes.

Susan Carson: I'm sorry, I'm not understanding.

Jeff Graham: Number needed to harm or number needed to treat on any of the outcomes?

Susan Carson: No, we did not calculate that.

Vyn Reese: If there are no further questions we'll take stakeholder input. Does anyone wish to speak? So we'll move on now to the motion.

Jeff Graham: Excuse me, Susan.

Susan Carson: Mmhmm.

Jeff Graham: Could you warn Kim that I may be calling her soon, that we might be a little bit ahead of schedule.

Susan Carson: Okay, I'll let her know. You'll call her?

Jeff Graham: I'll call her.

Susan Carson: Okay. And am I through here?

Jeff Graham: Yes, you are.

Susan Carson: Okay. Thank you very much.

Vyn Reese: Jason do you want to make a motion? It was your motion last time.

Jason Iltz: So as I'm, this is Jason. So as I'm going through this, and looking at the previous motion, I believe we have to add the 17 beta Estradiol combination products. Is that the only ones that I'm seeing that are different? Or did we assume that...

Vyn Reese: Actually [inaudible] all four.

Jason Iltz: Right, the last one was '04. So I'm not seeing some of those combination ones, I'm just seeing that we alluded to 17beta Estradiol. Estradiol acetate. So Estradiol acetate as well. And then those are both oral. So that would be an oral. Alright, so we might need a friendly amendment if I miss one here. So after considering the evidence of safety, efficacy, and special populations, I move that Estradiol valorate (oral), Estradiol acetate (oral), esterified estrogen (oral), estropipate (oral), synthetic conjugated estrogen (oral), conjugated equine estrogen (oral and vaginal cream), 17beta Estradiol (oral, transdermal, vaginal cream, and intravaginal ring),

17beta Estradiol plus norgestimate (oral), 17beta Estradiol plus norethindrone acetate (oral), 17beta Estradiol plus drospirenone (oral) are efficacious and have no differences in efficacy identified in special populations for the indication of menopausal symptoms and can be subject to therapeutic interchange in the Washington Preferred Drug List. There is insufficient evidence available to compare the relative safety of the estrogen products at this time. The committee recommends that practitioners prescribe the lowest effective dose of the particular estrogen product prescribed. Now, we may want to add the lowest effective dose for the least possible duration in there as well. So the lowest effective dose for the least possible duration of the particular estrogen product prescribed. And I don't know if we want to note specifically that short-term use is considered less than five years or do we leave that up to, I think we can leave that up to...

Vyn Reese: I don't think we have to specify that.

Jeff Graham: Vyn this is Jeff Graham. I don't think we ever included the combination conjugated equine and medroxyprogesterone in our previous motions. I'm reading through, I can't find them.

Carol Cordy: This is Carol Cordy. On the previous one it's just the estrogen. We didn't include the progesterones in any of them.

Jeff Graham: No, so I think that we might want to do that, because they're included in this study. Specifically named. The estrogen progesterone combinations.

Jason Iltz: Okay, so that's two more, right? So that would be the conjugated equine estrogen plus medroxyprogesterone oral? And then the other one at the bottom of that list which was the ethanol Estradiol plus norethindrone acetate? Is that included in? And that would be oral as well.

Vyn Reese: Is Estradiol hemihydrate the vaginal tablets, is that in the, I don't see that in the list either. The Vagifem tablet. The vaginal tablets, not the oral tablets.

Jeff Graham: Or if you'd like to, you could instruct us to just put in the motion all of these so we know that they're all included.

Patti Varley: This is Pattie Varley and that, I mean when I'm looking here at the tables as far as the lists of drug reviewed. You could do it by each table, by saying oral estrogens and then list what's in that list and then the second would be the estrogen progesterone combinations and list the drugs that were reviewed in that list and then transdermal estrogens and list those and then the topical products. Then you know you're inclusive and you're doing it by categories of how they were reviewed.

Jason Iltz: That makes good sense Patti. I didn't see those little titles up there. So I would accept that as an amendment, absolutely.

Carol Cordy: This is Carol Cordy. I think the other thing is that it says in here they can be subject to therapeutic interchange, which you would assume that's only within those three categories, but somebody might question whether you're giving a vaginal product for hot flashes.

Patti Varley: Well and, this is Patti Varley again. We were talking do you really want to substitute an oral for a vaginal or a transdermal for an oral.

Carol Cordy: No.

Man: Could we inject by category?

Carol Cordy: Yea.

Man: So subject to therapeutic interchange by category.

Bob Bray: This is Bob Bray. Siri do we need to state that? Or is that going to be clear enough with substitution? The laws regarding therapeutic substitution that it will only be within the same route?

Siri Childs: I would ask you to state it, because it's going to help me when we program it also.

Janet Kelly: This is Janet Kelly. I think we could just word that by saying that these are subject to therapeutic interchange within the route of in class of route of administration. That would probably...

Patti Varley: So here's, Patti Varley again with just a clarification question. When you look at the estrogen progesterone combination table versus an estrogen alone table, those are both oral. So are we saying those could be interchanged? I'm just asking for clarification: are you saying within, not just administration but combination? I'd like to know what people thought of that, because we do have two orals that are not the same.

Carol Cordy: And I would say yes because you don't want to give somebody estrogen alone if they have a uterus.

Vyn Reese: It should be within route of administration and class. Because some are combination products and some are individual estrogen products and some are topical. So it should be route of administration and class or subclass. It could be subclass.

Man: I don't have a mic, but we may still need to add that part in the last sentence where it says...

Jason Iltz: And then just for clarification we could now in parentheses list the four subclasses, if that would help. Would that help?

Patti Varley: So you would say oral estrogens, estrogen progesterone combinations, transdermal estrogens, or topical products, right?

Carol Cordy: Well it looks like there's also transdermal combinations. So there's five. Maybe we need five different motions.

Vyn Reese: It should be transdermal estrogen progesterone too. We have transdermal estrogen it should be then, transdermal estrogen-progesterone.
...most effective dose for the shortest amount of time.

Jason Iltz: This is Jason again. Do we want to...I think I heard that we wanted to delete all the specific medication names in favor of those five classes that you put down below as...listed them as sub classes. Is that right?

Carol Cordy: I think that simplifies it.

Jason Iltz: I think it will clarify it for the next time too.

Patti Varley: This is Patti Varley and my understanding and I could do it either way was to have it listed out as what is referred to in each table. Being that there are new ones as well as the old ones and therefore being clear about which ones within each group we actually reviewed.

Jason Iltz: And that's fine. We still need to add a few names then.

Patti Varley: Right. But I also thought it would be helpful if we categorized it like they are categorized in the tables.

Jason Iltz: Right.

Jaymie Mai: This is Jaymie. So did you want to remove all the highlighted down to the table?

Carol Cordy: If we can trust that somebody can just take these tables and put them in there I think we're okay.

Jason Iltz: And then not to be too picky but we probably want to delete the ones that are not available in the United States. There is one or two potentially that are in Canada only.

Patti Varley: This is Patti Varley. My thought was that we were listing them by drug, not by product. What I see here is that there are...all the drugs available in the U.S. and just different products within the drugs that are available in Canada. Am I wrong?

Jason Iltz: I was looking at the conjugated versus esterified estrogen cream. I only see the esterified one in Canada. I didn't see that one available in the United States.

Patti Varley: You are correct.

Jason Iltz: Can you say that one again?

Patti Varley: It will be in writing.

Jason Iltz: I'm just teasing.

Carol Cordy: I just want to make a comment. This is Carol Cordy. We say for the indication of menopausal symptoms, which is pretty broad and vague. It looks like these studies really are more specific to hot flashes that other menopausal symptoms aren't really effectively treated except for the vaginal...

Vyn Reese: [inaudible] of topical products that are included.

Carol Cordy: But menopausal symptoms is pretty broad.

Patti Varley: This is Patti. When I was listening or reading it I mean you're right that is the one that had the major evidence, but they talked about dementia, depression, vaginal dryness, urinary incontinence...

Carol Cordy: Many of these medications are not efficacious.

Patti Varley: I agree, but I feel okay with leaving it as menopausal...because that's what they reviewed.

Vyn Reese: Are we ready to move on and get a second for this lengthy motion?

Duane Thurman: This is Duane. Can I just clarify something? Do you guys want to take out the listing of all the drugs and say that I move that the drugs included in the following tables and then we'll clean it up and just list it as the drugs?

Vyn Reese: That looks nice and tidy.

Patti Varley: This is Patti Varley. I'll second.

Vyn Reese: All those in favor?

Group: Aye.

Vyn Reese: Opposed? Approved. Let's move on to the NSAID scan.

Kim Peterson: Hi, this is Kim Peterson with the Oregon Evidence Based Practice Center.

Vyn Reese: Hi, this is Dr. Reese, chair of the committee. Can you speak up a little bit?

Kim Peterson: How about now?

Vyn Reese: Great.

Kim Peterson: Okay.

Vyn Reese: We have the first slide up.

Kim Peterson: Okay. Great. Well, let's go on to slide number 2. So I'm going to be providing a summary of the findings of our preliminary update scan of the drug class review on NSAIDs. The current status of the DERP drug class review on NSAIDs is that the last time it was fully updated was back in November of 2006. So in consideration of whether the NSAIDs drug class was in need of another full update in October 2007 the Oregon EPC went ahead and performed a preliminary search of MEDLINE to get a preview of the volume and nature of any new potentially relevant controlled clinical trials that had been published since 2006. Next slide.

So on the next two slides, 3 and 4, what we have is the list of NSAIDs that we searched for new evidence on, which came directly from the previous key questions and inclusion criteria from the last update and represent all previously included drugs. So just to clarify the key questions and inclusion criteria have not changed since the last update. Why don't we go ahead and skip on to slide number 5. I don't think it would be beneficial to you if I read all the drugs to you.

So slide number 5 – this slide shows our search strategy that we used for this preliminary scan and as I mentioned we searched MEDLINE for any new potentially relevant controlled clinical trials that had emerged since our last update. Then we also searched the FDA and Health Canada websites to see if there were any new drugs, indications or new safety alerts since our last update. So what you have on that slide are the links to the websites – the FDA and Health Canada websites that we used. Next slide.

Results – so from our MEDLINE search we identified 38 new citations regarding NSAIDs, but of those there were actually only two that appeared to meet inclusion criteria based on the abstracts and titles. You can see them in Appendix A of the report, but just briefly one was a six-week crossover study of Diclofenac plus Misoprostol versus Acetaminophen and was looking at patient preference outcomes. And then the other was a long-term, one-year placebo-controlled trial of celecoxib, but we were mostly interested in for the possibility that it might have looked at rates of serious adverse cardiovascular events, but we couldn't tell that from the abstract. And then from our searches of the FDA and Health Canada websites we didn't find any indication that there were any new NSAIDs but we did see that celecoxib got a new indication for treatment of juvenile rheumatoid arthritis in December of 2006. Next slide.

So then finally also from our searches of the FDA and Health Canada websites we did not, this time, find any information about any new safety alerts that had come up since our last update. So overall since the evidence of the potential cardiovascular risks associated with the COX-2 came out there seems to have been a drop off in terms of the volume of new research being generated in this class and so the DERP governance group elected not to pursue a full update for now but we're scheduled to do another literature scan again in the upcoming November and the group will be reconsidering a full update again at that time.

Now I'll turn it back over to you and you can ask any questions you might have about the results of the scan or the methods.

Vyn Reese: Are there any questions from the committee?

Kim Peterson: It's pretty straightforward.

Vyn Reese: Okay. We'll move on to the...can you just stay on the line while the stakeholders present?

Kim Peterson: Sure.

Vyn Reese: The first one is Dr. Andrew Solomon. Remember you have three minutes.

Andrew Solomon: Hi. Good afternoon. My name is Andrew Solomon and I'm a clinical rheumatologist at the Seattle Arthritis Clinic in Seattle, Washington. I've been in clinical practice for almost 20 years now and have extensive experience using anti-inflammatories in a variety of diseases. The introduction of COX-2 selective anti-inflammatories was held as a remarkable achievement in as much as it was believed that we would be able to improve disease outcomes while at the same time reducing

complications related to anti-inflammatories. We're all aware of the VIOXX debacle, which resulted in pulling VIOXX off the market for increased cardiovascular risk, which seems to have sort of expanded to the entire class of inflammatories and Celebrex remains the only medication in the COX-2 selective class that is currently approved for a variety of uses in the United States. Now clearly we as rheumatologists believe that no anti-inflammatory is superior to one or another in terms of efficacy when viewed in large populations. However, clearly there are individual variations in clinical response and as such there are some patients who seem to respond to Celebrex better than other available anti-inflammatories. That notwithstanding there are a number of patients in whom the COX-2 selectivity provides special advances particularly in patients who are low dose aspirin which clearly increases the risk of GI events in and of itself. 81 mg of aspirin doubles the relative risk rate of ulcers. 325 mg of aspirin daily increases the risk of ulcer four-fold. There does not seem to be a concomitant increase in ulcer rates when patients combine aspirin with Celebrex and this in and of itself it not prohibited in the package insert.

Additionally, there are other groups of patients in whom Celebrex is a vital addition to the armamentarium. For example, patients who are a systemic anticoagulant we would be loathed to place them on a medicine that would interfere with platelets and increase GI risk. Patients with inflammatory bowel disease also seem to have less rates of recurrence or flairs of their disease when placed on a COX-2 selective anti-inflammatory as compared to a non-selected agent. As such I think that there is enough clinical data that would support the use of Celebrex in a formulary and restricting its access I think would compromise patient care. Thank you.

Vyn Reese: Thank you. The next speaker is Mark Galloway.

Mark Galloway: My name is Mark Galloway and I work at Northwest Orthopedic Surgeons in Mount Vernon, Washington. I've been in orthopedics as a PA for approximately 17 years and I've been asked to share my thoughts and experiences with Celebrex both in surgical and non-surgical patients.

Surgically, our ACS surgical center, all of our patients are treated with celecoxib pre- and post-surgery. We've experienced a significant decrease in postoperative pain and especially with opioid prescriptions that are written. They are significantly decreased and the GI effects including nausea and vomiting have significantly decreased. The use of celecoxib with a non-surgical patient who either can't tolerate aspirin or Tylenol I certainly think that celecoxib is efficacious. I think it warrants to have open access and because it's an orphan drug it's one of the few drugs, it's the only drug that I feel is safe to issue to my patients. I guess the take

away from this is its efficacy and safety profile. It was good to see that no new safety alerts have been reported. Thank you.

Vyn Reese: Thank you. And the last speaker is Dr. Tammy Dsouza.

Tammy Dsouza: Thank you. Once again I'm Tammy Dsouza, family practice physician at Sound Family Medicine in Puyallup and it comprises of a single specialty, multi physician group of 15 physicians, nurse practitioners and PAs. I'm here to request the pharmacy and therapeutic committee to add celecoxib to your preferred drug list at the Washington State Medical Plan. I'm aware Celebrex is currently available as an expedited prior authorized NSAID. This classification imposes undue burdens, redundancy in obtaining prior authorization, makes it cumbersome and time consuming. By redundancy I mean it's like going to the store and before paying I'm asked by the clerk if I'm sure this is the pair of shoes I want. If you find this silly the seriousness of prior authorization protocol is no laughing matter.

After careful consideration of the drug I want to pick for my patient I'm then asked, "Am I sure this is the drug I want?" Prior to my joining Sound Family Medicine I was the Medical Director of Tacoma South Medical Clinical in the Franciscan Health System. My patient demographics consisted of poor, indigene and under insured patients. These patients presented with numerous comorbidities, cardiovascular diseases requiring long-term aspirin use. Celebrex is an anti-inflammatory that is safe to use with aspirin.

A recent California Medicaid study referenced in the Family Practice News [inaudible] on December 1st reported a high rate of GI issues. In the same issue the guest editorial recommends open and unrestricted access to COX-2 inhibitors. By requiring me to try two traditional NSAIDs I expose my patients to unnecessary risk of GI bleeds, trips to ERs and gastroenterologists, which adds to the medical cost. To compound this problem we have a shortage of available GI appointments for DSHS patients. Prior authorizations often encroach on patient care decisions in both efficiency and time. Using recommended and package insert doses COX-2 inhibitors are relatively safe and are an excellent choice in treating patients in pain.

In my opinion, access to COX-2 inhibitors like Celebrex will benefit patients for long-term use and contain health care costs overall. Being poor should not be a hindrance to obtain the highest quality medical care.

In closing, I would urge you to consider my request to add Celebrex to the preferred drug list. I appreciate the opportunity to speak on behalf of the poorer of the state. Thank you.

Vyn Reese: Thank you. Now we'll open the committee's discussion on the NSAIDs.

Jeff Graham: Can Kim leave now?

Vyn Reese: Sure.

Kim Peterson: Thank you. Bye, bye.

Vyn Reese: Thank you. There's no discussion?

Ken Wiscomb: Ken Wiscomb. Siri, what's the prior auth for Celebrex now? Is it two NSAIDs?

Siri Childs: Yes. The same criteria...well, for any of the brand NSAIDs or the COX-2 NSAIDs we ask that they have tried and failed at least two of the preferred drugs on the PDL. And then all of the NSAIDs have the same criteria and that is must not have a history of a GI bleed. All of them including the regular ones and the COX-2 inhibitors.

Carol Cordy: Carol Cordy here, but it is available "dispense as written".

Siri Childs: Yea.

Vyn Reese: And I'm remind prescribing doctors that often, you know, you always should prescribe a PPI with non-selective NSAIDs. If the patient's going to be on it for any length of time it is sound medicine for your elderly patients, if you prescribe them at all. The NSAID risk with celecoxib is not...it's maybe less GI risk, but there is serious cardiovascular side effects, hypertension, renal disease and other things that are associated with that drug. It's not an entirely safe drug and these drugs should be avoided in the elderly.

Duane Thurman: This is Duane. Just a point of information. We need to accept the scan.

Vyn Reese: I'll take a motion to accept the scan.

Ken Wiscomb: I move that we accept the scan as an update. Scan of the NSAIDs as an adequate update for that class.

Vyn Reese: Can I get a second?

Man: I'll second it.

Vyn Reese: All those in favor?

Group: Aye.

Vyn Reese: Opposed? Approved.

Bob Bray: This is Bob Bray. I would offer that we should, again, make the same motion that I made earlier in 2006 regarding this class without change.

Vyn Reese: Do we have a second?

Carol Cordy: I just have a question. Is celecoxib not on this list?

Vyn Reese: It's in the bottom...celecoxib is efficacious and should remain non preferred and no subject to therapeutic interchange. It's part of the motion. Any other discussion?

Jason Iltz: This is Jason. I'll second.

Vyn Reese: All those in favor?

Group: Aye.

Vyn Reese: Opposed? It's approved.

Patricia Thieda: This is Patricia Thieda.

Vyn Reese: Hi Patricia. This is Dr. Reese, chair of the committee. Your first slide is up.

Patricia Thieda: Okay. I'm not sure what slide you're referring to so I'm going to go with the document I have. Basically, I'm reporting on the targeted immune modulators. The date of the last update that we did for this project was January 2007. Our searches were through August of 2006. The scope and key questions that we're covering are similar to the last update and they are currently up for public comment on the website for DERP. Our inclusion criteria stays the same. Primarily adult populations with the exception of juvenile rheumatoid arthritis in pediatric patients. Of course ankylosing spondylitis, rheumatoid arthritis, Crohn's disease, ulcerative colitis and plaque psoriasis as last time. We're currently looking at eight different treatments in four different classes. Similar effectiveness outcomes as covered previously and safety outcomes of course. Now when we did the scan that we submitted for your perusal it had 17 brand new randomized controlled trials. This is limited only to randomized controlled trials for the scan. So when we did the MEDLINE search we received 668 citations all together. I believe Dan sent you a slide that shows the impact of those different new RCTs in the different conditions. The ankylosing spondylitis is looking at a new indication for adalimumab.

Similarly for psoriatic arthritis and efalizumab, as well as adalimumab in psoriasis. So those are brand new studies that we haven't even had comparisons in.

There is a new drug under consideration, which is the certolizumab. As of now that's not been approved for use. So we'll see if it becomes approved within the next couple of months and then deal with it then. But we did take a quick look. We got 68 citations, 5 different randomized controlled trials. Most of these were in Crohn's and a small one in rheumatoid arthritis. Adalimumab, as I said earlier, was approved for moderate to severe chronic black psoriasis. As far as the safety alerts, their impact is basically on off label use, which is not something we cover, but it's still important to note that there have been alerts put out concerning progressive, multi-focal PML following Rituxan or Rituximab in the treatment of systematic lupus. And that's basically what's in the scan. As far as the actual update we'll include a lot more than just those 17 RCTs that will include observational studies, also follow up studies from earlier RCTs. And that's what I have to report. I hope that follows the slides you have to some degree.

- Vyn Reese: Thank you. Any questions.
- Jason Iltz: This is Jason. I have one. What was the medication you mentioned that had PML as a potential side effect?
- Patricia Thieda: Rituximab.
- Man: It's the one up on the slide.
- Jason Iltz: Got it. Thanks.
- Vyn Reese: Any additional questions? Any stakeholder input?
- Jeff Graham: Yes, we have some.
- Vyn Reese: The first speaker is Dr. Bernard Goffe.
- Bernard Goffe: Thank you for the opportunity of letting me speak today. I have been in clinical practice in dermatology for about 30 years doing mostly dealing with psoriasis and clinical research in psoriasis and I'm here to ask the committee to consider on the preferred drug list for Humira as well as Enbrel. Humira or adalimumab was mentioned in the discussion of the new drugs. It was just approved for psoriasis four weeks ago. Although it's been around for [end of Side A]

...involved in Phase II, Phase III, and Phase IV studies with this drug as well as with most of the other biologics that are in use for psoriasis and it's been used in over 2,500 patients in studies of psoriasis. Adalimumab has been used in 250,000 patients for all of its indications – rheumatoid arthritis first, ankylosing spondylitis, psoriatic arthritis, but as I mentioned it just got approved for plaque psoriasis four weeks ago even though we've been using it now for about five years. This group of drugs, as you know, is much, much safer than the predecessors, cyclosporine, methotrexate and drugs like that—very efficacious and safe therefore as I mentioned earlier I'm asking the committee to provide parity access on the preferred drug list for Enbrel and Humira to make both easily available for patients with moderate and severe psoriasis. Particularly we have Enbrel because of its pediatric use and it's about to get a pediatric indication for psoriasis. Right now it's pediatric indication is for rheumatoid arthritis, but we've been using it for several years in children as young as four. It has a long history of efficacy and safety as well as familiarity and Humira, although it's more recently on the scene, it has the advantage of efficacy in GI diseases as well as psoriasis, every other week administration and in my experience it often works in patients that fail Enbrel. Thank you.

Vyn Reese:

Thank you. Next speaker is Ms. Alison Pruim.

Alison Pruim:

Hi. I'm Alison Pruim. I'm a physician assistant at Cascade Eye and Skin Center. I've specialized in dermatology for nine years. We're really excited about the biologics availability and what they're able to do for patients with plaque psoriasis. I see Medicaid patients basically daily and I'm an endorsing prescribing for DSHS. I think Humira is an excellent drug in terms of safety. I won't repeat a lot of what Dr. Goffe said, but some of the old medications that we had the orals are just really liver toxic and these have shown to be incredibly safe. The nice thing about Humira as opposed to Enbrel, which is also an excellent medication and has had really good results Humira has half the amount of sub-q injections necessary for the patient rather than twice weekly it's only once every two weeks, which is a huge benefit to them. I think there's a place for all the biologics in all of our dermatology practices. The three TNF blockers that are available right now two of them are sub-q and one of them is IV. The IV obviously has a lot more side effects and it's just a lot less convenient for the patients' to inject and have injected because they have to go in and have it done in the office whereas the Humira and Enbrel they can inject at home. So I would just hope that you would consider giving it equal access to Enbrel because I have seen quite a few patients do excellent with Enbrel, but there are failures and those patients that I've seen that have failed on it have actually done incredibly well on Humira far better than I actually expected from our history. So please take it into consideration. Thanks!

Vyn Reese: Thank you. Next is Dr. Richard Jimenez.

Richard Jimenez: Thank you for the opportunity. I'm here representing both myself as a practicing rheumatologist for 25 years in Washington, but also the Washington Rheumatology Alliance, which is an organization of about 40 out of the 70 practicing rheumatologists in this state and the purpose of the organization is for information and dissemination and for helping patients get access to our therapies. I'm here to also request that Humira be given the same equal access as Remicade and Enbrel from the standpoint that, yes, these are all anti TNF agents and once the physician makes the medical decision that a biologic is needed and then the decision medically it should be an anti TNF drug as opposed to one of the other biologics then medically and socially we have to pick the best drug for the patient. The drugs are not the same in their effectiveness for different manifestations of even rheumatoid arthritis. Example, Enbrel does not treat the eye disease of rheumatoid arthritis whereas Humira and Remicade does. In patients with ankylosing spondylitis a lot of those patients we feel have occult inflammatory bowel disease and even though we may be treating their spondylitis we also want to cover them for potential other manifestations of illness and either Humira or Remicade might do that better. So we have medical decisions as well as the social decisions of if the patient with rheumatoid arthritis needs to have a daughter come over and give them their injection and they live in South Seattle and the daughter lives in North Seattle that if that's every two weeks instead of once a week that's the reason to pick one drug over another. All anti TNF agents are not the same. The decision medically and socially to use one over the other, you know, has many different aspects to that decision and it should be a medical decision particularly when the cost is relatively the same for all of the biologics and we're not inducing any significant difference in one therapy versus the other. Thank you.

Vyn Reese: Thank you. Next speaker is Dr. Annie Ogostolick.

Annie Ogostolick: Hi there. My name is Dr. Annie Ogostolick. Thanks for the opportunity to speak with you today about Humira. I am a national clinical executive in the clinical evidence and outcomes group at Abbott. In the next few minutes I'd like to highlight for you three of the key attributes of Humira. (1) Efficacy across a broad scope of indications, (2) Consistent safety across this broad scope of indications, and (3) Comparatively efficient maintenance dosing across indications. First, I want to talk about efficacy. Humira is the first fully human monoclonal antibody targeted against TNF currently indicated in rheumatoid arthritis, psoriasis, Crohn's disease, psoriatic arthritis and ankylosing spondylitis. This broad scope of indications encompasses rheumatology, gastroenterology and dermatology. The company has filed, in the second quarter of last year, with the Food and Drug Administration as a treatment for juvenile

rheumatoid arthritis. Within this broad scope of indications key outcomes are as follows: in rheumatoid arthritis demonstrated inhibition in randomized control clinical trials of radiographic progression of disease with administration of Humira with methotrexate, which was sustained out to five years in an open label extension study. Sustained efficacy in reducing ACR scores by 50% over up to seven years in approximately two-thirds of patients with rheumatoid arthritis from open label extensions of multiple randomized controlled clinical trials.

In Crohn's disease, in placebo-controlled trials of patients with moderate to severely active disease about a third of patients were in remission after Humira induction therapy within four weeks and they maintained that clinical remission out to 56 weeks. About 30% were able to discontinue steroid treatment, and about 30% had complete fistula closure. Humira administration resulted in fewer Crohn's disease, hospitalizations and all caused hospitalizations compared with placebo. In a four-week randomized control clinical trial with patients who had become intolerant or had lost response to Remicade about one in five patients achieved clinical remission of their Crohn's disease versus placebo.

In plaque psoriasis following 16 weeks of treatment with Humira about 70% of patients in a 52-week double-blind placebo-controlled trial had 75% reductions in their disease scores, 45% of patients had a 90% reduction in their disease scores and fully one in five patients had a total clearing of their psoriasis. That's 100% reduction in their disease scores. This efficacy is unique among the self-injected TNF inhibitors.

Next let's talk about safety. With this broad scope of indications there has been an immense amount of safety data collected in diverse patient populations. Rates of serious infections, tuberculosis and lymphoma rates were all within the range of other documented anti TNF inhibitors and biologic naïve RA patient incident data. A recent analysis [inaudible] presented of Humira reconfirmed the safety of the product in global clinical trials across all indications. This data is as of April 2006 representing over 20,000 patient years of exposure. No new safety signals have emerged over time.

Finally, let's talk about the dosing of Humira. The recommended maintenance dose of Humira for adult patients with rheumatoid arthritis, psoriasis, psoriatic arthritis and ankylosing spondylitis, Crohn's disease and psoriasis is 40 mg administered once every other week as a subcutaneous injection. There is a four-week induction period for patients with Crohn's disease and there is an initial one-time 80 mg dose in patients treated for psoriasis. It's important to note that this brief one time initial loading dose in contrast to other self-injected TNF inhibitors where several months of up dosing is required in the treatment of psoriasis.

So, in conclusion, Humira is a unique agent among the self-injected TNF inhibitors. We talked about the broad scope of indications with proven efficacy, the in depth safety data across multiple indications with no new safety signals and efficient maintenance dosing across all indications. Thank you for allowing me to share this information with you. We would ask that you take this data into consideration to allow parity access on the PDL for self-injected TNF inhibitors.

Vyn Reese: Thank you. Any additional questions? We can excuse Patricia.

Patricia Thieda: Thank you.

Vyn Reese: Are you still there?

Patricia Thieda: I'm here and thank you.

Vyn Reese: Wait a second. One more person to talk? Carrie Johnson, Dr. Carrie Johnson.

Carrie Johnson: Thank you for the opportunity to speak today in support of Enbrel, a product that has over 15 years of collective clinical trial experience, has been used in over 500,000 patients worldwide across indications and now surpassing 1.3 million years of patient exposure. I'm Carrie Johnson. I'm a PharmD and medical liaison for Amgen and I'm requesting that you maintain the current PDL status for Enbrel.

In the next few minutes I'll highlight five key attributes of Enbrel that warrant this. The first is mechanism of action. Enbrel has a unique mechanism action among the TNF antagonists. It is the only fully human TNF soluble TNF receptor, not a monoclonal antibody and as such has not been shown to cause cell lysis or induce neutralizing antibodies. Two, is indications. It has the broadest scope of indications crossing both rheumatology and dermatology. These include rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis and a pediatric patients for juvenile rheumatoid arthritis. The pediatric indication differentiates Enbrel and is important for a Medicaid plan such as yours where the relative pediatric population may be large. Enbrel has been studied in patients down to two years of age and shows sustained efficacy and safety out to eight years in this pediatric juvenile rheumatoid arthritis population. It is the only TNF inhibitor indicated for juvenile rheumatoid arthritis.

Efficacy – Enbrel has demonstrated sustained clinical responses in patients with rheumatoid arthritis out to ten years at a stable dose. Enbrel in combination with methotrexate has demonstrated three years of halting of radiographic progression in patients with rheumatoid arthritis.

Dosing – Enbrel provides predictable dosing. It has not been shown to cause the formation of neutralizing antibodies, which may affect efficacy and maintenance of response over time.

And finally safety. The only adverse events seen more often in treated versus untreated patients in Enbrel clinical trials has been and continues to be injection site reactions. Rates of serious adverse events and serious infection have remained low, stable, and not significantly different from placebo or methotrexate controls.

In conclusion, Enbrel is unique among TNF antagonists. Enbrel has over 15 years of collective clinical trial experience, has been used in more than 500,000 patients worldwide across indications and has more than 1.3 million years of patient experience.

Rates of serious adverse events have remained low and stable over time and other than injection site reactions not significantly different from placebo or methotrexate. Enbrel has a pediatric indication, predictable dosing and published sustained, long-term safety and efficacy data. Thank you for your time.

Vyn Reese: Thank you. Would you like to speak?

Darla Langdon: Yeah.

Vyn Reese: Can you introduce yourself?

Darla Langdon: My name is Darla Langdon. I am representing the public on behalf of Humira. I have been a patient of plaque psoriasis for 20 plus years using various forms of medications, topical and sub-q. I have used Enbrel for the past year and fortunately I have now decided to use Humira, which I had heard of the benefits outweighing the lesser. For me, Humira in the past month has already started to show improvement in my psoriasis, which is chronic to severe and I just look forward to what the next year of my life with bring and I hope that you would allow parity access to your patients who the competitor has failed. Thank you.

Vyn Reese: Thank you. Any additional speakers? Okay. I'll take a motion to accept the scan.

Bob Bray: This is Bob Bray. I move to accept the scan as an adequate update.

Ken Wiscomb: Ken Wiscomb, second.

Vyn Reese: All those in favor?

Group: Aye.

Vyn Reese: Opposed? The scan's accepted.

Jeff Graham: I think Patricia could probably be excused now.

Patricia Thieda: Thank you.

Vyn Reese: Are you still there? Now you can be excused.

Patricia Thieda: Thank you. Bye.

Jeff Graham: Vyn, this is Jeff Graham again. I think I should let you know there will be a full update coming out of this...for this class. Probably we'll have it presented early next year or in the fall. There's one being done.

Vyn Reese: Any further discussion on the TIMs?

Ken Wiscomb: Ken Wiscomb. I have a question of Siri. When are we do for a full review?

Jeff Graham: Ken, that's what I just said.

Ken Wiscomb: I'm sorry. I was pouring a glass of water. What did he say?

Vyn Reese: He said the full review is coming either in the fall or early next year.

Bob Bray: This is Bob Bray. Just as a comment I find it difficult for us to be very specific about recommendations in this group when things change quickly and as far as indications. Obviously they're very expensive and risks as we've seen the black box warnings. They are significant for this group and I'm wondering if we really should make recommendations at this point?

Vyn Reese: The thing is...one thing is that under the motion it says of targeted immune modulators for the treatment of immunologic conditions for which they have FTA indications. I think the FTA indications are expanding as more and more of these drugs get the indication. And so therefore the pool of drugs is going to expand that are going to be accepted for like plaque psoriasis or other indications. So I think we kind of covered that in this original motion.

Jeff Graham: This is Jeff Graham again. We did that on the agency side when Humira received, was it for ulcerative colitis...for Crohn's and because you've

given us that latitude in here and didn't say you had a specific, you have this one drug, we went ahead and did that when it happened.

Vyn Reese: And these drugs are continually bidding against each other and as the new indications are coming in you're accepting the prescriptions for those drugs.

Siri Childs: Well, when we do the review we are comparing the drugs for the specific indications and as they come in we would...they would follow the PDL rules in that they would not only have tried and failed the preferred drug for that indication, but they also would need the specific criteria for that particular drug. We have all of these drugs on EPA for safety—the indication, the dose, everything is on EPA, even the preferred drug in this category.

Vyn Reese: Any additional discussion or questions? This was my motion before and I can't make it.

Man: Yes you can.

Vyn Reese: Can I make it?

Man: Sure you can.

Vyn Reese: Okay. I'll actually make the same motion I made on February 21, 2007 as written above. Any discussion?

Woman: I'll second it.

Patti Varley: This is Patti Varley. My question is in the motion that stands from 2007 there's the indication of the need for, and I can't say the name, infliximab to be included, but now there are others that have been approved for Crohn's. So does that statement need to change to must include one, which has been approved for treatment of Crohn's and ulcerative colitis as opposed to specific identification of one? I would also say as a pediatric person that we still need to say the one regarding juvenile rheumatoid because I did not see that any other ones have gained indication unless I'm incorrect on that.

Jason Iltz: This is Jason. I'd agree completely, Patti, and there was one that pending potential FDA approval for the juvenile. So I guess that the other part of your question would be can we just say that there needs to be a medication included to treat each of the FDA approved indications for these agents and really not name any of them by name as Bob eluded to this class is changing very quickly and there's always new evidence and if we're really

trying to make sure they are available, you know, they're already on EPA. So I think that just makes sense from a choice standpoint as well.

Vyn Reese: I would take a friendly amendment just to delete that sentence – Infliximab must be included for treatment of Crohn's disease and ulcerative colitis in addition to a self-administered agent for other indications. We could just delete that sentence and just leave the Enbrel for JRA.

Patti Varley: But then again actually what Jason just said though I'm hesitant now to include that one medication because if another one comes along and gets FDA approval for juvenile rheumatoid arthritis I want to make sure that that's included as well.

Vyn Reese: But it hasn't happened yet. We could just...if you want to we could just delete both, but until that happens we need to make sure Etancercept is on the...

Jason Iltz: And it would be if we had this statement for all of the approved FDA indications.

Patti Varley: Right. That's my...

Vyn Reese: How would you amend it?

Patti Varley: I was going to say you could say the PDL must include a drug approved for the treatment of specific conditions such as Crohn's disease, ulcerative colitis and juvenile rheumatoid arthritis.

Jason Iltz: And then there was also the psoriatic arthritis, which I don't know if we need to say that. And then the plaque psoriasis as well.

Vyn Reese: Basically you're just saying for the treatment of immunologic conditions for which they have FDA indications. That's the first part of it.

Jason Iltz: Yep.

Patti Varley: So maybe we're covered.

Vyn Reese: Maybe we could just delete the whole...

Patti Varley: Can I ask those of you who are approving these would that cover it if we just left that statement in the first sentence that as long as that particular med was being prescribed for that particular indication it would be allowed?

Duane Thurman: This is Duane. I think it would be helpful to clarify that...your first statement is saying that you find them equally safe and efficacious for the FDA indications. I think it would be helpful to the agencies to say that the preferred drug list must include a drug for each of the FDA...

Patti Varley: For each of the specific conditions?

Duane Thurman: ...for each of the approved indications.

Vyn Reese: The PDL must include a drug...

Patti Varley: FDA approved for each specific...

Vyn Reese: Approved for the treatment of immunological conditions for which they have FDA indications.

Jason Iltz: That wouldn't do it.

Vyn Reese: For treatment of immunologic conditions for which they have FDA indications. You can just sort of back up. Approved for the treatment of immunologic conditions for which they have FDA indications.

Duane Thurman: Would it sound a little better just to say PDL must include a drug approved by the FDA specifically for each...

Patti Varley: For each of the FDA indications?

Duane Thurman: One remaining question I have is you reference in your previous motion that you must include a self-administered agent. Is that still relevant here?

Vyn Reese: I think that has to be included except it's, you know, we're not certain which indications still have...I think almost all of them have approval now for self-administered agents.

Carol Cordy: Can I just add...Carol Cordy here. In that same sentence the PDL must include a drug approved for treatment for each immunological condition for which they have FDA approval.

Duane Thurman: I guess the question, this is Duane, is in that sentence do you want to say for each condition for which they have FDA indications and including of self-administered agent for each of these indications.

Vyn Reese: Where approved. So how did we say it before? A self-administered agent must be included...

Patti Varley: Should include a self-administered as available.

Vyn Reese: Not as available, as indicated.

Patti Varley: As indicated. You could put should include a self-administered preparation?

Vyn Reese: Agent.

Patti Varley: Agent? Okay.

Vyn Reese: Whatever. Maybe if indicated.

Jason Iltz: Before we vote I'd like to make a safety comment once we're done with the verbiage here.

Carol Cordy: I would change for to of. For treatment of each immunological...

Vyn Reese: Dr. Bray, what was your question or comment?

Bob Bray: My concern about safety is for rituximab because of the concerns about fatal infusion reactions and the progressive leukoencephalopathy. They all have some very serious safety problems, but that seems to be somewhat unique to that agent at least as reported currently. And since that is different I'm wondering if we should not include that drug since it doesn't have an indication that's unique?

Vyn Reese: I'd have to go back to our previous reviews to remember whether other agents have that same concern. As I remember multifocal leukoencephalopathy has been associated with other agents in this class before. We don't have the full review in front of us.

Bob Bray: I don't believe there's a black box warning regarding that for the other agents. If anybody has other information to correct that I'd be happy to hear that.

Vyn Reese: Did you want to delete rituximab?

Bob Bray: Yes.

Carol Cordy: I just checked a couple of them and they do have black box warnings for other things.

Bob Bray: For other conditions? Correct.

Vyn Reese: I don't know if we have enough information that we shouldn't use it entirely or if that's just a warning to be extremely cautious about it. If

that's the only drug that is indicated and the patient's tried several others...

Jason Iltz: This is Jason. What are the questions that the EPA goes through? Could that be something that could be picked up on an EPA for a specific...

Siri Childs: I have to say that I've got our EPA criteria right here and we do have it on EPA still, but it's used for non-Hodgkin's lymphoma as well so we do have other indications that it's used for.

Jeff Graham: So Bob, if something was added to the EPA criteria that reinforced monitoring and stuff like that would that help?

Bob Bray: Well, the concern I have is I don't think that monitoring is...in those two issues with fatal initial reactions and progressive leukoencephalopathy. I'm not sure monitoring is going to be able to detect that. I think that's an issue specific to the drug.

Vyn Reese: With Remicade there's a black box warning about hepatosplenic lymphoma. It's not in some of the other drugs. So I mean each of these drugs...that's another drug that might be...you could also say we shouldn't include.

Patti Varley: This is Patti Varley and that was going to be my question is that at least to my limited understanding that each of them have a rare, but significant side effect risk. But they are not all the same and that...it's just a question of how would you address that in there beyond the fact that they all have EPA?

Bob Bray: I think one compromise could be that since the only indication that we're speaking to in this class is not the oncology related indications. The other thing we could do would be to state that it should not be used as the first agent for rheumatoid arthritis because of safety concerns.

Jeff Graham: This is Jeff Graham. Its indication is for rheumatoid arthritis where there's been inadequate response to other [inaudible].

Bob Bray: So I don't think currently the EPA reflects that from what you mentioned. Is that true Siri?

Siri Childs: The EPA code only addresses the lymphoma and by looking at that I would guess that, and I'm only guessing, that what has happened in the past is that we did not include it in the drug class because of its cancer indication. We don't have it listed with EPA criteria for its rheumatoid arthritis.

Patti Varley: This is Patti Varley and it was only reviewed in this review, I believe. It wasn't reviewed...it wasn't indicated so it wasn't reviewed in this group prior to this review just so you know. If you look it says that it's the new added one to the list when you look at...there's a page where it said this was being evaluated as the...if you look at the motion template for 2007 it says this one was added to the update. It was reflective in our old review.

Vyn Reese: And also it's indicated only where other TNF drugs have failed. So it couldn't be the primary drug indicated for RA. I mean it's for moderate to severe RA where other TNF drugs have failed. That would be taken care of by that FDA indication and I doubt it's going to be the lead drug in this class for RA since it would not be indicated for that.

Bob Bray: Well, Bob Bray again, I think the thing that would make me feel better is that we know that...and this is a new issue, that that is indeed part of the EPA. Unless you specifically stated that it is an FDA indication and the FDA has made certain suggestions about it, but I think we would want to make sure that...I think we should make sure that that limitation is part of the EPA process. Then I would be happier.

Vyn Reese: We don't have to say that in a motion though do we? It's not indicated as a first line drug for RA.

Siri Childs: This is Siri again and what we do with every single one of these agents is use the FDA labeling. So the FDA labeling for this one would indicate that it's a second line agent.

Man: So the one you could clarify FDA indications and safety warnings.

Duane Thurman: This is Duane Thurman. Remember that we transcribe these meetings also and in terms of the actual motion I think that gives us enough to implement a decision and I think you're on the record as having directed or suggested that we include those in the EPA and I think Siri can do that.

Siri Childs: Yeah.

Duane Thurman: Do you want to just commit to that on the records?

Siri Childs: What I'll commit to is we'll follow the FDA labeling for this product just like we do for the others and that will include that this is a second line agent.

Carol Cordy: Can I just ask a process question? It looks like this was approved in February of last year and then I'm looking at the most updated...the up-to-date preferred drug list, which does not include these two new drugs. Is that right? Okay. I am confused then. I thought that this page was

referring to what happened in February of last year. It's not. Is that right? Both of these choices drugs reviewed I was thinking that referred to February. It was reviewed?

Duane Thurman: Carol, are you referring to the motions?

Carol Cordy: No, I was looking at the templates of February 21, 2007.

Duane Thurman: It was included in that update and it is also included in this scan.

Carol Cordy: So my question really was this happened in February, but it was not added to the PDL.

Bob Bray: What was not?

Carol Cordy: The Rituxan and the Orencia.

Jason Iltz: This is Jason. Carol, I think what happened is the dates got transposed on the PDL to where the one on top should have said 2/15 and then the next one should have said 2/21/07 because I believe the motion, that last motion there, is the same motion that is on our template. Does that make sense?

Carol Cordy: Yea. No, I was just wondering what the process is once it's approved in this committee? Then when does it get implemented on the PDL?

Duane Thurman: That's a complicated issue at this point. Normally what we do is we collect the data beginning after your decisions here. We look at the supplemental rebates we've done and then we do a cost analysis. One issue right now is that we're backed up on implementation of new drug classes pending an implementation of the new point of sale system at Medicaid and the three agencies have traditionally tried to implement all at once and so right now we're working through issues as to when physically we can get the thing posted. So that's going to become an issue that you'll hear more of.

Carol Cordy: So it can take up to a year?

Duane Thurman: Look at this, yes, but looking at this it should have been included on here and I'll look into why it was not.

Jason Iltz: Just this date is wrong right here.

Man: That's correct. This should say February 21, 2007.

Jason Iltz: Just this date.

Man: Rituximab is in this class. Do you see it there? It's in bold.

Duane Thurman: This is Duane. I think we have the information we need. We know what you're talking about. I think we need to formalize this motion.

Vyn Reese: I want to re-read the motion as this has been heavily modified. After considering the evidence of safety, efficiency, effectiveness and special populations for the use of targeted immune modulators for the treatment of immunologic conditions for which they have FDA indication, I move that etanercept, adalimumab, abatacept, rituximab, and infliximab are safe and efficacious. No other Targeted Immune Modulator medication is associated with fewer adverse events in special populations. PDL must include a drug approved for the treatment of each immunologic condition for which they have FDA indications (rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis) and should include a self-administered agent if indicated. These medications cannot be subject to therapeutic interchange in the Washington Preferred Drug List.

Carol Cordy: I will still second it unless there's more.

Vyn Reese: I'll call for the motion. All those in favor? Any other modifications?

Jason Iltz: I think we need to back up and ask ourselves as a committee...the last time why there were some medications not included on that list. There's a total of eight medications we reviewed and they were available the last time, too and I don't recall if there just wasn't sufficient evidence, but there's the third, fourth and fifth one listed on that list the alefacept and the anakinra and the efalizumab are also available; a couple of which are approved for psoriasis, one approved for arthritic conditions. Did we leave them out for a specific reason? I don't recall the discussion around that.

Patti Varley: This is Patti Varley. I'm confused. My understand is if you read our last motion everything was included in our last motion, but then what gets put on the PDL is determined by the powers that be after we say they can have any of them. Is that what's confusing?

Duane Thurman: That's correct.

Patti Varley: So had the people responsible for the PDL final listing based on rebates, financial, all those things they could have included all of them based on our recommendation, but they don't have to. They just have to do what we say, which is to have them in the treatment of disorders and a juvenile, which is what we said last time.

Duane Thurman: Correct. Your motion sets the floor that those are things that must be included. Our cost analysis may result in the fact that we would have more than one drug included.

Ken Wiscomb: Ken Wiscomb. So just following that's going to address Jason's question. It seems like until then we have a full review we can't be putting drugs back? Is that correct?

Duane Thurman: I'm not sure I understand your...

Ken Wiscomb: Well, if we don't list all the drugs here, for some reason we took them out before. For some reason we took them off the list before. We can't add them back until we have a full review.

Duane Thurman: Right. I would suggest you await the full review and look at the whole class again.

Vyn Reese: Any other discussion? I will call for the motion again. All those in favor?

Group: Aye.

Vyn Reese: Opposed?

Angelo Ballasiotes: Aye.

Vyn Reese: The motion is carried. We now are adjourned for a break. Come back in...

Patti Varley: ...because for instance in this last class a lot of us are getting older and we can't remember everything that we discussed and I just didn't know if that was a realistic request.

Siri Childs: Patti, would you want us to include a copy of the previous report?

Patti Varley: Yea, either the previous report or a summary. Because like for instance some of us are saying, "There must have been a reason we left those meds off," and we can't remember why that was. So a way for us to be able to have material to look at so we can refresh our memories.

Vyn Reese: It's a good question. I think that there were some of those drugs we didn't have on the list that had either...they weren't as efficacious or they had more side effects. We couldn't remember why we left them off and that doesn't happen in every drug class. That was an unusual drug class, but that would be great if we could have that in a more complicated drug class like that in the future if we could have our prior...I don't know if it's a

copy of the discussion or just a summary of the discussion and why certain drugs were left off. That was an unusual thing and it did kind of trip us up.

Siri Childs: So a copy of the transcript of the previous meeting included in your packets?

Vyn Reese: Of the discussion regarding...not the entire meeting, but the discussion regarding that drug class that's being reviewed or a summary of it. It needs to be something that...if there were drugs that were left off and why they were left off.

Patti Varley: This is Patti Varley. Maybe in most cases if we just got copies of as we were making the motion because usually those things are pointed out as part of our discussion around the final motion. I'm trying to figure out how we could expedite it to the facts that we really are most concerned about.

Vyn Reese: Yea. If you could just list those drugs and just say why we left them off that would be, you know, based on our prior discussion that would be helpful.

Siri Childs: I think that what we could do is provide the transcript, but I don't think any of us would feel comfortable going in and re-writing it and interpreting it, but we can provide the transcript around the motion.

Vyn Reese: Okay.

Patti Varley: And this is Patti again. Maybe...would it be appropriate for, Vyn for you to look at maybe just the discussion of the final of this particular one in regard to the actual motion? And see if that did contain it what we would have wanted?

Vyn Reese: If you could make a...

Jeff Graham: I think we hear you. We can do that.

Vyn Reese: I know. We sort of need to move on. I know that DUR...can we approve the DUR minutes from the last meeting as transcribed? Since it's a transcription it should be pretty easy.

Man: I move.

Vyn Reese: Okay. Can I get a second for the minutes?

Man: Second.

Vyn Reese: All those in favor?

Group: Aye.

Vyn Reese: Opposed? Okay. Let's move on. And Jeff I'll turn the meeting over to you now.

Siri Childs: I think we want to turn it over to Gary Franklin.

Vyn Reese: Jeff is going to introduce Gary.

Jeff Thompson: Right. I'm just going to give you the context. We're going to give you four or five quick presentations. We have some people out in the audience that want to talk. This is specifically about our inner agency and agency medical director's work on a narcotic guideline and as we move this forward we wanted to have a discussion with you as well the discussion with the community about where we're going and make sure you're aware of it. If you have any recommendations we want to hear about it from the three agencies because this is not just a Medicaid endeavor. This is about how we want to establish a standard within the state purchasing for fee for service. So Gary's going to give a presentation. I have to give Gary a lot of credit because he's really been a leader in this. You can also catch all the [inaudible], but we've all contributed and I think it's actually turning out to becoming a national guideline that many other Medicaid states are looking at adopting. Go ahead.

Gary Franklin: Thanks. Thanks for having me back. I think I was here just before we kind of were ready to roll this thing out when it was still in draft form before it was finalized. So this is kind of the one-year follow up and hopefully I can go through these slides fairly quickly since time appears to be sort of short right now. You'll notice I'm not a formatting expert with that line through the date there.

Just to remind you most state regulations changed in 1998 and Washington and around that time all the states changed and the policy changes were most likely due to low grade studies like port noise study, which supported the rarity of true addiction. There was a lot of efficacy going on and I call this...I've developed this term disciplinary fatigue among doctors, you know, basically tired of hardly ever being able to use...because it was basically illegal to use opioids before this time. The kinds of guidelines that our state has had both in the DOH regulators and L&I regulations. They were all the same; they are really the same all over the world. Such things as a single physician, a single pharmacy having some sort of a contract between the patient and the doctor and remember we're only talking about chronic, non-cancer pain here. We're not talking

about cancer pain. So this is the kind of example of the kind of language that L&I has had in its opioid treatment agreement for many years. But like I said every major international guideline on this issue includes this kind of an agreement.

We started to get concerned in 2001/2002 because we started seeing deaths at L&I, which we had never seen before. I've been at L&I before and had never seen a death associated with opioids until soon after 2000 and we did a study looking at all of these deaths and reported 32 definite or probable deaths just in the worker's comp system. You can see that they really didn't start to occur until the policy changed pretty much. And then actually this is a more up-to-date slide of the deaths in Washington State in general from unintentional poisonings and this is from the epidemiology section at the Department of Health. So this is a much more up-to-date look at the deaths from unintentional poisonings. Most of which are related to opioids.

The National Center for Health Statistics has done some work. These reports are not too easy to find, but I contacted people at the CDC who've been working on this and at the National Center for Health Statistics this...by the way if you would like a copy of these slides just let me know and I'm glad to send them to you.

So this is the age-adjusted deaths. This is in the whole country for the leading causes of injury death and you can see the bottom line, which is poisoning deaths, which would include the unintentional poisonings associated with opioids that in 2004 the poisoning death rate for the first time since 1968 became greater. This is the mortality rate that became greater than firearm deaths. So the number of deaths in the country associated from unintentional poisonings particularly from opioids is basically a national epidemic at this point.

The other point to make is that there have been a lot of focus on methadone as one of the bad actors here, but actually I don't think you can really pick a drug that is a worse actor than another drug. I think it's all the schedule 2 high potency drugs and in combination long acting, short acting and in combination with benzodiazepine sedative hypnotics all of which you really shouldn't be using on a regular basis in these patients, but these kinds of patterns are being seen in some of these patients. The deaths that we reported very few of the patients had concomitant benzodiazepines and none had alcohol or illicit drugs because we defined those out.

You can see here that the number of poisoning deaths associated with methadone is way lower than the total from all other drugs and other causes combined. So if you just count up the number of deaths associated

with opioids methadone is still in a vast minority compared to other schedule 2 drugs.

Our own studies associated with the death report that we did a couple years ago showed that there was a dramatic increase in schedule 2 prescribing, but not an overall increase in prescribing in terms of the number of patients. It went up very little actually from before to after, but what did change was a dramatic shift from use of schedule 3 to schedule 2 drugs and then the most important thing was that the average daily dose went from about 80 mg a day in 1996, before the regulations changed, to over 130 mg a day in 2002 and actually now I think it's over 150 mg a day on average. So that's the average daily morphine equivalent dose, 150 mg a day. So it went up by way more than 50% just in those few years.

There were previous reports from the DEA on oxycodone. I mentioned this to you before. It's on line at the DEA and then, you know, these deaths have all increased just as, you know, since the regulations changed throughout the country.

There was a recent study of the most frequent suspect drugs in all deaths related to these types of things and this is deaths from all drugs. I think this was reported in the archives of internal medicine just in 2007. And you can see the rank and number of deaths associated and opioids are, you know, number one, number two, number four and number six on this list of all drug deaths. Opioids are really up there as the number one culprit from the unintentional poisoning deaths. Obviously the issue is, "What is causing the deaths?" And dramatically increasing average daily dose, which is not associated with improved pain and function. It's probably related as Jane Balentine has said to ramp in tolerance. So I think what's happening in these patients is they are developing tolerance and they may be developing tolerance to the euphoric effects of the drugs before they develop tolerance to the respiratory depression effects.

Purdue Pharma published an opinion on May 9, 2007. We got a letter from them, a two or three-page letter, concerned about our opioid dosing guidelines and their feeling, and I think this is more or less the party line, that almost all the deaths are related to misuse and basically there is no evidence at all that misuse is more common or less common than mis-prescribing. I believe that most of these cases there is a combination of stuff going on related to both patient behavior and to physician behavior. The main thing is that there is very little work on this right now. So I wouldn't make any assumptions about it until more research comes out.

A day after we got that letter Purdue pleaded guilty to criminal charges for miss marketing Oxycontin. This was in the New York Times the very next day after we got the letter.

And then Jane Balentine if you don't read anything else you should read this article. It's a review article by Jane Balentine from Harvard on the whole issue of use of opioids for chronic, non-cancer pain and basically the main thing is that overall the evidence supporting long term analgesic efficacy for improving pain and function is very weak. The putative mechanisms for failed opioid analgesia may be related to either ramp intolerance or opioid induced hyperalgesia or both. There is very little study by the way and the premise that tolerance can always be overcome by dose escalation is now questioned and I think that's the main problem going on here right now.

There are good results from K series, but the review of the open label follow up studies has shown that 56% of patients abandoned the treatment because of lack of efficacy or side effects and then many trials have methodologically poor stuff going on such as enrichment, which selects out non responders before the trial even starts.

And then there was a big epidemiologic study published by Erickson in 2006 which demonstrated that if you just look at a whole population and look at people with chronic pain some of them were taking opioids and some of them were not. There is no difference in self-reported health outcomes and function, quality of life, etc. among those taking opioids and among those not taking opioids.

There's no clear case definition for addiction. So it's very hard to even identify who is developing addiction and who is not. So she's concluding that after a decade or more of acceptance to therapeutic opioid use was unlikely to result in addiction. It was said to be around 5% when these rules all changed. A systematic review published in '92 reported that addiction rates were up to 19% and that this material had failed to penetrate educational materials for physicians.

We did the opioid dosing guideline and basically it was just an educational pilot. It was never meant to be anything other than educational pilot and it's got one simple principle, which is that you can increase the dose in patients with chronic, non-cancer pain, but if you've gotten to 120 mg and you cannot document or say that the patient's pain and function have improved then you should take a deep breath and ask for some help or reconsider what you're doing. That's all it is. That's the whole premise of the entire guideline and we believe that this is an extremely reasonable approach to this epidemic of deaths that we're seeing related to these high doses.

The plan right now is to conduct a formal evaluation of the impact of the guideline during this coming spring and summer and fall and we plan to

reconvene the original pain management group. Remember that it was pain docs that came up with the dosing guideline in the first place. It was not the agency medical directors. We work with those folks, but they are the ones who came up with the consensus dose at 120 mg of the sort of warning dose.

We will be meeting with that group again. We have met with them since. We finished the guideline and we will continue to meet with them, but in the fall of 2008, after we have more data on the evaluation we will meet with them again, bring the evaluation information back to them and see what they would like us to do.

Some of the evaluation ideas are to look at the degree of diffusion. As you know we've had the ability for docs to do free on-line two hours of CME on a web-based test for the opioid dosing guideline. Anybody in the state or the country, any pharmacist, any doctor can get free CME. We were able to arrange that. And so one of the things that we asked docs who took this on line was whether they would be willing for us to talk to them to see what their experience has been with the guideline and so we've got probably 30, 40 or 50 docs that we will talk to in the coming months as to their experience with the guidelines.

I don't want to go into the details of the guideline. We did that before. We do have some antidotal stories of docs that we have recently asked as to their experience and the docs as far as we can tell, the primary care docs and the pain specialists are finding this opioid dosing guideline a terrific tool in their office to use.

That's about all I have to say today. I know there's a lot of other stuff that Jeff and his team wants to present. Maybe we should leave questions until the end or do you want to take questions now?

Jeff Thompson: It's up to Vyn.

Vyn Reese: Any questions now? I have one. How many patients statewide are on higher than 120 mg of opioid equivalent or morphine equivalent a day? Do you have any idea about the numbers involved?

Jeff Thompson: We're going to show you the Medicaid data, but only the drug companies know that number.

Gary Franklin: We don't have the data here, but we could probably come back to you with that data. I mentioned to you earlier that the average daily dose among the patients in L&I taking opioids was over 150 now. So that's the average. There's a tail on that. So there's many, many people that are taking not just over 150, but hundreds of hundreds, perhaps even 1000 mg

a day and so that would probably...the number of people over 150 is probably, you know, in the thousands I would think, maybe a couple thousand.

Vyn Reese: My concern is that given that number of patients are there a number of pain specialists in the state that are going to handle all those consults?

Gary Franklin: Right. So there's been a major issue about the number of pain specialists who are on the web site and who have agreed...they are not being overrun by consultants for some reason. And so that either means that the primary care docs are actually comfortable using the guideline per say without asking for help or they are just not asking for help and I'm not sure what the reason is. We have started to, because of the concern around this; we have started doing some experimentation around using say telemedicine and other techniques to try to get pain management consultations to the primary care docs where there might not be pain consultations available. For example, there's not a single pain guy in Spokane that will do these consults. So we are working on several methods, including web-based training for primary care docs perhaps to offer them an enriched educational opportunity and also we are experimenting and have done some telemedicine in specific cases in Eastern Washington. So we're working very hard to try to improve that particular situation. But these pain guys who were signed up to do this are not being overrun with consultants so it doesn't seem to be...there doesn't seem to be a capacity problem right now from that standpoint, but we realize that we need to do something about the training and the availability for primary care guys.

Carol Cordy: I have a question. Where does buprenorphine fit in this?

Gary Franklin: You mean what is treatment for high dose therapy?

Carol Cordy: Yea, and coverage for the medication and people that will prescribe it and such.

Gary Franklin: Well, it's not directly related because the main part of the guideline is to try to prevent the next cohort, the next 5,000 people who might end up on high doses without improving pain and function. So part one of the guideline, which is the pain part of the guideline are directions as to how to deal with a chronic, non-cancer pain patient where you're just increasing the dose right now. Part two has to do with people you might have in your practice who are already on high doses and L&I is doing some experimentation with various pain docs around the state on a few cases of paying for buprenorphine and additional services in patients that are complicated enough that look like they may need to go in that direction. So we're looking at that right now and we're also looking at the

whole managing chronic pain issue from a broader standpoint of comprehensive services. So we're starting to look at that as well.

Jeff Thompson: So Carol, in Medicaid it's covered by the FDA indications. Siri did a very nice job of putting that together. We met with the buprenorphine people.

Ken Wiscomb: I have a question. When looking at both the groups of the increasing number of accidental poisonings and the group of people that are required more than 120 mg, has there been any change demographically in that group of people? Is there any trend that they are getting younger, older, or?

Gary Franklin: Not that anybody has recognized, no. As a matter of fact I just don't know.

Angelo Ballasiotes: I guess I hear and I see a lot of people addicted accidentally to opioids and things of this nature, but I really don't see much communication about the psychosocial issue. I think those go hand in hand. You hear a lot about dose limits and things of this nature and you're right with respect to...long-term pain is a doable or solvable problem, but we don't do anything on the psycho social issues and a lot of these people have personality disorders. Why aren't they doing anything to stop that until those issues are dealt with? That's my opinion.

Gary Franklin: We just published a paper in Spine January 15th that if an injured worker with a low back injury gets seven days or more of opioid in the first six weeks, if you adjust for severity and pain and function it doubles their risk of one-year disability. That includes adjusting for the psychosocial factors. I think that we do have to look at all that stuff, but unbelievably there's hardly any research on the stuff out there.

Jeff Thompson: I can tell you that most of my peers and Doug Porter are actually at Samsco(?) today talking about integrated databases because what I call the trifecta – chronic illness, addiction and mental illness those are the most expensive and most vulnerable clients. So we are working on that issue, but I'll tell you it's a big education because all three of those provider types don't necessarily like to talk to the other provider types.

Man: We need to move on if we're going to get you out of here.

Vyn Reese: Do we have stakeholder input?

Gary Franklin: We have two presentations just to show you about the toolkits that we've been working on. David Mancuso from our research division and Scott Best from our lock in program are going to present some Medicaid data so you can actually see the numbers and see actually the trends that when we

do work with the community we can actually have some very good outcomes. Then I think we could take community and I'll do the last.

David Mancuso:

The presentation I'm going to give kind of ducktails on the psychosocial question that was raised. I'm going to give some information about some research we were doing internally within DSHS about four years ago that helped to some degree to lead to the narcotic review program that Jeff and Siri and others got underway maybe about three years ago and that research was really looking at the nexus between poor, patterns of medical service utilization especially, emergency department cycling, how that's associated with mental illness and chemical dependency problems and associated with high narcotic prescribing patterns. So basically motivated out of concerns related to some of the information that Dr. Franklin showed about rising evidence of opioid abuse, misuse, deaths associated with opioid use and concerns about excessive medical service utilization and concerns about the inadequacy of funding for chemical dependency treatment. In my division of DSHS, I'm in the research division, we're asked to look at these issue and we were looking really at this population of, you could think of them as SSI related, I'm not sure that that's a term that resonates with folks outside of DSHS, but essentially we're talking about low income people who need some formal disability criteria. The particular population we'll be looking at in a moment it's about 150,000 people in Washington State in a typical year. It's a fairly large group of people, very expensive from a state budget perspective. These are people who are generally in fee-for-service medical care. So even though there are highest need in terms of need for health care services, medical and behavior health care services and long-term care services, and despite that there are folks who are in essentially fee-for-service and generally not in a managed care relationship. And they are also a group that has, depending on how you slice and dice, about 50% you would say would have some recent indication of a mental health problem and about 20% who have some recent indication of a chemical dependency or substance abuse issue. So let's move on and look at the first data slide.

We're really good at putting together complicated slides that are hard to see from a distance. I'm going to take a swing at trying to get you oriented in what we're looking at here. Basically, what we're trying to show in this slide is how the likelihood that you are a frequent emergency department visitor is a function of basically...largely a function of whether you have indications in mental illness or chemical dependency or both. And if you were to look over at the very left hand side of the slide broad population here is about 150,000 folks. This is this Medicaid disabled population. Close to 100,000 of those folks didn't go to the outpatient emergency department at any point in the year we're looking at here. This is 2006. Of those about 6% have some indication of a co-occurring mental illness or alcohol or drug problem. Another 7% have an indication of an

alcohol or drug problem alone. Another 25% have an indication of mental illness and the vast majority, 62% have no indication in the data that I have, which is primary claims and other service data of a behavioral health problem.

As you go up the ladder of the number of outpatient emergency department visits the clients have in the year...and I'm going to go all the way to the far end just to focus the ideas and look at that group. We're at 31 or more outpatient emergency department visits in the year. That's the far right hand side. Almost all of those folks, 98%, have some indication of a behavioral health problem and the vast majority have indications of co-occurring mental illness and substance use disorder.

The next thing that we wanted to look at is...so we come out of this with some idea that frequent emergency department use may be related to drug seeking behavior and that rapidly rising risk of either co-occurring chemical dependency issues or substance abuse issues alone being identified for the client is, you know, what leaves us to think in that direction.

If we go to the next slide we look at the volume of narcotic prescriptions filled, same groups of clients in the year, and you see that for those frequent ER cyclers, the frequent flyers they averaged about 29 narcotic prescriptions filled per client per year and that's about 15 times the number of prescriptions filled for the clients who aren't cycling through hospital emergency departments. By the way, that number...we've seen actually some really significant changes here since we first looked at these data about four years ago. Prior to the implementation of programs like the narcotic review program and expansions of the patient review and coordination program that Scott's going to talk about...when we looked at the same kind of breakout four years ago the most frequent flyers got 42 prescriptions per client per year and that's dropped about 30% over four years. What we've seen is actually no reduction in the number of prescriptions filled among those clients who are not frequent ER cyclers. They've actually seen a modest increase in the average number of narcotic prescriptions filled per client. So if you look down at the clients with no ED visits or one or two or three to five ED visits they're actually getting slightly more prescriptions filled...slightly more narcotic prescriptions now than they did four years ago, but we've really seen a reduction at the high end in the volume of narcotic that these Medicaid disabled clients who are frequent ER cyclers are getting.

Now unfortunately we haven't seen a reduction in the absolute number of ED cyclers. The number of these clients in these frequent...in these cells of frequent ER visits is still about as high as it has been, but they are getting fewer narcotics paid for by Medicaid.

In the interest of time let's skip the next slide. That slide basically showed that a key risk factor for going to the emergency department not just in general but for the treatment for conditions, which are primary care treatable or don't require emergent care that we see the pain medication is a key risk factor for sort of avoidable emergency department use, not just emergency department use in general.

I want to move on to talk about one of the major initiatives that Jeff Thompson and Siri and other led in medical assistance. To pilot a program to look at clients who are getting extreme volumes of narcotics, to provide information to the prescribing providers about what's happening with those clients so they can see what other prescribers are doing for them. The program also had a prior authorization aspect to it and also included referral to the patient review now called Review and Coordination Program that Scott is probably going to talk a little bit about. So this program, it was originally called the Top 320 Program because there happened to be 320 clients who fell into this category of extreme narcotic use where extreme was defined by 10 or more prescriptions filled in a month or I believe it was seven or more prescriptions filled on average over a six-month period and this was after excluding cancer patients and hospice patients and I think HIV/AIDS patients also from the list.

The next thing I'm going to do is describe basically what happened in terms of some key outcomes for those clients, those clients who were getting extreme volumes of narcotics and who went through this narcotic review program which included prior authorization, some review and restriction and sharing of information with prescribing providers about sort of cross provider history of narcotic prescribing. We're going to look first at what happened in terms of the volume of narcotic prescriptions that these clients were getting filled. If we could go on to the next slide.

One of the challenges in trying to use observational data to understand the impact of an intervention...this was not a clinical trial. This was a group of clients who were targeted for an intervention, no randomized control, and in particular because they were selected based on their being the most extreme clients in our population in the particular time period we were looking at there really is no contemporaneous control group or comparison group that we have to look at to understand how their behavior, the changes in their behavior really reflects the impact of Jeff and Siri's intervention. So we created a comparison group by looking... [end of Side A]

...because of the episodic nature of health care we're using this comparison group of people who are extreme at an earlier time period in their narcotic use. We didn't do anything special with them. We looked

at what changed for them in terms of volume of narcotics received and costs and access to chemical dependency treatment and that's our benchmark for comparison. We want to understand whether we did better than that control group and basically understand whether we beat regression to the mean in the change in behavior we saw for this intervention group. And the answer is, "Yes, we did." In terms of narcotic prescribing for the Narcotic Review Group, the Top 320 we saw a 61% reduction in the average number of narcotic prescriptions filled per client per month. It went from 5 to 2. Five prescriptions filled per client month in the before intervention period to 2 per client per month afterwards, a 61% reduction. That beat the 43% reduction that we saw in our control group who again got no intervention in people who look similar in their behavior in an earlier time period.

If we move on to the next slide, which is a little bit harder to see, but basically there's a darker line that is tracking the proportion of the intervention group who's actively in chemical dependency treatment month by month and there are a series of lines marking when people were identified for the intervention and the time period where the intervention was actually operating. If you look at the post intervention period what you see is a rising proportion of our intervention group who are actually in state-funded chemical dependency treatment relative to the comparison group and over the 18-month, actually it's about a 16-month follow up period we're looking at here, by the end of this period our intervention group actually had about twice as many of these clients actively in chemical dependency treatment.

The next slide looks at what happened with emergency department cycling. And again what we're looking for is, "Are we beating regression to the mean? Do we see a bigger relative reduction in outpatient emergency department visits for our intervention group relative to our comparison group?" The answer is, yes. A slight yes, a small yes, a 5% relative reduction, a 44% reduction versus 39% reduction. So a five percentage point greater reduction for our intervention group. That works out to be about half a visit per year less for our intervention group in relation to the comparison group.

Our last slide that we're going to look at is what happened to Medicaid paid medical expenditures for the two groups. These are per client, per month costs. That base line for our intervention group that's \$3,000 per client per month. That's about \$36,000 per client per year medical only. If we threw in long-term care costs and mental health costs, cash grant costs, we get to a number substantially bigger than that, but what we saw for our intervention group is we saw a 34% reduction in per-client per month medical cost. That beat the 25% reduction we saw for our untreated comparison group and that 9% relative decrease translates to

about \$275, \$300 per member per month in terms of a reasonable estimate of the per member, per month cost impact of this intervention, which is a pretty healthy savings.

What we saw basically is across these areas we saw a pretty significant impact in improving sort of patterns of service utilization, reducing volume of narcotics prescribed, increasing the number of clients in chemical dependency treatment, and impacts which are pretty large in relation to other interventions that we've studied in terms of things we do in DSHS and I would argue very fair comparisons here where the bar is pretty high. We're beating a measure of regression to the mean which itself would say we should have expected to see pretty big changes and we've seen changes in several areas here well beyond those impacts. All right. I'll pause here.

Carol Cordy: I have a couple of questions. When you showed the graph of the number of prescriptions did that also correlate with the amount of narcotic?

David Mancuso: Yea. And what we haven't done in this analysis is bring in more sophisticated measures of volume like the morphine equivalence measure. We have looked at still fairly naïve measures around days supplied and we do see the same effects...if we look at days supplied as opposed as prescriptions filled the answer would be yes.

Jeff Thompson: You're going to see in the next set of slides what happened to prescriptions and morphine equivalent. Scott will show you that.

Carol Cordy: And the other question is did anyone in here did you see any diversion where...did you undercover patients who were selling their drugs?

David Mancuso: Although we can see a lot in the administrative data that we have that's not something that we can really readily see. One thing that we might be able to give a look to is we do have tied to all of this information from the state patrol that includes whether folks have been arrested for sale, possession, manufacturing of drugs and I suppose some of that diversion if somebody were arrested for selling the narcotics that they may be getting potentially in some cases through Medicaid that we might be able to see some of that, but I doubt that we would see much of that. That would probably be a pretty rare event. It's not something that we can really see here and get our hands around in the data I have.

Carol Cordy: Okay. Thanks.

Ken Wiscomb: In one of your slides it addressed the provider aspect of it I think early on. Have you looked really at diversion among providers? That might not be following best practices.

Jeff Thompson: There actually have been a number of providers who have had federal charges against these including FBI raids and other things. It's been in the papers that are mixed in with these clients, but that's not what this program is about. This program is about safety with our clients, but unfortunately over the past five years since Siri and I have been doing this the Department of Health with licensing activities, restrictions of licensing and opioid prescribing as well as, unfortunately, federal charges have been...

Ken Wiscomb: I realized that wasn't the purpose, I just wonder if that data had become apparent and then some action had occurred or something.

Jeff Thompson: We see this anecdotally but I can share with you if you want. I mean we've had...the state patrol has looked into this with diversion. It happens. There's a recent report, 522 pages, from our colleagues just north of us in British Columbia looking at diversion. It happens. It's not something we like to measure and mix in with the clinical, but it is occurring.

Scott Best: My name is Scott Best and I work for the Patient Review and Coordination Program. I have a set of slides also, but I thought I'd...of course...because we don't capture data on diversion it's really hard to quantify it and put numbers to it, but I do know that out of the 2006 320 project and subsequent projects we uncovered a ring of seven clients that were using a DEA number, the same DEA number and ordering the same...getting the same medications and worked with law enforcement officials to get that put to rest and also put their Medicaid ID numbers into our program, which helps to limit that over use also. But the Patient Review and Coordination Program is a health and safety program that's required by the federal government for us as Medicaid providers and basically what it is is a program in which we identify people who are over-utilizing medical services to the point where it is dangerous for themselves or others and we then limit the...they usually call it a lock-in program and so we limit the providers that they can go and see. We limit them to one primary care provider and then they can be referred by that primary care provider to specialists as needed. We limit them to one pharmacy to fill all their prescriptions. That way if they're filling multiple prescriptions and they're dangerous to be given together that pharmacist has that opportunity to explain that to them. We limit them to one hospital for non-emergent care. We don't limit whether they can go to the emergency room because you can't do that.

However, in the Patient Review and Coordination Program we are constantly looking at whether we're having success in our program and all the next sets of slides even though they are numbered one through seven is

the seven months prior to being placed in the Patient Review and Coordination Program and the following seven bars represent their utilization after they were placed in the program.

The first slide is referring to the trend of total narcotic claims and their claims of course go down prior to being placed in the program and then they stay low throughout the program.

The next slide goes into detail on the number of prescribers...oh, this is a group of people we looked at for the year 2006. This is everybody who was identified as a high narcotic prescriber. There were 516 clients that were identified and were placed into the program because of high narcotics. High narcotics and narcotic abuse accounts for about half the clients we have in our program at any given time. Right now we have about 2,800 clients and about half of them were for high narcotic or narcotic abuse. So after being placed in the program these clients had a decrease in the number of prescribers. Of course when you lock somebody into one primary care provider who knew that they would have a decrease in prescribers. Next slide.

This is the count of clients filling narcotic prescriptions. So the number of clients that are actually on narcotic prescriptions decreases. Some of them just quit filling prescriptions after they go into the program. Next slide.

This is the average number of prescriptions per client per month and the average narcotic claims per client per month. And so for each of those months you can see that the average number of prescribers per client and the number of prescriptions per client as far as narcotic prescriptions has decreased and levels out as they go into the Patient Review and Coordination Program. Next slide.

This is the total morphine equianalgesic dosage per days supplied because we're looking at clients who were placed into the program on different months. I just looked at from seven months before they were placed in to seven months after and we found that their overall morphine equianalgesic dosage decreased as they went into the program and leveled out and then the last slide.

During 2006 we also looked at all clients who were giving narcotics during a three-month period and we chose three months and they had to receive narcotics during each of those three months and during a three-month period because we were looking for clients who were being treated chronically for pain and we of course didn't include anybody who had a cancer diagnosis, or had hospice, or had...there was a list of about six other diagnoses that were pain related diagnoses that we did not look at.

The next slide shows that when you have people who are being given lower doses the bottom there is 90 to 119 mg morphine equianalgesic dosage. Their chances of having greater than one prescriber are just about 1 in 100 and then as they go up it almost goes up 10-fold by the time they go up to 180 mg – they've got a 10-fold increase in the clients who are getting it from more than one prescriber and that group is also the group that Dr. Thompson will be referencing when he has slides, too. It is the same group that he will have for that three-month period in the middle of 2006.

Angelo Ballasiotes: When you're talking about the narcotics were there people with benzodiazepines involved in that, too? Is that kind of intermixed or are they just straight narcotics?

Scott Best: I didn't discount people because they were using benzodiazepines and I didn't change anything based on benzodiazepine use, but we have found anecdotally...we've uncovered groups of people where they are trading benzodiazepines for narcotics. In Kitsap County we came across a group of people where some of them were going out and trying to get benzodiazepine prescriptions and others were getting narcotic prescriptions and then they were getting together and having parties.

Carol Cordy: I have a question. Maybe I missed something. It looked like in all your graphics the seven months before the trend was down. What's that about?

Scott Best: Well, what happens is we identify people as meeting the requirements for a period that goes back a certain number of months. After we informed them that they have been identified then we give them several months to decide whether they are actually going to...whether they are going to fight the decision to be placed in the program or not. Sometimes these can be carried out for...we've had hearings that went on for six months and so some of those clients, because of that, we've had people who were actually identified; received their first letter in that six-month period. I went back seven months to try and capture, you know, more and when I went back further than that I was having trouble with huge queries that were overwhelming my computer.

Jeff Thompson: What you see when you look at these and I can't get an explanation why these people cycle. They go up and then they go down regardless of any intervention we do. I mean they don't just go up and then they are taking a ton of narcotics because they wouldn't breathe after that. So I don't know why they cycled, but I think what Dave and Scott have tried to do is show you the best we can control for regression of the mean is by comparing them to populations or looking at a time series. If somebody can tell me why, you know, and it seems seasonal they go up to a high dose and then they go down. It's an interesting dilemma for us.

Carol Cordy: It seems like that letter did something.

Jeff Thompson: Yea, but I'm talking about without any intervention. If you look at them before you've ever done anything it's acyclic and it's almost seasonal.

Ken Wiscomb: I think in the bulk of those slides there was a downward trend in almost all of them consistently.

Scott Best: That's right. And if you go back before this I haven't gone back in these because these were very complicated queries, but if you go back they tend to build right to that point, to that seven-month period and then they start dropping because the client finds out that we're looking at them basically is what a lot of it comes down to. And then some of it is the regression of mean.

Ken Wiscomb: Is the actual calendar data for that mid point the same on all those slides?

Scott Best: Yea. They have all been adjusted to that. The first day of the eighth month that is listed there is the day they started in the program. Prior to that they received letters, they received all kinds of things, but that is for everybody in 2006 that's the first day and those are the seven months before and the seven months after.

Man: In the group where they are exceeding 180 and they have multiple providers were you able to account for multiple providers within the same group excluding those folks looking only where they had multiple providers that don't know each other? Because that's the implication is that we don't know that someone else is also prescribing. Were you able to look at that?

Scott Best: We could look at that. I know that in the clients that are in Patient Review and Restriction the reason why the number of provider's decreases isn't just because they're placed in the program. It's also...part of that is because their primary care provider is given detailed records if they do end up going to the ER a lot. We end up giving their primary care provider a list of, "Hey, he went to the ER on these days and you need to be aware of that." And then they sit down with the client and let them know and my experience has been that the primary care provider in most cases does not know that the client has been getting narcotics from other providers.

Man: This isn't meant to be a big criticism but I guess I can also imagine a situation where the people that use the most, or get the most narcotics may have your partner write the prescription because they are coming in frequently enough, on my day off or whatever. So the number of

providers could go up and they may be very legitimate in the sense of they all came from the same location.

Scott Best: In this case, but why would that change when it's above 180 mg and below? But in this case...in the case of the clients that are placed in PRR if somebody has their partner that's considered a reasonable use of services. We always have a nurse that looks everything over and anytime there is something like that it's medically justified and we don't place them in the program then unless they are over-utilizing.

Siri Childs: So, Jeff, are you going to wrap it up?

Jeff Thompson: There was some community comment and then I'll just wrap it up with what we want to do with the next steps.

Deneta Whojenski: My name is Deneta Whojenski(?) and I'm a nurse who works with pain and palliative care. I'm also the president of the Washington Alaska Pain Initiative and a state leader for the Power Over Pain Action Network. Thank you for the opportunity to submit comments to your committee considering the AMDG opioid dosing guidelines for non-cancer pain. This guideline proposes to address an important public health concern for the state of Washington regarding the appropriate and safe use of opioid medications. There's rising awareness of the increasing abuse, misuse and diversion of prescription medications and the consequences of this trend. While it is very important to address this very public health concern, it is equally important to provide solutions that do not contribute to the public health concern of under treatment of pain. A balanced approach to the dual problems of prescription misuse and abuse and the under treatment of pain is the most recommended health policy approach. Many organizations concerned about the best practice approaches to caring for people suffering from pain have raised grave concerns about the AMDG suggested guideline.

The organizations represent the leading state and national pain professional and patient education organizations including the Washington Alaska Pain Initiative, the American Academy of Pain Medicine, the American Academy of Pain Management, the American Pain Society, the American Pain Foundation. All of these organizations have expressed serious and grave reservations about the AMDG guideline and project significant and dire consequences for people affected by pain if these guidelines are followed. We ask that the DUR committee review the attached statements from these organizations when considering any level of endorsement of the AMDG suggested guidelines. Thank you.

Jeff Thompson: Thank you.

Marilee Donovan: My name is Marilee Donovan, PhD RN and I'm going to read you some credentials just because I want to be able to address some things. I've served on the American Pain Society Board of Directors, coauthored the American Pain Society Quality Improvement Guidelines for the Treatment of Acute Pain and Cancer Pain, written two books and multiple articles and chapters on pain management, served as a consultant for the joint commission on their pain standards, coauthored the landmark study that identified under treatment of pain as a critical problem in this country, and I currently serve on the APS AAPM panel with Jane Balentine developing guidelines for the use of opioids in chronic, non-cancer pain. I am also the founder and continue to serve as the regional coordinator of Kaiser Permanente Northwest Regional Pain Clinic which serves patients in southwest Washington. I'm also a Washington resident. So I'm actually speaking as a Washington resident. I would actually like to commend Dr. Franklin and the group on the guideline for its emphasis on some key factors that have been ignored in previous guidelines. The initial emphasis on ongoing risk benefit evaluation, which includes the assessment of pain and function, adverse effects, and behaviors indicative of misuse of medication. This is the truth strength of the guideline. There are three specific areas of the guideline that I feel are problematic to the health and well being of the people of the state of Washington. Specifically these are setting a dose limit, which has no...Dr. Franklin admits it is consensus and there's no real consensus in the nation on that.

Secondly, requiring specialty consultation you ask a question how many patients with chronic pain would need this specialty consultation. Based on national estimates there are between 48,000 and 60,000 Washington residents taking opioids above the dose limit. There are not nearly enough pain specialists to begin to address that problem.

And the third has to do with some confusion in the guideline regarding the concepts of addiction, relative insensitivity to opioids and the general lack of sensitivity to certain types of opioids or certain families of opioids. On page 11 the statement is made that patient variability in response to these EDs can be large due primarily to genetic factors and incomplete cross-tolerance. But the guideline seems to ignore that some patients require extremely large doses of opioids because they are genetically less sensitive to opioids in general or have been trialed on opioids that they're not sensitive to.

In summary, not only are the numerated three areas problematic, but the setting of a dose limit I believe overshadows the important message of the guideline that risk benefit evaluation is ongoing, that there needs to be assessment of the causation of pain, of the effects on pain relief and function both before deciding to prescribe and regularly during the course of opioids in the treatment plan.

This guideline, I feel, will not do what it sets out to do which is to help primary care providers who do not specialize in pain medicine to prescribe opioids safely and effectively. It will instead frighten them into prescribing nothing at all. Thank you.

Vyn Reese: Thank you.

Man: Good afternoon. I'll make it quick. This is good news. I am a public health physician and a primary care physician and I would have to say these guidelines are a godsend. Thank you very much. We implemented these at the Port Gamble [inaudible] Tribe where there legitimately is pain, there's legitimately abuse and misuse. These guidelines have brought some order to the tribe. Okay? What we do in the tribe is we use these as a starting point. Every person who goes on a chronic pain contract per these guidelines gets a mental health evaluation, gets a substance abuse evaluation, and must see a pain management specialist. It does not limit access to pain medicines. What it does is it prevents the misuse and abuse, which is a welcome addition to the tribe and I thank you for doing these. I am a primary care physician. I am not afraid of using them and it is a godsend. Thank you. And I am not representing a drug company.

Vyn Reese: Thank you.

Jeff Thompson: I'll be honest with you. I went up and did a consultation with them and we talked and it was bariatric surgery and I asked him to come. So I asked him. Alright? Alright? I'm guilty. So just real quick I'm just going to...so what we've done over the past four years, as best as we can, it's not randomized, double-blind, placebo-controlled, but we showed you that when you work with the community and give them information, prescription history, which requires to stop and take a big deep breath we reduce ER, we reduce the number of narcotics, we reduce the dose, we increase the referral to DASA related activities, we've actually showed that we saved costs in addition to this. We reduced the amount of prescribers because we inform prescribers of what happens outside their offices. And we're working really closely because the other thing you haven't seen and I'll just show you really quickly, we're trying to better coordinate with DASA, our drug and alcohol colleagues, as well as our mental health colleagues, as well as our chronic disease colleagues because truth be known many of these people have a mental health issue, they have a substance abuse issue, and they suffer from some chronic diseases. Until we start coordinating it unfortunately some untold consequences. Next slide.

Just really quickly you asked about numbers Medicaid population. Here is at least back from May to July one-quarter of '06. So we're looking at 90

to 120, 120 to 180, 180 and above. We're talking in the range of 3,500 clients in Medicaid that we're looking at that are above this standard. So this is one-quarter back a couple years ago. Next slide.

So when you look at these and you look at the number of psychiatric diagnosis as you increase the amount of dose, you increase the likelihood that they carry a psychiatric diagnosis with this and we've seen many of our bipolar and schizophrenics know they are on very large doses of narcotics. That many of our RSN providers don't know about and that's why we want to share information with them. Next slide.

The unfortunate part about it and we tried to do it today and we are actually...we're repeating Gary's L&I. We're actually looking at death certificate data and trying to see in the Medicaid population for this group of people what is happening to deaths? If you just look at straight death because we actually load death certificate data on our administrative data file because we don't like paying dead people claims you can actually track this. And so when you look at, again, one-quarter of '06 no deaths between 90 and 120, 120 to 180 no deaths, but when you hit 180 the deaths go up. Now what we need to do is go in and find out were they related to the narcotic? Because obviously it's non-cancer, non-hospice, but you can have people with some curious chronic illness, you know, that nearing the end of their lives, but I think what you're going to be surprised at is how many unintended consequences we have where they have just been overdosed and then they stop breathing. So we're willing to go through that. Last slide.

What I'm asking is we've shown you all this with the 320 project. We know these people need some help. We know we want to communicate, coordinate and share information with the provider group. So what we're asking you to do is allow us to instead of 10 narcotic prescriptions per month change that to 120 morphine equivalent, review how many prescribers there are within each of the doses so that we can scale this so perhaps we'll start out with sharing information with 120 over when they've got six or more prescribers and then we'll run that. We want to resource this appropriately so they get their medication and we'll share prescription histories with them, which will include not only their narcotics, but full prescriptions, ER and outpatient and hospitalization and so if the provider thinks that they want this prescription to be handed across the counter they get it. But what we're asking them to do is for a scaleable project is we just share this information, stop, take a big deep breath, have the provider review this like we did the 320 project, and then if the provider says, "I want this," we're fine with that. But if they now know some information that they didn't when they first wrote the narcotic prescription then they can have a conversation with their client. And what you saw with the 320 project in the best we can do under all the secular

changes it helps. So that's what we're asking and we'll integrate this also with the Department of Health project that will probably happen in 2010 where you will get actually real time prescription histories for narcotics much like Kentucky for both private, public and castrate, but that's not for at least a couple of years. In the interim we want to just move this project from 10 prescriptions to the 120 poly prescribers and share information.

Vyn Reese:

Thank you, Jeff. There's a real balance here between actively treating pain and also severe public health consequences of too much pain medication. I think we've gone from one extreme to the other and now is the time that we have to think about carefully, you know, decrease the number of opioids that we're prescribing and the amounts. You are right though that some primary care docs are just not going to prescribe opioids. I think that's going to happen. That may be an unintended consequence of the...

Jeff Thompson:

Can I actually talk about that? In the Spokane area we've heard this over and over again, but I can tell you one of the unintended consequences. There was a physician in a PA that were over prescribing, they've had federal charges, they've had to shut down, they lost their license, that dumped over 250 clients in the Spokane area. There have been a number of lawsuits, malpractice suits. So if we don't do something, you know, that also is an unattended consequence.

Let me just address the three issues. On the dose limits, you know, Gary worked very hard to get a representative sample of experts, community, east and west, up and down, primary care...and so while it's not a nationally agreed, you know, sort of stop and take a big, deep breath. It's not a limit. It's just, please, please, take another consideration and that was agreed upon by a group of what, 15 doctors?

Number two, it's referrals. Yes, we don't have enough specialists, but, you know, we can transport Medicaid clients. We will work to get a cadre of good specialists. I've talked to Rick Reese, addiction medicine specialist. We can work on that as we go forward. But if we wait until we have 700 doctor specialists and then we launch then I've got the other problem of having too many dead bodies in Medicaid. Now I'm not over-reacting on that one.

And then lastly, no evidence. Yes, there is no evidence on, you know, is the sky the limit, but I think there's an increasing amount of evidence that we're doing some harm here and all we're asking is, "Can we just produce," stop, take a big deep breath and work with the provider...where the provider is in charge not the agency.

Man: I just wanted to comment that of the 250 people that were sort of loosed on the community because of that individual's practice closing I think 249 of them tried to come to our office and it's a problem. It's a big problem and so I think the good part is it's helpful to...it's helpful to use this like the...like you were mentioning. When you really don't think somebody is appropriate you have more than just, "I don't want to give you the prescription." You've got a guideline to say, "This is what it says." But I really think it's important to move forward like you talked about and for those folks that we think this is justified and this is a good idea and I'm one way or another obligated to go on and get a consultation to have that access. So I think that access is going to be huge and certainly in Spokane it's true. You can't get anybody to see...I can't get anybody in Spokane to see anybody for a pain problem period unless it is directly correlated with a procedure.

If I just want somebody to review a pain program I can't find anybody to do that and I certainly can't find anybody on Medicaid. So I think moving forward to be creative and finding ways to get that to happen is helpful. I don't mind that. I don't mind the help when I have a difficult pain patient. So I think that's great if we can move forward on that too.

Vyn Reese: Dr. Franklin, do you have any rebuttal to all these comments and questions?

Gary Franklin: I don't really have a rebuttal. The feedback that we're getting from doctors is that they really like the guidance center. Again, as Jeff said this is not a limit. This is guidance...take a deep breath at 120 and if the pain and function is improving there is no limit. You can keep moving up. As far as the dose itself the pain doctors of 15 folks actually started out at 90. 90 was their initial dose. We didn't think that would actually be doable because so many people are on much higher doses. So we moved it up to 120 and then there were two folks in the crowd that thought maybe it should be 180, but then Jeff's data with the number of deaths that only occurred after 180...so if you actually want to prevent these deaths from occurring you've gotta start before the dose at which you're seeing the deaths. So I am 98% certain that 120 mg is a reasonable, soft kind of flag to use for the...whether pain and function is improving or not.

[inaudible] most recent information, he's the one who started all of this, the neurologist at Cornell. Most of his patients that he followed for many years have been on not more than 40 or 50 mg a day and so I have no problem with that. You can put every single pain patient in the state as far as I'm concerned when that much of it can tolerate it and stay functional on that amount, but that's not what we're seeing. We're seeing people who are not making it, whose function is not improving and some of whom are dying. So I think this is a very reasonable approach. I look

forward to the APS meeting in Tampa in the spring. I'm going to be on a panel with Dr. Balentine and several other people to discuss the guideline. I look forward to the feedback from the organizations.

Vyn Reese: One other question. The 180 mg dose those are patients that were found dead from opioid overdoses? Or are they just deaths...

Man: No. They are patients who were chronic pain patients.

Man: They are deaths among people that were on opioids and as Jeff said they have not...they are doing a death certificate search right now and review, but they haven't gotten that detail yet.

Man: But there were no deaths below 180. So some subset of those over 180 were likely from...associated with opioids, but they can't say that right now specifically.

Vyn Reese: Probably multiple actors.

Man: Multiple actors.

Alvin Goo: Hi, it's Alvin. So do you have an idea of how many patients were looking at over the 120 equivalent?

Man: It's about 3,500 and what we'll do to make this program work is not take 135 and dump it down. We'll look at the poly prescribing and so 120 and over and then look at, start out with...we'll see who are getting it from 10 or 15 doctors or 5 or 6 doctors or 3 doctors and we'll just march it down. It is a sensitivity specificity. Just even like 10 prescriptions per month that was legitimate for some, but it was not legitimate for others. So at some point we're going to have to make a decision when this is good enough and we'll just keep the education of the guideline up. But the other thing that we'll do in addition to this guideline is the tools that the patients require and restriction or coordination. We're doing a lot more coordination with our case management. We're talking to [inaudible], Children's, mental health. We'll work with the RSNs to make sure the mental health RSNs know and I think, you know, what we try to do with this program because \$35 million went for increasing in treatment—substance and alcohol treatment, this is a nice way of referring them in. It's not always 100% access in some areas, but we doubled the amount in a very difficult population.

Alvin Goo: No, I think that's good. Are you going to be placing a hard stop on the equivalence, or are you going to be providing feedback to the providers saying, "This is what we're finding? Do you want to continue or not?"

Man: The way it would work is the...where we set the people over whatever limit we have. Let's say it's 120 with 6 providers, the narcotic prescription would stop at the pharmacy. Then we would communicate, you know, hopefully that day or the next day the 12-month prescription history, ER, outpatient, and then the physician gets to decide yes or no. If they need an emergency supply we allow emergency supply of narcotics. So in essence it is a hard stop, but the physician or prescriber is in total control. And this is how we ran the 320 project for three or four years now. I think it's been a success, but it's that stop and take a big, deep breath that really is the success of the program. Because if it's just...you know what a guideline does. It's just that. It's a guideline. What we're doing is we're just sharing information now and then the physician gets to decide.

Alvin Goo: And is there going to be any availability or funding for behavioral therapy as far as chronic pain? Instead of referring my patient to a pain specialist I'd rather have availability to a behavioral therapist.

Man: Well, which behavior do you want? It's the chicken or the egg. Is it, "Yes, we have gotten them into DASA related services, which is narcotic and substance abuse management." We will work with the RSNs because again is the schizophrenia driving the narcotic use or vice versa? So we'll work with any provider that's willing to do that. GAU is problematic. They don't have a mental health benefit.

Angelo Ballasiotes: If you treat both of those together you're not going to have good results.

Man: Right. And that's what we haven't done yet. We treat them separately. We treat them like a contract rather than an individual that has a problem.

Man: Right. So is there a way to sort of coordinate that?

Man: Yes.

Man: And later on it would be interesting to find the data as far as, you know, prescriptions, number of prescriptions. Are these chronic medications going out? And the percent of patients that complete the treatment program. I mean they are enrolled in it, but how many continue on?

Angelo Ballasiotes: You can track that pretty well.

Man: Well, the treatment expansion that Dave Mancuso will be monitoring will pull all this together because the legislatures are going to want to know, "Did they get \$35 million plus from value?" So these will all be coordinated. Picking out each individual, you know, sort of...did the

guideline do this? Did the patients require coordination? Did treatment expansion? It's next to impossible.

Man: Can I make one comment? Several people have mentioned the issue of behavioral treatment and mental health stuff. On a whole other realm the state is looking at how we purchase pain clinic services and I think that is really what you were getting at. For example, in Spokane there's plenty of interventionalists, but not a single person willing to actually take care of a patient from a pain management standpoint and we need to look at how we are purchasing these services and to also look at the cognitive behavioral stuff and the physical therapy, reactivation stuff and we need to be looking at how we're doing these services earlier on after say a back injury. And so we're going to be having massive conversations about this because of a recent decision on lumbar fusion from the State Health Technology Program and we can come back and talk about that at some point, but we are looking at how we are purchasing these services in general and I'm looking at it as a broader topic and I think the patients were seeing on these very high doses of opioids really the tip of the iceberg. If you could get to help them earlier on in their situations we'd be a lot better off here.

Angelo Ballasiotes: Yea, the emotional...as the emotional pain and stress increases so does the medication issue.

Jeff Thompson: So we're asking for your sort of recommendations. Is this the proper path? 120 poly prescriber, stop and take a big, deep breath, share prescription, ER, hospital information with the prescriber and the prescriber gets to decide.

Angelo Ballasiotes: You said 3,200?

Jeff Thompson: It's about 3,500, but what we'll do is we'll parse it out by the number of prescribers.

Man: Jeff, I think you had 2,600 or something at 180.

Jeff Thompson: Right. And then there was another 700...

Man: And then another 600 or 700 between 120 and 180 and I wonder if you might want to consider starting the pilot at 180.

Vyn Reese: It looks like to me that's what you should do.

Man: To see how it goes at that level.

Jeff Thompson: Again, what we'll do is regardless of whether we start at 120 or 180 we have to include something so we can resource this. What Siri and I have talked about is 120 is at least the denominator that we get and then you start looking at the number of prescribers. Then you start slicing it above.

Vyn Reese: Let me make sure I understand this. So you have to have both 120 mg of morphine equivalence in a month and multiple prescribers at the same time?

Man: Right. And/or or?

Vyn Reese: So it has to be 120 and more than one? More than two? How many?

Jeff Thompson: What we'll do...I hoped to have this data and I just didn't have the chance to do it is there will be a curve and there will be a few patients that will have 20 to 30 narcotic prescribers in a year that are different tax IDs. We have people going to emergency rooms all over the state, single people getting narcotics. We'll start off with those and we'll just start going down the line. We don't want to start off with 120 morphine equivalent a day and one prescriber. That's probably not the at-risk population. The at-risk population is 120 with multiple prescribers and we have the resources because people have to answer the phone, do the fax, blah, blah, blah, so we'll start with the multiple prescribers, but with the cohort of 120 and over.

Siri Childs: We'll take only what we can handle.

Jeff Thompson: Right.

Siri Childs: And meet our customer service. We have people who are watching our call center statistics day by day... End of tape.