



Washington State Health Care Authority
Prescription Drug Program

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UNOFFICIAL TRANSCRIPT*
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING

June 20, 2007
SeaTac Hilton Hotel
9:00am – 4:00pm

Committee in Attendance:

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

Committee Absent:

Angelo Ballasiotes, Pharm D

Dan Lessler: Of the committee. I was asked to request, since we're in a different location here today and actually, stakeholders are sort of around and about, if you could keep any conversation to a minimum because you're exposed to various microphones and so forth, and things are getting recorded and that makes it difficult. Sometimes the mics pick up background conversations and I suppose also sometimes things are being said that you would rather not have recorded. So just would appreciate the quiet. I think we're going to go around and introduce ourselves so everybody knows who you are and, begin all the way down.

Regina Chacon: Hi I'm Regina Chacon, I'm the program coordinator for the prescription drug program.

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

Elizabeth James: I'm Elizabeth James, I'm a contracting pharmacist for Uniform Medical Plan.

Donna Sullivan: I'm Donna Sullivan, I'm the pharmacy director for Uniform Medical Plan.

Duane Thurman: Duane Thurman, from Healthcare Authority.

Ray Hanley: Ray Hanley, from the Healthcare Authority.

Janet Kelly: Janet Kelly, P&T member.

Ken Wiscomb: Ken Wiscomb, P&T member.

Dan Lessler: Dan Lessler, chair.

Vyn Reese: T. Vyn Reese, P&T member.

Alvin Goo: Alvin Goo, P&T member.

Bob Bray: Bob Bray, P&T member.

Jason Iltz: Jason Iltz, P&T member.

Jeff Graham: Jeff Graham, Healthcare Authority.

Doug Tuman: Doug Tuman, Labor and Industries.

Jaymie Mai: Jaymie Mai, Labor and Industries.

Siri Childs: Siri Childs, HRSA.

Steve Hammond: Steve Hammond, HRSA.

Dan Lessler: Okay, Thank you. I'm just going to turn it over here to Jeff because I know you've got some announcements.

Jeff Graham: We'd like to remind the pharmaceutical industry to not contact our P&T members in their capacity as P&T members. If you have other things to talk to them, that's fine. But as you recall all of our information comes from the evidenced based practice center at OHSU so we would ask you not to contact them if you are trying to talk about P&T issues.

Dan Lessler: So I think the first order of business we wanted to take up had to do with the immune modulators. Just a modification here to the last.

Jeff Graham: Yes, the agencies are requesting that you consider a modification of the motion from our last meeting. As you recall, at that time there was a drug that was almost FDA approved for Crohn's disease which was Humira. And I think it was approved within two days afterwards. So at the time you couldn't make any other decisions except for what was already FDA approved. We're asking if you would look at, it's down where we get to the treatment of Crohn's disease. So this is just a suggestion, this does not have to be done by you. It's up to you that you would say that an FDA approved drug must be included for the treatment of Crohn's disease. And also an FDA approved drug for ulcerative colitis.

Dan Lessler: So, just to be clear for that, continued, restate what Jeff said. Humira now has FDA approval for those two indications, which it didn't.

Jeff Graham: Actually it doesn't. It only has it for Crohn's disease.

Dan Lessler: For Crohn's, okay. So it would just be somewhat rewording our previous motion. Vyn.

Vyn Reese: This is Dr. Reese, so instead of Infliximab we would just say an FDA approved drug must be included for the treatment of Crohn's disease and ulcerative colitis in addition to a self administered agent for other indications.

Jeff Graham: Will that cover it?

Dan Lessler: So are there any comments on or concerns about doing this relatively minor modification?

Jason Iltz: This is Jason. Just for clarification we should probably say after Crohn's disease also say and an FDA approved product for ulcerative colitis.

Dan Lessler: Thanks, that makes it clearer. So I think it might help, and then if you'd be willing just to put this in the form of a formal motion.

Vyn Reese: Can you just scroll it down a little bit so I can read the whole. So I'm going to issue a revised motion. After considering the evidence of safety efficacy, effectiveness in special populations, the use of targeted immune modulators for the treatment of immunologic conditions, for which they have FDA indications. I move that etanercept, adalimumab, abatacept, rituximab, and infliximab are safe and efficacious. I probably should include, why don't you just, it's adalimumab.

Dan Lessler: It's on there, adalimumab.

Vyn Reese: Is it up? Okay, it's already there. Are safe and efficacious. No other Targeted Immune Modulator medication is associated with fewer adverse events in special populations. An FDA approved product must be included for the treatment of Crohn's disease and an FDA approved product for ulcerative colitis, in addition to a self administered agent for other indications. Etanercept must be included for the treatment of juvenile rheumatoid arthritis. These medications cannot be subject to therapeutic interchange in the Washington preferred drug list.

Dan Lessler: So is there a second to that?

Ken Wiscomb: I'll second again.

Dan Lessler: Okay, second. Any further discussion? All those in favor say , "I."

Group: I.

Dan Lessler: Opposed same sign. Okay. So the modification passes. We can move on. So I think the first set of business has to do with the drug, the scans on a number of different classes of drugs.

Jeff Graham: That's true. This is Jeff Graham. We're doing these for the first time and we believe that most of them, or all of them have sufficient evidence to use them as an update. But if the committee feels that it's not sufficient evidence, they can ask the agencies that we want a more full update. So please consider these when you're going through them that if there is enough, you can say this is an update.

Dan Lessler: So Jeff do you want to take these each one at a time and then have a motion as to whether or not the scan is adequate.

Jeff Graham: You should do a motion for each one.

Dan Lessler: Yea, okay.

Jeff Graham: And I'm asking, is Tracy Dana on the line?

Tracy Dana: Here too.

Jeff Graham: Pardon?

Tracy Dana: Kim is here too.

Jeff Graham: Oh and Kim is, both of you are there?

Tracy Dana: Yea.

Jeff Graham: Great, okay, so we can get started. And we have, the first one up is skeletal muscle relaxants.

Tracy Dana: Right, so we did a scan of the, in December of 2006. Trying to find out if there was enough evidence to do an updated report. Last report was completed in May 2005 and that was a second update. So the search that we conducted was actually from November 2000 to December 2006. Jeff, does everyone there have a copy of the scan?

Jeff Graham: Yes they do, and we have some very short slides that I put together.

Tracy Dana: Okay, great. So you have the population for skeletal muscle relaxants for adults and children. [inaudible] skeletal [inaudible]. And then we have the list of included drugs. The important thing that I want to point out is there were oral preparations only. That's important because when we did this scan, we searched MEDLINE only. This was just supposed to be a quick check to see what new evidence there was. We identified 144 citations, however of those about 40% of them were for injected [inaudible] drugs. [inaudible] baclofen. So those were not considered includable based on our criteria [inaudible] report.

So after we did the scan we got these 144 citations and looked through them, and it turned out that there were only three that were potentially relevant and includable. The scan that you have actually includes four, but in looking it over again, I saw that one of them was placebo controlled trials of diazepam, and that would not actually meet inclusion criteria. That would be number three on the potentially relevant new studies list. So that one actually doesn't even count.

So that leaves us with two active control trials, and one systematic review. The systematic review is a [inaudible] review, but it also included the injectable drug, and that did not find any evidence for the oral drug or they found insufficient evidence to make any sort of comparative claims regarding effectiveness or safety. The two active control trials were cyclobenzaprine and tizanidine. So I don't know Jeff, what else I can say if there's any questions I'll try and answer them or if there's anything else you'd like me to cover. You know.

Dan Lessler: Okay, so we're just seeing if there are any stakeholders here who signed up to speak specifically to the muscle relaxants. And in the mean time I think if the committee could just look at the prior motions which is from June of 2005. So it doesn't appear that there's, at least on the basis of the scan, there's anything compelling that really impacts on the previously adopted motion.

And it looks like, let me just confirm this, it appears that nobody, is there anybody who wanted to speak to the skeletal muscle relaxants here? Any stakeholders who, I don't have anybody signed up. No, okay. Are there any questions or comments from the committee for the folks at OHSU regarding the scan? Okay, and given that there aren't any questions or comments, and considering that the previous motion, I'm wondering if anybody would like to put forth a motion at this point or if there are any comments. Again I think what we really need to do is accept the scan as an adequate update, and then probably as well indicate that if we're not going to change our previous decision that that in fact is the case. That that will stand from June 2005.

Bob Bray: So, I would, I could put it into a motion if there's no discussion but I would suggest that we accept it and that we also put forth the same motion that we made previously, unchanged.

Dan Lessler: Any, so why don't you put that into motion format, that'd be great.

Bob Bray: So I move that the prior motion for skeletal muscle relaxants be put forward again today.

Ken Wiscomb: I'll second that.

Dan Lessler: Any further discussion?

Man: I'm wondering though, for the motion it says that if we should include tizanidine, now that it's also generic and put that in the motion for the indication of muscular skeletal relaxants. Methocarbamol, cyclobenzaprine, metaxalone, orphenadrine, and then also add tizanidine. Is that necessary?

Man: I think, for the indication of spasticity tizanidine and baclofen are found to be.

Dan Lessler: So all those in favor of the motion say "I."

Group: I.

Dan Lessler: Opposed same sign. Okay, so the previous recommendation stands. And Jeff, do you actually need us to specifically say that we accept the update or is it adequate enough that we had the discussion and on the basis of the update are.

Jeff Graham: I think you should make a motion to say we accept this as an update.

Dan Lessler: Okay, could we just have a, would somebody be willing to make a motion that we accept this scan as an update for this drug class?

Jason Iltz: This is Jason. So I move that we accept the scan as an adequate update to the skeletal muscle relaxants.

Dan Lessler: Is there a second? All those in favor say, "I."

Group: I.

Dan Lessler: Opposed same sign. Okay. So I'll go back and see what's next here. So next are the Anti-Emetics. Is this going to be?

Jeff Graham: Kim is on the line.

Dan Lessler: Kim is this?

Kim Peterson: Yes.

Dan Lessler: Okay, so actually give us a second here, we're just going to get the, I guess we don't need it.

Jeff Graham: She can start.

Dan Lessler: You can go ahead, just start right in.

Kim Peterson: Okay, so I'm going to be summarizing the findings from our November 2006 preliminary update of the literature search for the drug class review of newer Anti-Emetics. This is a search of MEDLINE, the FDA website, and the Health Canada website. That went from February of 2005, which was the date of our last search, through November of 2006. And there was two randomized control trials, indications, and safety alerts for the same drugs and populations as last time. And we were also looking to see if there were any drugs in the class, been approved since our last review.

And the truth of the summary of what we found, there were a total of 19 new trials we deemed potentially relevant and of those, seven were head to head trials. The best were placebo controlled. Among the seven head to head trials, there are some things that I think are worth pointing out.

First, two of the head to head trials compared the orally disintegrating tablets of Ondansetron to the IV form of Ondansetron in children that were undergoing chemotherapy. And then adults post operatively. And the significance of these trials, that these are the first trials to directly compare the orally disintegrating tablets, other Anti-Emetics. Previously all we had

were placebo controlled trials that the orally disintegrating tablets [inaudible]tron.

And then next I wanted to point out that Meyer 2005 trials represent the first head to head trial of newer Anti-Emetics as used to treat established nausea and vomiting. Though previously there were trials of using these drugs to prevent [inaudible] operative nausea and vomiting but none to treat it after [inaudible] has failed. And this new head to head trial compares IV forms of Dolasetron to Ondansetron, using need for rescue medication as a main measure of efficacy. And although it's not mentioned in the, I'm assuming that it mainly focuses only on [inaudible] efficacy endpoints.

And then the last head to head trial I want to point out is the Janicki 2006 trial of dolasetron versus granisetron for the prevention of postoperative nausea and vomiting in adults. Previously our [tape cuts] Dolasetron and Granisetron that were based primarily on indirect findings, so this trial possibly would offer an opportunity to strengthen our conclusions about particular comparison. And then as for the placebo controlled trials, there's just one thing I wanted note there.

We found two new trials of Aprepitant, they are both focused on using it as add-on to 5HT3 antagonists. So they don't address the previous question about using it as monotherapy. So though the only trials we have about Aprepitant placebo controlled is this add-on [tape cuts]. So as far as we could tell from the abstracts of the MEDLINE search there isn't any new trial evidence that would address the previous gaps, evidence in the areas of use in pregnant patients or in patients undergoing radiation.

And also there were no new trials [tape cuts] Palonosetron, which is the newest 5HT3 antagonist and which, as you may recall, was found to be superior to IV Ondansetron in one previous head to head trial of the [tape cuts] undergoing chemotherapy. As for the findings from our searches of the FDA and Health Canada websites, we didn't find any indications of any new drug approvals.

As for new indications, we found the Aprepitant got approval for use in patients undergoing moderately, as well as, severely emetogenic chemo. And as for new safety alerts the only one we found was about Dolasetron and it was from the Health Canada website. And the new notice indicated that Dolasetron should now be considered contraindicated for prevention of postoperative nausea and vomiting, due to some reports of cases of some cardiovascular adverse events in this population.

So those are the only things that I wanted to point out about our [inaudible] scan. The participating organizations of DERP decided against

going forward with a full update of this drug class at this time. So the next time we're going to look at it will DERP be, I think in a year, so November of 2007 we'll do another scan. So anybody have any questions?

Dan Lessler: Thanks Kim. Any questions for Kim? OHSU. The scan.

Jeff Graham: Dan, this is Jeff Graham. I just wanted to point out to Kim that this committee excluded Aprepitant from this class the last time that we considered it.

Kim Peterson: Okay.

Kim Peterson: Are there? It doesn't, there would be any reason, any new evidence to support adding it.

Dan Lessler: Having, it appears that there are no stakeholders that wanted to speak to the Anti-Emetic class, is that correct? Okay. And if members of the committee could look at our last motion which is from February 15, 2006. And I guess two motions to consider here. One is a motion to accept the scan as an adequate updated and the second is regarding the previous motion, and whether any changes are needed to that or whether it can stand. So with respect to the scan as an update is there a motion to accept the scan as an adequate update on the Anti-Emetic class?

Man: I would propose that we accept the scan as an adequate update.

Dan Lessler: Okay, is there a second?

Man: Agree, so second.

Dan Lessler: And all those in favor, say "I."

Group: I.

Dan Lessler: Opposed same sign. Alright, so we accept the update and with respect to the specific motion, is there a motion regarding the Anti-Emetic class here?

Bob Bray: Bob Bray, I would move that we reaccept our prior motion and put that forward today.

Vyn Reese: [inaudible] Reese, I second that.

Janet Kelly: Yea I have, this is Janet Kelly, I have a question I guess about the statement that Palonosetron can be subject to therapeutic interchange within their right of administration. Since it's an IV drug, are we talking

about clinic administered medications? I mean because most patients would not be going home and told to self administer Palonosetron or. So I'm not really sure why we included that in last time. I think, does it include clinic administered medications? I did not think so.

Donna Sullivan: No, they don't. This is Donna Sullivan. It would only be a prescription that's picked up in an outpatient pharmacy.

Dan Lessler: As it is it speaks for itself and obviously it's speaking to the therapeutic interchange actually of the four agents, so one clearly could not be interchanged in that way I suppose.

Janet Kelly: Yea, it's probably not an issue as long as, I just wanted to clarify that we weren't talking about clinic administered because that would be a whole another kettle of things. So it's probably a moot point at this point, because I can't imagine a patient walking in to the pharmacy with a prescription for Palonosetron IV. And if that's the case the pharmacists need to change it anyway. So let's give them the power to do that.

Dan Lessler: Alright, so it sounds like that's okay. So the motion's on the table to basically let our previous motion of February 15, 2006 stand. It's been seconded. All those in favor say, "I."

Group: I.

Dan Lessler: Opposed same sign. Okay, so we can move on. Next I believe are the Triptans.

Kim Peterson: Yes, that's me again, Kim.

Dan Lessler: Okay, go right ahead.

Kim Peterson: Alright, so the preliminary update scan of the drug class review of triptans was completed in March of 2007 so just a couple months back. And to recap on this one, this drug class review has been fully updated twice since it was originally done back in 2003. And the most recent full update was completed in November of 2005. So our search for this current preliminary update scan went through May of 2005 through March of 2007. Again we were [tape cuts] for new randomized controlled trials. [inaudible]. And then searching the FDA website [tape cuts] Canada website for the information about new indications, new drugs, or new safety alerts. So we, from our MEDLINE search we found a total of 18 new potentially relevant studies and [tape cuts] those in the appendix of the report.

And the majority of the new [tape cuts] were placebo controlled and were exploring alternative usages of triptans such as alternatives to the standard use for moderate to severe migraine pain. And the alternative usages include [tape cuts] using triptans [tape cuts] early treatment of mild pain. And the studies involved Eletriptan, Rizatriptan, or Sumatriptan. And then there was at least one for specifically morning migraines and then specifically probable migraines, both with Sumatriptan.

So there was only one new head to head trial, and it compared Eletriptan tablets to Rizatriptan wafers in patients with moderate [tape cuts] severe migraine pain. And that's the Lainez 2006 trial that's on page nine of the preliminary [tape cuts]. But otherwise there were no new head to head trials of Eletriptan compared to conventional unencapsulated Sumatriptan which still seems to be [tape cuts] very ongoing question in a head to head trial comparing those two directly would be the best way to resolve that ongoing question. But we didn't find any new trials of that comparison.

In terms of the results of our searches of the FDA and Health Canada websites, we found no new triptans, no new indications for existing triptans, but we did find a few new safety alerts. One warning contained some additional types of adverse events that have been observed in patients taking ingestible Sumatriptan. And then the other related to all triptans and one against taking them in combination with SSRI's and SNRI's due to the concerns about the onset of serotonin syndrome. So those are the only comments I have about our [tape cuts] update scan for this drug class review, triptans.

Dan Lessler: Thanks. Actually there are some stakeholders that are signed up to speak, but before we go to the stakeholders I was going to ask if any members have specific questions for Kim.

Bob Bray: This is Bob Bray. I just wanted to clarify that the new warning about triptans and SSRI's and SNRI's are cautions, not contraindications, correct?

Kim Peterson: You know I'd have to look at the report. I don't have that in front of me, but what, is there a specification in the report about that?

Dan Lessler: In just looking at the safety alert it doesn't mention contraindication. I don't see anything other than the discussion.

Kim Peterson: Okay, I'm going to have to. I'm not at a computer. Could we put that question on hold and can I come back to that?

Man: It's a warning.

Dan Lessler: Sure. It's a warning. Okay. So maybe we could just confirm that.

Kim Peterson: Okay.

Dan Lessler: Thanks, any other questions? Okay, there are some stakeholders that are signed up to speak. And the first is Ross Arno from Merck. I wanted to ask, in addition to identifying yourself and any affiliations, or if you're sponsored by any company if you'd let us know and then as well please limit your comments to three minutes.

Ross Arno: Thank you committee member. My name is Ross Arno, I'm employed by Merck and Co. Neuroscience where I've served for 10 years in the neuroscience franchise. I'm a scientific advisor for the western United States and would like to point out some the attributes of the product. And for clarification I have some GSK people over here. The serotonin syndrome warning was added to all labels last summer. Mainly for dose escalation, but it is attributed to SSRI's, SNRI's and 5HT agonists as well. With Maxalt the Rizatriptan benzoate, we've been on the market nine years this June and I wanted to review some studies briefly, I know we have a three minute time frame.

We are indicated for acute migraine [inaudible] and adults over age 18. We're not for prophylactic basilar hemiplegic migraine or cluster and some of our studies I'd like to go over. We've done IHS studies over the last few years. We have four primary pivotal trials where we looked at the pain relief at different intervals. 20% response rate on the product, 10mg at 30 minutes, 46% response rate at one hour, and 77% response rate at two hours with a mean average looking at Kaplan-Meier analysis of 72% response rate pain relief at two hours on 10mg of the product.

There's no interactions noted on commonly prescribed medications. We looked at Paroxetine, oral contraceptives, no interactions noted whatsoever on that. We also recently looked at two additional studies we did looking at pure menstrual migraine and menstrually associated migraine which was defined by the IHS in 2004. And we found at two hours the pain relief response was 70 to 73%. More importantly, 24 hours out people were not allowed to use any rescue or other 5HT agonists within two to 24 hours. 46% pain relief at 24 hours out at the endpoint for menstrual migraine associated symptoms as well.

So, also looking at the dosing, we've changed our packaging in recent years from quantities of six to quantities of nine. We offer a 5mg formulation which is specifically for people on Endaural[?], rapid metabolizes at MAOA and so the [inaudible] you see plasmid concentration is increased 70%. So that's a 5mg dose although 10mg is recommended starting dose. So you can do 10mg every two hours, 30mg

in a day. For those on Endaural, 5mg three times a day up to 15 maximum. I want to thank you very much. Any questions whatsoever?

Dan Lessler: Question? No, thank you.

Ross Arno: Thank you sir.

Dan Lessler: Next is Jennifer Brzana. I'm sorry if I.

Jennifer Brzana: It was perfect. Thank you for the opportunity to address you this morning. My name is Jennifer Brzana, a medical scientist with Glaxo Smith Kline. I'm speaking on behalf of Sumatriptan, the most widely studied migraine medication worldwide. It's been used to treat over 800 million migraine attacks and is widely used in the Medicaid market. As we've discussed before at this meeting, Imitrex offers unsurpassed pain free efficacy. It is the fastest acting oral triptan on the market, and it's the only triptan available in three formulations. But specifically there are two points I would like to make today regarding the data you were looking at in the OHSU triptan reports.

The first point I'd like to make comes from update number three of the OHSU triptan report, dated November 2005. This report provided an excellent comparison to the triptan studies using both internal and external validity criteria. However on page 28, table 13, the report concludes that Rizatriptan 10mg is superior to Sumatriptan 100mg for various outcome measures. This conclusion is based one study, that included non-responders to Imitrex, while excluding patients with prior exposure to Rizatriptan thereby introducing study bias in favor of Rizatriptan. Four other head to head studies which have been excluded from the OHSU triptan report have failed to confirm the superiority of Rizatriptan over Sumatriptan. Since other important outcomes were not examined in the one study reviewed such as 24 hour sustained pain relief, the report concludes that the evidence is insufficient to judge the advantages and disadvantages of Rizatriptan versus Sumatriptan.

Point number two pertains to the preliminary scan report. Specifically page eight. Data from the ASSET trial was included in this scan report which found Excedrin to be superior to Sumatriptan 50mg for the treatment of migraine. It's important to note that patients in this study who vomited in greater than 20% of their attacks or required bed rest for greater than 50% of their attacks were excluded from this study, potentially introducing bias. With the exception of patients with severe head pain at the time of treatment, most had no migraine associated symptoms with their attack and may well have been treating tension type headache. Which would explain the lack of response to Sumatriptan.

In addition it's important to remember that Acetaminophen containing compounds are the second highest cause of medication overuse headache according to a report done by Bigal et al. in 2004. In consideration of the well documented efficacy and safety data for Sumatriptan, which is all covered in the OHSU triptan report, coupled with the multiple formulations available, it's recommended that Sumatriptan be maintained in the Washington state Medicaid Formulary in all formulations. Thank you.

Dan Lessler: Are there any questions? No, thank you. And finally, Christopher Conner from Pfizer.

Christopher Conner: Christopher Conner, and I am sponsored today by Pfizer. I'd like to thank you, Mr. Chairman for the invitation to come speak with all of you today real quickly about Relpax. I've got really two quick points to make.

The first is about the scan report. And there are no data that I saw on the scan report that was dated March 2007 that contradicted the Relpax evidence cited in the last full triptan report. And that evidence cited multiple, well designed head to head studies that showed that Relpax is still the only triptan to show superior efficacy in repeatable studies versus Sumatriptan 100mg. As in my previous testimony, I'd like to remind the committee to consider a close reevaluation of the DERP encapsulation meta-analysis study. The findings of which were presented in page 15 of the last full update. To my knowledge, that particular analysis still has yet to meet the rigor of a full peer review. If you look at the results of that particular meta-analysis on page 15, you examine those box and whisker plots, you'll see that the 95% confidence intervals for both Sumatriptan 100mg and Eletriptan 40mg both cross in the encapsulated and the unencapsulated studies that were a part of that particular graph. So that results suggest that encapsulation doesn't appear to have any significant impact on the efficacy of both of those agents. So in light of these evidence I recommend that the committee consider maintaining Relpax as a preferred agent on the Washington PDL list. Thank you.

Dan Lessler: Thanks, any questions? Okay, thank you. Any comments or discussions, again I think for the committee to, we're looking here at two motions. One is to accept the scan as an adequate update and the other would be a motion speaking to our previous motion regarding this drug class and whether or not it stands.

Donna Sullivan: Dan this is Donna Sullivan. I just want to ask, when you make your motions can you refer to the date of the previous motion that you're actually referring to, just so we make sure that we always keep the right one?

Dan Lessler: Okay.

Donna Sullivan: Thank you.

Dan Lessler: So the most recent motion on this is from August of '06. So first with respect to the scans is there a motion to accept the scan as adequate as an update?

Vyn Reese: Dr. Reese. I would move to accept the scan as an adequate review.

Bob Bray: Dr. Bray, second.

Dan Lessler: Alright, any discussion? All those in favor say, "I."

Group: I.

Dan Lessler: Opposed same sign. Okay, and now with respect to the motion itself.

Bob Bray: Dr. Bray, I would move that we again put forth the motion, the same as previously moved on August 16 of '06 for the triptans.

Dan Lessler: Is there a second?

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

Dan Lessler: Any other discussion? Okay, all those in favor please say, "I."

Group: I.

Dan Lessler: Opposed same sign. Okay, so the previous motion stands and we can move on to the next class which I think is calcium channel blockers. Right, calcium channel blockers. So is this Kim, again?

Kim Peterson: Yes.

Dan Lessler: Great, you're on a roll.

Kim Peterson: Okay, so we conduct [tape cuts] preliminary scans of literature for the drug class review calcium channel blockers back in December 2006. And again to recap, this drug class was reviewed back in 2000 and we updated twice since then. Most recently is March of 2005. And so for the preliminary updates then, we searched MEDLINE from February of 2004, with end date for the last update through December of 2006. Looking specifically for new potentially relevant randomized control trials. Then scanned the FDA website and Health Canada website for any new indications, new drugs, and or new [tape cuts] alerts for any drugs in this

class. So we, from our MEDLINE search we found a [tape cuts] of 24 new potentially relevant publications and those are listed in appendix A of the [tape cuts] report.

And overall the majority is just new publications [tape cuts] involve use of calcium channel blockers in patients with hypertension. And a large number of the new publications simply represent additional analyses about [tape cuts] in high risk [tape cuts] subgroups [tape cuts] hypertension patients. From trials that are already included in the March 2005 report. So, such as ALLHAT, INSIGHT, CONVINCENCE, INVEST. Those are some examples of the pre-existing trials for this [tape cuts] scan.

We found subgroup analyses for. And I noticed that assessment of calcium channel blocker use in patients with comorbid hypertension and type two diabetes seems to be a common theme among new hypertension publication. There were also a couple new studies of patients with angina and one of them is a [inaudible] one year follow up study of patients taking Verapamil which may very well be the longest term study available for this population. I just wanted to point that out.

There were also a couple new studies in patients with arrhythmia, and these compared either Diltiazem or Verapamil to other active drugs. We already have some head to head trials that directly compare those two calcium channel blockers, Diltiazem and Verapamil so it's unclear what these two active control trials would add to that evidence.

As for the results of our searches of the FDA and Health Canada websites, we found no new drugs, but noted that Bepridil was discontinued due to ventricular arrhythmias.

As for new indications, September of 2005 angiographic documented coronary artery [tape cuts] was approved by the FDA as a new indication for Amlodipine. And you may have noticed that there was at least one new study in the preliminary of, and appendix that was evaluating the use of Amlodipine in this population. Which wouldn't meet our current criteria, but we anticipated that if this report is ever updated, that that population might be added [tape cuts] DERP.

And then in terms of new safety alerts, note that there were several for multiple calcium channel blockers that all were [tape cuts] new requirements to strengthen language on [tape cuts]. Prorated rhythmic effects. And so those are the only things I thought that needed to be pointed out about our [tape cuts]. Any questions?

Dan Lessler:

Great, thanks Kim, and questions? And it appears that nobody signed up to speak to this class. Is that accurate? Okay. Once again, two motions. First

to accept this scan as an update, and then looking at our previous motion and whether or not that should stand.

Patti Varley: This is Patti Varley, I move that we accept the scan.

Vyn Reese: It's Dr. Reese, I second.

Dan Lessler: [inaudible] accept the scan as an adequate update. I think that's the wording we're using. Okay, any other discussion?

Alvin Goo: Hi it's Alvin Goo. Wondering if we should also, in the wording include generic Felodipine.

Dan Lessler: First did we just vote on accepting the scan here?

Alvin Goo: Sorry.

Dan Lessler: So all those in favor of accepting the scan as an adequate update please say, "I."

Group: I.

Dan Lessler: Opposed same sign. Okay, so now we can move on to the motion itself. Alvin when you bring up that, your point again was.

Alvin Goo: If we could include generic Felodipine.

[end side A]

Dan Lessler: As a preferred non-dihydropyridine.

Alvin Goo: Did we include it, yea. Because we specifically [inaudible].

Dan Lessler: Those two.

Alvin Goo: Two.

Dan Lessler: Right. The only problem before was that we, Amlodipine has been approved for angina and Felodipine hasn't. So it's like it's a complex issue. Though Felodipine is a great drug for hypertension. And so it's like, would you, if somebody was on, had angina and was on Amlodipine, would they automatically have Felodipine therapeutic interchange. If both were on the preferred drug list they wouldn't, wouldn't have to. So you're just saying add it. Okay. That's reasonable.

Any other comments on Alvin's suggestion to add Felodipine, specifically?

Bob Bray: This is Bob Bray. I just wonder if under the list of drugs reviewed we should eliminate Bepridil since it's been removed. Just remove that from the list of drugs reviewed.

Dan Lessler: Okay.

Bob Bray: Because we really haven't reviewed it if it's removed.

Dan Lessler: So Alvin do you want to, since you made the modification would you like to make the motion?

Jason Iltz: This is Jason. Can we clarify too, the previous motion. It's written like that in one place, and then on the actual list here it's two separate paragraphs. And so, not that it really says anything much different than that, but when you look at the preferred drug list, the '04 that we're working off of is a little bit different than what we have up there.

Donna Sullivan: Jason I think what you're, this is Donna, I think what you're seeing is the first paragraph on the back is the motion from the time before, and that the second paragraph is the actual motion that we made at the last meeting.

Dan Lessler: So it's really just that second paragraph that we're looking at.

Jason Iltz: Okay.

Dan Lessler: Okay.

Jason Iltz: And then can we spell Verapamil correctly in the motion?

Woman: We want it to be the same, we have to spell it wrong.

Man: Correct. Oh, yea, no. It's all another motion.

Alvin Goo: This is Alvin. I move to, the P&T recommendation for calcium channel blockers. After considering the evidence and efficacy and safety, I move calcium channel blockers be considered two subclasses, the dihydropyridines and non-dihydropyridines. All generic forms of Verapamil and Diltiazem are to be preferred non-dihydropyridines and Nifedipine XR and Amlodipine and Felodipine are to be the preferred dihydropyridines and all calcium channel blockers can be subject to therapeutic interchange within their respective subclasses.

Janet Kelly: Janet Kelly. Alvin I have a question about, I understand the desire to add Felodipine to the dihydropyridine. My question is do we need to specify that we have to have Nifedipine XR, Felodipine, and Amlodipine. I know we wanted Amlodipine but do we need all three or can we have either Nifedipine XR or Felodipine.

Alvin Goo: Well I think as far as Nifedipine, or the non-dihydropyridines. There's not a whole lot of great head to head, so I think as far as hypertension and angina, even though Felodipine doesn't have an FDA approved indication, we have used it for that case with good success. So I think it would be, since all three are generic, I don't see why it shouldn't include all three. But I'm open to other suggestions.

Man: Does XR mean anything, or just long acting Nifedipine? It sounds almost like a type of, a branded generic almost. I mean I'd just say long acting Nifedipine, Amlodipine,.

Alvin Goo: I would accept that.

Dan Lessler: If you'd just put Felodipine up above with all generic forms of Verapamil, Diltiazem, and Felodipine are to be preferred and then.

Man: Inaudible.

Dan Lessler: Right, I'm sorry, forget that. Sorry. Okay. Are there any other comments? So, maybe Alvin you want to read the motion one more time here? And then we can have it seconded. It's right up there. And Donna we still need to spell Verapamil correctly.

Donna Sullivan: Is that right?

Man: Inaudible.

Dan Lessler: Okay.

Alvin Goo: I actually don't have my reading glasses on.

Dan Lessler: Okay, I'll read it for you. After considering the evidence of efficacy and safety, I move calcium channel, and this is on behalf of Alvin Goo, I move calcium channel blockers be considered two subclasses, the dihydropyridines and the non-dihydropyridines. All generic forms of Verapamil and Diltiazem are to be preferred non-dihydropyridines and long acting Nifedipine, Amlodipine, Felodipine are to be preferred dihydropyridines. And all calcium channel blockers can be subject to therapeutic interchange within their respective subclasses. So, is there a second?

Man: Second.

Dan Lessler: Okay. All those in favor say, "I."

Group: I.

Dan Lessler: Opposed same sign. Alright, thanks. So finally we have the ACE inhibitors. And Kim, are you?

Kim Peterson: Yea this is going to be presented by Susan Carson.

Dan Lessler: Oh by Susan, okay Susan, thanks.

Kim Peterson: Yea, so she's going to call in from a different location. I'm going to hang up and give her a quick call and then she'll call you. So it'll be one minute between, a little break of one minute before she gets on the phone.

Dan Lessler: Does Jeff have your number in case we needed to get back to you if anything happened?

Jeff Graham: I do have her number, and I also have Susan's number.

Dan Lessler: Okay, great, thanks a lot Kim.

Kim Peterson: So, hope these presentations have been helpful.

Dan Lessler: They've, it's been very helpful.

Kim Peterson: And I'll let Susan know that you're ready for her. Thanks, bye.

Dan Lessler: Thanks, bye. Did she call [inaudible]? Susan are you ready?

Susan Carson: Yes, I am.

Dan Lessler: Thanks Susan, this is Dan Lessler. You can go ahead and start right in.

Susan Carson: Okay, thank you. I'm presenting the update scan on the ACE inhibitors report. I'm hearing an echo, is there a way to get rid of the echo?

Dan Lessler: We don't have the echo here, so.

Susan Carson: Maybe the phone is too close?

Man: No, we're coming through a system that I don't know, could be.

Dan Lessler: It could be the connection. I mean if it, do you want to try hanging up and calling back?

Susan Carson: Yea, I would. I'll call you right back, thanks.

Dan Lessler: Why don't you go ahead and let's see if that helps.

Susan Carson: I think that's better. Oh, no I still hear it but I'll just ignore it.

Dan Lessler: Okay.

Susan Carson: Okay.

Dan Lessler: You can go ahead.

Susan Carson: Okay, great. So this is the ACE inhibitors update scan. The last report was finalized in June, 2005. And we did this update in February, 2007. So, to sort of review the key questions briefly, we included adults with hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, and recent MI. We didn't include trials that only had blood pressure as an outcome because it was considered an intermediate outcome measure. So the trials had to include outcomes like mortality or improvement in symptoms in heart failure. So the results of our scan showed no new ACE inhibitors. There was a new indication from the FDA for perindopril for reducing mortality and MI in patients with fatal coronary artery disease. And then there are a few new safety, some new information about safety. There was an FDA alert issued in June, 2006 for the entire class. And this was for increased risk of congenital malformations in infants whose mothers had taken an ACE inhibitor in the first trimester. So the pregnancy category hasn't been changed because of this information. It's still category C in the first trimester, and it's D in the second and third trimesters. And the reason it wasn't changed was because the number of cases was small, and because the FDA said the information came from only one observational study and hasn't been replicated yet.

There are also some new precautions and warnings added to the lisinopril label. One is about nitritoid reactions in patients who were being treated with injectable gold and an ACE inhibitor. Another warning about diabetic patients being, that they should be monitored closely for hypoglycemia, especially in the first month. And then there was some changes to the head and neck angioedema section that was revised to include warning about rare fatalities associated with laryngeal or tongue edema. So the warning says that patients might need prolonged observation when there's swelling of the tongue, even in the absence of respiratory distress. Another warning is in the hepatic failure section, revised to include a warning about rare

cases of a syndrome that starts as jaundice or hepatitis that can progress to hepatic necrosis or death.

So moving on to the trials that we identified in our literature search. There were 23 that we considered potentially relevant. They appear to meet inclusion criteria by a review of the abstract. And if you have the report there, the full text of the abstracts are attached to the back of the report.

Dan Lessler: Yea, we have that.

Susan Carson: You do, great, okay. So I'll just briefly summarize them. We found no new head to head trials. And many of the citations are for subgroup and secondary analyses of large trials that we already have included in our report. There are three reports from the ASK trial. ASK is the African American study of kidney disease. And it had three arms, ramipril, amlodipine, and metoprolol. Previously they looked at all the three drugs combined. They reported results that way. This new report looks at the effect of each individual drug on end-stage renal disease and death. And there's a couple of other new analyses from ASK that look at health related quality of life and cardiovascular events. Also there's four new reports from ALLHAT. ALLHAT included lisinopril, amlodipine, and a diuretic. New reports look at coronary events and safety outcomes. Also the incidence and predictors of angioedema. Renal outcomes in high risk patients, and an analysis that stratifies patients by whether or not they had diabetes.

And then there's a new subgroup analysis from the PROGRESS trial, which was perindopril, which looked at vascular events in the subgroup of patients who had atrial fibrillations. And then a report from the HOPE study of ramipril. HOPE was originally, had 4.5 years of followup in the primary report. This new report adds an additional 2.6 years of followup. And then a subgroup analysis from EUROPA, which was perindopril. Looks at the subgroup of patients with diabetes, and there's also a report on the influence of risk factors on benefit of treatment. And then for trandolapril, a subgroup analysis of the PEACE trial looks at the affect of treatment on patients with reduced renal function and whether it was different from the overall group. And the last one to mention is the DREAM trial, which measured the incidence of diabetes related to ramipril. It looked at ramipril for the prevention of diabetes.

So that's the new information that we found.

Dan Lessler: Great, thanks Susan. Are there any questions from committee members for Susan? Okay I think we have one stakeholder signed up, Bill Beckman.

Bill Beckman:

Good morning everyone, my name is Bill Beckman, I'm the director of corporate accounts with King Pharmaceuticals. I'm pinch hitting this morning so bear with me. I wanted to talk to you this morning just briefly about Altace, and I know, you know everybody's heard of the HOPE try and so on. But I just kind of wanted to reiterate. First of all, Altace, or ramipril, is indicated for the reduction in risk of MI, stroke, and death from CV causes in patients aged 55 years or older who are at high risk of these events either because of a history of CV disease or because of diabetes, plus at least one other CV risk factor. It's also indicated for hypertension and heart failure post MI. The heart outcomes prevention evaluation, the HOPE study, evaluated the long term effects of ramipril in reducing the risk of the primary outcome, which was a composite of death from CV causes, MI, and stroke, as well as each outcome separately. The HOPE study was a multi-center, randomized, placebo controlled, two by two, factorial designed, double blind study conducted in almost 9,300 patients who were aged 55 years or older and considered at high risk of developing a major CV event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that was accompanied by at least one other CV risk factor.

The following benefits of ramipril were observed. Among patients who were already taking standard risk reduction therapies such as aspirin or other anti-platelet agents, beta blockers, lipid lowering agents, as well as diuretics and calcium channel blockers, there was significant reductions in the following secondary outcomes. Revascularization, complications related to diabetes, heart failure, cardiac arrest, worsening angina, and new diagnosis of diabetes. As Susan just mentioned, the HOPE two study, which was an extension of the HOPE study itself, evaluated whether the reduction of risk of major CV events with ramipril treatment in the HOPE study was maintained during the additional 2.6 years of followup. Approximately 72% of those originally assigned in the ramipril arm and 68% of those to the placebo arm received open label ACE inhibitor therapy. In both arms, greater than 90% who were on open label ACE inhibitor therapy received ramipril throughout the 2.6 years of followup. So during those 2.6 years of followup, a trend toward a further reduction in the primary composite outcome of stroke, MI, and CV death were seen in patients who were event free at the end of the HOPE study itself.

And just to summarize some of the key points. Altace, again is an ACE inhibitor indicated to reduce the risk of stroke, MI, and CV causes in patients aged 55 years or older who are at high risk of these events either because of a history of CV disease or because of diabetes plus at least one other CV risk factor. The benefits of Altace were observed among patients who were already taking standard risk reduction therapies, such as aspirin, or anti-platelet agents, beta blockers, lipid lowering agents, as well as diuretics, and calcium channel blockers. Altace was beneficial in reducing

the risk of CV events in high risk patients aged 55 years or older with diabetes. And Altace has been shown to reduce the incidence of stroke in patients who are at high risk.

Dan Lessler: Thank you.

Bill Beckman: Can I just summarize?

Dan Lessler: No, I'm sorry.

Bill Beckman: Okay, alright.

Dan Lessler: That's great. Are there any questions? Okay, thank you. So, Susan are you still on the line or? Well I think, let me just ask if there are any other questions from committee members for you. I don't think there are so, I think we can let you go. Thank you very much.

Jeff Graham: Susan this is Jeff Graham. Would you see if Marian might be available 15 minutes earlier?

Susan Carson: Yea, I'll give her a call.

Jeff Graham: Thank you.

Susan Carson: Okay, bye.

Dan Lessler: Okay, thanks Susan. So then, two motions. First regarding accepting the scan as an adequate update. Is there a motion to do that?

Vyn Reese: This is Dr. Reese and I move to accept the scan as an adequate update for the ACE inhibitor review.

Dan Lessler: Is there a second?

Man: Second.

Dan Lessler: [inaudible] seconds, okay. All those in favor say, "I."

Group: I.

Dan Lessler: Opposed same sign. Alright, and next we can, people could look at the previous motion from September of 2005, and.

Vyn Reese: This is Dr. Reese. The last, we sort of waffled on the last part of that motion. Where it said ramipril may be made available to patients meeting HOPE study criteria. I'm thinking it probably should be, instead of may,

should be made available. What do other people think about that? We went back and forth on that issue several, for several minutes I remember.

Dan Lessler: So do you want to, how are you guys handling ramipril in those patients?

Siri Childs: This is Siri Childs, HRSA. We have Altace on EPA criteria. And the criteria is stated here. A history of cardiovascular disease. So, it seems to be holding its own just fine.

Dan Lessler: We could also make that change and it might be a bit more clear. Although it, from a practical standpoint it's already being done as if it were written that way. So, would you like to.

Vyn Reese: This is Dr. Reese. I'll go ahead and just move to make the motion that I made in 9/21/05 regarding ACE inhibitors.

Dan Lessler: So the same motion then would be on the table as it appears before us here. Is there a second?

Man: Second.

Dan Lessler: Any other discussion? Okay. All those in favor say, "I."

Group: I.

Dan Lessler: Opposed same sign. Okay, so we've adopted the motion. Jeff, do you want to wait and see if Marian.

Jeff Graham: Well why don't we just plan on coming back at 10:30.

Dan Lessler: Okay.

Jeff Graham: I've already warned her too, so we'll hopefully.

Dan Lessler: Okay, so we're going to adjourn until 10:30. Thanks.

P&T Committee Meeting
June 20, 2007

Tape 2 of 4

Marian McDonagh: Dan, I'm here.

Dan Lessler: Okay, great, thanks. Give us one, just a minute here. Just so you know, your first title slide is projected here, so as usual Marian you can just tell us when you want the slides changed.

Marian McDonagh: I will.

Dan Lessler: Okay, why don't we. I think we're ready, you can go ahead and get started.

Marian McDonagh: Okay, so this is the newer antiplatelet agents report. And this year's completed as of March, 2007. Originally this report was done by RAND, and when they turned in their update to us, we decided to have another look at it because it was very difficult to use. So we've redone a lot of the work in this report, but the original report is based on the work done by EPC at RAND. So if we go to the second slide, this shows the key questions for the report. So this is the [inaudible] the antiplatelet agents for acute coronary syndrome, coronary revascularization using stenting or bypass grafting, patients with prior stroke or TIA, or symptomatic peripheral vascular disease. And then the usual sub questions on safety and subpopulations.

On the next slide, it's simply a statement of the included populations and study design. Let's go on to the next slide. These are the three medications that are included in this report. So the extended-release dipyridamole combined with aspirin, Clopidogrel, and Ticlopidine. On the following slide are the inclusion criteria for outcomes. And primarily we were looking for mortality, either all-cause or cardiovascular. With either cardiovascular events, invasive vascular procedure failure. And as you will see in a lot of what we actually found on the report are combined outcome measures.

On the next slide is a summary of our literature search. The searches that were done by RAND. And they were completed in May of '06. Moving on to the next slide. Acute coronary syndrome. The original report had no head to head trials, and one good quality active-controlled trial. The CURE trial, which is an extremely large, over 12,000 patients. And in this update, there is a small head to head trial. Clopidogrel versus Ticlopidine that was added. But it only [inaudible] at six months, so it didn't contribute a lot to the finding. In addition there are multiple subgroup analyses coming out from CURE so we've included some of those where they are relevant.

On the next slide, summarizing what's in the report and was in the report previously. Based on the CURE trial, Clopidogrel plus aspirin was found to be more effective than aspirin alone. And that is in preventing a combined outcome of non-fatal stroke, MI, or cardiovascular death. And the NNT is 48 for that [inaudible]. However, on the flipside for adverse events, compared to aspirin Clopidogrel combined with aspirin does have higher rates of major bleeding, and the number [inaudible] is 100. So in

comparison of those two, then the NNT of 48 and an NNH of 100 is considered to have a balance to be in favor of the benefits. Now we don't have evidence for Dipyridamole plus aspirin for this particular patient population.

On the next slide, looking at subgroup analyses, there are [inaudible] shows very similar results in patients who are less than or equal to 65 years old, male and female, and also patients taking a variety of different drugs. However, the subgroup of patients with diabetes in this trial, they see, there was no significant difference between the groups for the primary outcome measures. In addition to [inaudible] analysis of the aspirin dose, because dosing of aspirin could vary in [inaudible] quite widely. They looked back to see if there was an impact and in fact there was. Lower doses and higher doses, the aspirin did not do as well as the more moderate doses, which is closer to what we would use here in the [inaudible].

Moving on to the next slide, coronary revascularization. There are no trials for patients [inaudible] revascularization. In the original report there were six head to head trials of Clopidogrel versus Ticlopidine and one of those being the large, good quality trial CLASSICS. Results showed five indirect trials including PCI-CURE and CREDO. And in the new report we have also added a new study of Clopidogrel versus Ticlopidine and also the ARMYDA trial, which is evaluating a higher loading dose of Clopidogrel compared to the standard.

Moving on to the next slide. For stent revascularization in the short term, so less than six months of treatment, Ticlopidine versus Clopidogrel, we have five trials. Three with loading dose of Clopidogrel and two without. And here there was, in all of these there was no significant difference between the two drugs for the major outcomes.

So the following slides began looking at Ticlopidine versus Clopidogrel. And I'm going to have to apologize. The first bullet point should say without loading dose. So this is looking at longer term treatment, so 2.7 years of follow-up. This is the [inaudible] study. And for cardiac death, the relative risk was 0.32 with an NNT of 20, favoring Ticlopidine. On the lower part of the slide is the summary [inaudible] results, the meta-analysis that also looked at Ticlopidine versus Clopidogrel. And this is reporting differently in that it's Clopidogrel versus Ticlopidine. Clopidogrel had an increase in the death rate, or death or MI rate compared to Ticlopidine in this meta-analysis.

On the next slide, looking at adverse events. The comparative adverse events for Ticlopidine and Clopidogrel. There were no differences between the drugs in individual rates of specific adverse events. But

looking at pre-planned composite adverse event outcomes in the short term, Ticlopidine versus Clopidogrel with a loading dose, here we have major peripheral bleeding, bleeding complications, neutropenia, thrombocytopenia were all combined together, and Ticlopidine had worse outcomes compared to Clopidogrel with a number needed to harm of 16. Similarly withdrawal due to adverse events was worse in the Ticlopidine group with a number needed to harm of 50. But when looking at the comparison of Ticlopidine versus Clopidogrel without a loading dose, there was no significant difference between the groups.

On the next slide we have, moving on to indirect evidence. Comparing Clopidogrel with aspirin compared to aspirin alone. So looking at PCI-CURE and the CREDO trial primarily. So the loading dose of Clopidogrel plus aspirin compared to aspirin alone is that longer term follow-up, eight to 12 months. And in this, the combination of Clopidogrel versus aspirin was superior to aspirin alone in both trials. With an NNT of 29 in PCI-CURE and 33 in CREDO. The outcome there for PCI-CURE was cardiovascular death, MI, or urgent revascularization. Which is different for the CREDO outcome, which was death, MI, or stroke. Then interestingly also, in this analysis, the cardiovascular risk reduction was non-significant in subgroups of diabetic patients. And they removed significant increases in the risks of major bleeding over [inaudible] with aspirin alone.

On the next slide, this is summarizing the findings of the ARMYDA study. So at one month, the composite outcome of death, MI, or revascularization was lower in the group that had the 600mg loading dose compared to the 300mg loading dose with an NNT of 13. There was a small difference in the age of the two groups. And we do think that this information should be interpreted with some caution. And no major bleeding or thrombocytopenia was seen in either group in the 30 days of follow-up.

Moving to the next slide, this is the prior stroke or TIA patient population. And in this part of the report, we did a lot revamping. The CHARISMA and CAPRIE trials had not been included in this section before, but here we have subgroups of patients who were enrolled because of prior stroke. So in this part of the report we have indirect evidence, and no head to head trials. But five good quality trials that we could make direct assessments from. The ESPS-2, the TASS trial, the AASPS, CATS, and CAPRIE. In this update we've also added the [inaudible] trial, and CHARISMA, with a subgroup out of CHARISMA. And I guess I should point out that there is a head to head trial on the way comparing [inaudible] to Clopidogrel. And we're waiting for that to come for the next update.

On the next slide we have the summary of the Dipyridamole extended release plus aspirin evidence. And this is Dipyridamole plus aspirin reduced recurrent stroke. Either fatal or nonfatal compared to aspirin alone. And the NNT was 33 in one study. However in the second study, so this is ESPS-2 in a three year [inaudible] study. The differences did not reach statistical significance. A bit of conflicting evidence there. Then looking at the combined outcome of nonfatal MIs, stroke, or death from any cause, there was a significant reduction with an NNT of 34 favoring the Dipyridamole plus aspirin group. Dipyridamole was not superior to aspirin alone in preventing death from any cause.

On the next slide we're comparing the adverse event profiles of the drugs primarily from these two trials. The increase in major bleeding with the combination compared to aspirin [inaudible] were not found. Also, differences were not seen in the discontinuation rate or the gastrointestinal symptoms rate. But headaches, diarrhea, and vomiting were all at a higher rate with the combination compared to aspirin alone. And I do want to point out that in these trials, Aggrenox, the combination of products was used in only a very small proportion of the patients. In general the product that was used was an extended release Dipyridamole that's not available in the U.S. And then combined with aspirin doses that vary and were somewhat different to what's used here in the U.S.

On the next slide, so moving into the evidence for Clopidogrel in patients with prior stroke or TIA. There were two studies, CAPRIE and CHARISMA [inaudible] patients. With prior stroke or TIA and [inaudible] studies found a benefit for Clopidogrel with the primary outcomes, which again were composite outcomes in those two trials.

On the following slide for safety, Clopidogrel combined with aspirin did have higher rates of bleeding compared to aspirin alone, with NNHs, numbers needed to harm, of 100 and 125 depending on whether the classification was major or moderate bleeding. However gastrointestinal hemorrhage was lower with Clopidogrel alone, compared to aspirin alone in the CAPRIE trial. And neither study found differences in intracranial hemorrhages or discontinuation due to adverse events.

On the next slide, moving to the other two slides on Ticlopidine in patients with prior stroke. Considering the adverse events profile of Ticlopidine, I'll go through these fairly quickly. In the first slide, the TASS trial was comparing Ticlopidine to aspirin, and using a cumulative event rate, Ticlopidine was significantly superior to aspirin alone. [inaudible] for recurrent stroke and also the composite outcome of stroke or deaths of any cause. However, if you turn to the next slide, this study was then repeated in a group of African American patients with prior ischemic stroke or TIA and Ticlopidine was not found superior to aspirin in this trial and the study

was discontinued early. The differences in withdrawal or adverse event rates were not found in this trial.

On the next slide, summarizing the adverse event evidence comparing Ticlopidine to aspirin from the TASS and the AASPS trials, we have discontinuations due to adverse events, rates of diarrhea and rash were all higher with Ticlopidine, and GI bleeding was the only adverse event that was significantly higher in the aspirin alone group. At the bottom of the slide we have a summary of the evidence about neutropenia from this trial and then also combined the data from other trials, indicating they have 2.4% neutropenia and 0.85% severe neutropenia and agranulocytosis [inaudible] Ticlopidine.

Now on the next slide we have a summary of the evidence for systematic peripheral vascular disease. In this update we did not add new evidence, so this is really just a quick summary of the CAPRIE trial. There was a subgroup of patients in CAPRIE with peripheral vascular disease. So that's where this evidence is coming from. And we [inaudible] Clopidogrel, we don't have evidence for Dipyridamole extended release with aspirin, or Ticlopidine.

On the next slide, summarizing this evidence. Clopidogrel was slightly better than aspirin alone for the combined outcome, which was ischemic stroke, MI, or vascular death in patients with [inaudible]. And the relative risk was 0.92 with a fairly high NNT of 87. [inaudible] 95% confidence interval reaches all the way up to 0.99. So it's not a small, it's not a large decrease, and also it's close to non-significant. Differences in bleeding were not found, and also discontinuations due to adverse events were not found.

On the next slide, [inaudible] specifics on adverse events. There were lower rates of gastrointestinal hemorrhage and also GI symptoms with the Clopidogrel group. And on the other side, there were higher rates of diarrhea and rash with Clopidogrel compared to aspirin. And that's a quick summary of the report. I'm happy to talk about any questions.

Dan Lessler: Thanks Marian. And I'm going to open up to P&T members to ask questions of Marian.

Vyn Reese: Hi this is Dr. Reese. I seem to remember a study that compared Clopidogrel to aspirin, low dose aspirin plus a PPI that, where the patients had prior history of peptic ulcer disease where the eating rates were actually higher with the Clopidogrel group. Is that, do you have access to that study? Or was that reviewed?

Marian McDonagh: Yea, no that study was not included in the report, but I am aware of it and I know the study is talking about.

Vyn Reese: So would you want to comment on that?

Marian McDonagh: Well, you know I think that, I wouldn't really because it's, I know it was protected. So adding the PPI was protected. But I couldn't say more than that at this point.

Vyn Reese: Thanks.

Dan Lessler: Are there questions? Okay, Marian, are you available to stay on the phone just for another few minutes here?

Marian McDonagh: Sure.

Dan Lessler: Great, because we have time for some stakeholder comment here. And first is Kyle Downey from Sanofi.

Kyle Downey: Good morning committee members, my name is Kyle Downey, and I'm a regional medic liaison for Sanofi Aventis. I'm here to comment on Plavix. Plavix is a medication that has demonstrated efficacy in coronary cerebrovascular as well as peripheral circulation, or better known as artherothrombosis. And artherothrombosis is an ongoing inflammatory process that is a systematic disease affecting all three vascular beds. Around this indications and use, you guys have seen the report. And we have an indication for recent MI, stroke, or established peripheral arterial disease, as well as for two coronary syndromes where there's a new indication for not only NSTEMI but also ST segment elevation MI that has been added to the [inaudible] since the report came out.

CAPRIE showed a, basically in 20,000 patients that approximately 25% of those patients had ischemic vascular disease in more than one vascular bed. And to summarize basically the four key trials for the Plavix indications they are, CAPRIE, CURE, CLARITY, and COMMIT. In the interest of time I'll skip ahead to the CLARITY and COMMIT studies. The CLARITY study looked at approximately 3,500 patients presenting with ST segment elevation and the addition of Plavix loading dose and 75mg compared to placebo on top of aspirin and [inaudible] therapy, reduced the primary end point by 36% of [inaudible], death, and MI.

Also the COMMIT study, which studied 45,000 patients with a history of MI that were admitted to the hospital with ST segment elevation, depression, or [inaudible] showed that the addition of Plavix 75mg out to one month reduced the primary end point of death alone by 7% and the composite end point of death, MI, and stroke by 9%. The guidelines are

very supportive of Clopidogrel. The [inaudible] guidelines show that basically Clopidogrel should be administered in addition to aspirin for acute coronary syndromes upon admission and then administered for at least one month and up to nine months for patients undergoing PCI, the continued risk for at least one month and then again up for nine months in those in not high risk for bleeding. And then also for long term therapy in those patients who have acute coronary syndrome but aren't treated with a stent.

Lastly there was the FDA advisory committee that would [inaudible], presented in December of 2006 that recommended with drug eluting stents, that the off label use of drug eluting stents increased the risk of both early and late stent thrombosis and they also recommended that in accordance with the PCI guidelines that Clopidogrel be treated out to 12 months.

In summary, the guidelines that support Clopidogrel are the 2002 [inaudible] guidelines, the AHA CPR and emergency guidelines, the arterial disease guidelines, and the stroke guidelines. And I'll open it to any questions.

Dan Lessler:

Thanks, any questions? Okay, thank you. Next is Dr. Jon Beaty.

Jon Beaty:

Good morning, I'm Jon Beaty, I'm a representative of the medical affairs department at Boehringer Ingelheim, and I appreciate the opportunity to make the following comments to you. Stroke is the third leading cause of death in the United States. It is the leading cause of disability. Aggrenox, one capsule b.i.d. is indicated for the prevention of recurrent stroke in patients who have had previous ischemic stroke or TIA.

Aggrenox is a novel formulation. The capsule contains a 25mg aspirin tablet and 200mg of Dipyridamole pellets. Each Dipyridamole pellet has an extended release coating, and a core of tartaric acid for increased absorption. In individuals with low gastric acid, the extended release Dipyridamole in Aggrenox provides 50% higher bioavailability than immediate release Dipyridamole, also called Persantine.

The Aggrenox prescribing information contains a cautionary statement mandated by the FDA that Aggrenox is not interchangeable with the individual components of aspirin and Persantine tablets. Aggrenox inhibits thrombosis through the combined actions of its two components aspirin and Dipyridamole. Aggrenox has been shown to be twice as effective for stroke prevention as aspirin alone.

In the ESPS-2 trial, Aggrenox showed a statistically significant 22% relative risk reduction for stroke, with a P value of 0.008 compared with

aspirin. This result was corroborated by the non-industry supported ESPRIT trial. 50mg of aspirin per day is accepted for recurrent stroke prevention by the FDA, the AHA, the ACCP, and the NSA. There is increased risk of headache with Dipyridamole compared to placebo. Studies with extended release Dipyridamole showed that headache is generally mild and transient. Addition of Dipyridamole to aspirin has not been shown to increase bleeding risk.

Aggrenox is the only combination anti-platelet therapy endorsed as a first sign therapy prevention of non-cardioembolic cerebral ischemic events in the ASA 2006 stroke guidelines. The combined use of Clopidogrel in aspirin in high risk stroke patients is strongly cautioned against in these guidelines due to the increased risk of bleeding.

One final note about the [inaudible] trial. Enrolled are more than 20,000 patients at over 600 sites worldwide. The trial is designed to investigate the superiority of Aggrenox versus Plavix in secondary stroke prevention. The enrollment completed in June, 2006 and the trial is expected to report in 2008. Thank you very much.

Dan Lessler: Thank you. Are there any questions? Great, thanks. So, before we let Marian go I just wanted to ask if there are any more questions for Marian before we go on. Doesn't look like it. Marian thank you very much.

Marian McDonagh: I, thanks very much.

Dan Lessler: Alright, bye.

Marian McDonagh: Bye.

Dan Lessler: So unlike the previous scans, this is a full update. So we can turn our attention to crafting a motion. People on the committee could just take a look at the previous motion.

Vyn Reese: This is Dr. Reese. I don't see a lot of new evidence to change our prior motions. As far as I can tell. And I'd be willing to make a motion which would be the first part of the motion made in 9/21/05 and I could just read it, or we can just, we can say I, it's too hard to say that I just. Want to re-motion the first part of the last motion so I'll just read it.

After considering the evidence of safety, efficacy, and special populations for the treatment of acute coronary syndrome, ACS, and percutaneous coronary intervention, PCI, I move that Clopidogrel is safe and efficacious. No single anti-platelet medication is associated with fewer adverse events in special populations. Clopidogrel cannot be subject to

therapeutic interchange in the Washington preferred drug list for the treatment of ACS and PCI. I'll make that motion again.

Dan Lessler:

Is there a second? Okay.

Janet Kelly:

Janet Kelly, I'll second it.

Dan Lessler:

Okay. Any discussion? Bob.

Bob Bray:

The, I guess the one thing that I'm noticing is on page six of our slides, where we have evidence that says that Ticlopidine, or Ticlopidine was superior to Clopidogrel in stent revascularization in prevention of CV events. And on the next slide on page seven it talks about how the risk factors at least for significant bleeding were non-significant if it was given without a loading dose. And so it does appear that there is some further evidence of benefit of Ticlopidine versus Clopidogrel at least in one indication. And previously the third part of our motion was to exclude Ticlopidine primarily out of concern for risk factors. So I'm just wondering if we should rethink that last part of our serial motions last time.

Man:

Bob I'd refer you to page 12 of this new review. Summary of stroke or TIA with Ticlopidine. Basically the combined data from trials indicates a rate of 2.4% neutropenia and 0.85% severe neutropenia and agranulocytosis with Ticlopidine. Those are pretty significant risks, and that's why we decided not to have it on before, because Clopidogrel was clearly a safer drug. Those are pretty substantial risks of serious adverse events. Not that there are black box warnings for Ticlopidine that aren't on Clopidogrel.

Dan Lessler:

So I guess Ticlopidine would still be available, it would just require prior authorization and a discussion.

Man:

In some rare circumstance where for some reason they couldn't take Clopidogrel, you could still get it, you'd just have to do, go through a special request to do that. So I mean it's clearly not as safe, maybe a little bit more effective, but not as safe.

Man:

As long as it's available for those folks for that indication with prior authorization I would have no objection then.

Man:

Thanks. Siri?

Siri Childs:

This is Siri Childs, HRSA. We do ask that they have tried and failed one of the preferred drugs prior to using it. That's the only criteria.

Dan Lessler: Alright, so.

Man: Can I make one comment about that? If somebody's going to be using it though, for prevention of events after a stent revascularization, they're not going to have an opportunity to fail the other drug. If the person putting in the stent prefers to use Ticlop – that first one. So if I see somebody trying to make a case for that it would be the person who says, "I want to use it post stent revascularization." So would that be something that would be considered on a prior authorization. Because there's, by definition, there's no failure of another drug.

Siri Childs: This is Siri Childs again. Well, we also have the criteria on all of our drug classes intolerant to. Which could be, I mean they could give us some weird reason why they're not using Plavix and that they would prefer to use the Ticlopidine.

Vyn Reese: This is Dr. Reese. I don't think many cardiologists are using Ticlopidine now. I mean I find that basically it's fallen off the end of the world. You know, it's not there. So I think it would be very uncommon to have it used as a [inaudible] agent.

Dan Lessler: Okay, so the motion that is before us has been seconded, it sounds like Bob's comfortable with it after that discussion. Any other comments or discussion? Okay, then I think we can go ahead and vote on this part of the motion. Or this indication for the use of these antiplatelet agents. All those in favor say, "I."

Group: I.

Dan Lessler: Opposed same sign. Okay. So now as we did before we should consider these agents with respect to stroke prevention. Alvin.

Alvin Goo: I can make a motion but, do I make a motion first and then we discuss or.

Dan Lessler: Yea why don't, well let's see. Is there any, before we put a motion forward, looking at the previous motion are there any observations or comments that people wanted to make relevant to. No.

Alvin Goo: Okay, so I'll make a motion. This is Alvin. After considering the evidence of safety, efficacy, and special populations for the treatment of stroke and transient ischemic attack, I move that extended release Dipyridamole and aspirin is safe and efficacious, extended release Dipyridamole and aspirin combination cannot be subject to therapeutic interchange in the Washington preferred drug list for the treatment of stroke and transient ischemic attack.

Dan Lessler: Is there a second? Okay, so Ken seconds. Any other discussion? Alright, all those in favor.

Group: I.

Dan Lessler: Opposed same sign. Okay, so the motion passes and we're ready to move on. Do we have, do we need to. Is anybody on the line?

Susan Carson: This is Susan.

Dan Lessler: Susan. Go ahead.

Jeff Graham: Hi Susan, you can ignore, this is Jeff Graham, you can ignore my message I left for you.

Susan Carson: Oh, I never got it.

Jeff Graham: Oh that's because I just left it.

Susan Carson: Oh, okay.

Dan Lessler: Oh, you know excuse me, there is, thank you, Carol pointed out that we did have a third motion which specified that Ticlopidine should not be on the preferred drug list for safety reasons.

Man: I'll just make that motion again. I still think the same reasons stand that were there previously. I move that Ticlopidine not be on the PDL due to safety concerns. Now could be requested as a, this is an aside, could be requested as a non-formulary drug, but it's not going to be on the PDL.

Dan Lessler: Right. Is there a second?

Jason Iltz: I'll second, it's Jason.

Dan Lessler: Okay. All those in favor say, "I."

Group: I.

Dan Lessler: Opposed same sign. Okay. So now we can move on. Susan, so you're there?

Susan Carson: I'm here.

Dan Lessler: Great, thanks. So I think we have a full update. We just need a second to call up your power point here.

Susan Carson: Okay.

Jeff Graham: And I wanted to point out that Susan also is going to do their scan update, which was just completed in November I believe. So at the end of this show I'll go over that.

Dan Lessler: Okay so, alright. We're set, we have your first slide, title slide on the newer sedative hypnotics.

Susan Carson: Thanks. So this is the first update of the insomnia drugs report. It was completed in July '06. As Jeff mentioned we did an update scan in November which I'll go over following this presentation. You'll notice the name was changed. It used to be called newer sedative hypnotics. We changed the name to more accurately reflect which drugs are included. And next slide.

We added two new drugs this update. The first new drug is Zolpidem extended release formulation. This was FDA approved in September, 2005. The second new drug is ramelteon which is a selective melatonin receptor agonist. And it was approved in July, 2005. None of these drugs is approved for use in children. And the initial starting dose in older adults is half the usual dose in all of the drugs except for ramelteon. You'll also see that we have Zopiclone on the slide. It's not approved for use in the U.S. but we included it on our report because one of our organizations is from Canada where the drug is approved. So I'm just going to skip over the information about Zopiclone in this presentation.

Next slide. Slide three. Included population. We added children this update. Another change was that we didn't specify in the key questions that, we limited the active controlled trials to studies of sedative hypnotics versus benzodiazepines or [inaudible]. We searched for evidence of the newer insomnia drugs versus any active comparator at this time.

Next slide. Literature searches were conducted through the end of 2005. And I then said it was finalized in July, 2006. We received four dossiers from industry. Dossiers on Zolpidem, Eszopiclone, and both of the new drugs, ramelteon and Zolpidem extended release.

Next slide. Again, we identified no studies in children that have been published. We identified one new head to head trial of Zopiclone, the Canadian drug versus Zolpidem. But the study was rated poor quality, and it didn't change the overall summary of the evidence. Three new placebo controlled trials were added this update and all of them were in the new drug. Two were for Zolpidem extended release and one for ramelteon. And although we did search for studies of newer insomnia drugs versus any active comparator, we didn't find any new active controlled trials this

update at all. So no new head to heads, and no new active controls. We also included one new good quality systematic review that looked at the benefits and harms of sleep agents. It included the newer insomnia drugs and other drugs such as benzodiazepine and this is in older adults. We also added one new observational study of hip fracture in older adults.

Next slide. This is a summary of the eight head to head trials, what the comparisons were. Again, the only new one is the poor quality trial of Zolpidem versus Zopiclone. The most evidence is for the comparison of Zolpidem for Zaleplon. There's four head to head trials of that comparison. And there's no head to head evidence for either of the new drugs.

Next slide, slide seven. We included two placebo controlled trials of Zolpidem extended release. One was conducted in younger adults under age 65 and another in older adults. Both of these were available as posters only at the time of the report. One of them has subsequently been published. But we did include the posters because they did include sufficient information for us to assess their internal validity. And we rated them both fair quality. One issue with them was that we couldn't determine if an intention to treat analysis was used because the number analyzed wasn't reported in the poster. Also the trial in older adults had differences between groups at baseline, but it was adjusted for in the analysis. So the two reports have identical design, the same group of authors, and they were presented at the same meeting in 2005. Because of the way they reported outcomes in these posters, we couldn't use them to make indirect comparisons to the other, newer insomnia drugs. For example, polysomnographic outcomes were reported adjusted for baseline, and also subjective [inaudible] blatancy was reported as the percent of patients reporting improvement, whereas in other studies, this was reported as the number of minutes it would take to fall asleep. So it was difficult to make indirect comparisons to other drugs.

Next slide shows more details of the two trials of Zolpidem extended release. Soubrane 2005 was the trial of the younger adults. Had two nights of PSG recording in a sleep lab, then 12 nights of outpatient treatment, and then again another two nights in the lab, and then five nights of outpatient treatment, and then a two night [inaudible] where they measured rebound effects. So patients improved compared to placebo on objective and subjective measures. More patients in the active group reported improvements in sleep latency, total sleep time, sleep quality, and the statement treatment helped me to sleep. There was evidence of rebound insomnia on the first night after discontinuation, but by the next night the effects went away. And then the second trial in Zolpidem extended release, again also reported only in the poster, had adults over age 65 in the same design as the Soubrane study. In objective and subjective sleep

outcomes were improved compared to placebo and the actual percent of patients who reported improvement wasn't reported. And as in the study in younger patients there was evidence of next day rebound insomnia, but no effects on psychomotor performance tests. So, but the two trials both found efficacy better than placebo for both subjective and objective sleep outcomes.

Next slide. The other new drug we added is ramelteon or Rozerem. We included two placebo controlled trials that have been fully published. One in adults and one in older adults. Other trials have been conducted but they're not yet fully published, and the abstracts that we had didn't have enough information for us to fully assess their internal validity, so they're not included in this report.

Next slide. First results of the trial of ramelteon in younger adults, under age 65. This study included three doses of ramelteon versus placebo. And the primary outcome was objective sleep latency measured by a PSG recording in a sleep lab after two nights. And this study was similar in design and population to a trial of Zolpidem versus Eszopiclone versus placebo that we had in our original report. So we were able to use these two trials to make indirect comparisons about objective sleep latency among the three drugs, ramelteon, Zolpidem, and Eszopiclone. So the difference versus placebo was about 13 minutes for ramelteon, 21 minutes for Zolpidem, and 17 to 19 minutes for Eszopiclone. So in other words ramelteon was less effective than the other drugs for sleep latency by about four to eight minutes. But as you can see on the slide, the confidence intervals for the mean difference from placebo did overlap for the three drugs.

Next slide. On subjective sleep outcomes in the same study, there was no difference between ramelteon and placebo, with the exception of sleep latency at the 16mg dose. So, for most of the subjective sleep outcomes, ramelteon was no better than placebo, although they did find efficacy on objective measures. And then also they found no evidence of next day effects with ramelteon.

Next slide. The other placebo controlled trial of ramelteon. This one was conducted in older adults aged 65 and older. And the slide shows results for sleep latencies and total sleep time for two doses of ramelteon versus placebo at different time points. The primary outcome was subjective sleep latency and the study had mixed results for this outcome. But it did show efficacy versus placebo for sleep latency at most time points. There is no difference from placebo on number of awakening, ease of falling back asleep, or sleep quality, the other outcomes that they measured.

Next slide. This is moving on to the comparison of Zolpidem versus Zaleplon. We had no new evidence for this comparison, so our current conclusions don't change. Our current conclusions are that Zaleplon was more effective for sleep latency, but Zolpidem more effective for sleep duration and sleep quality. Zolpidem caused more first night rebound insomnia. And the two drugs were similar for short term adverse events, number of awakenings, and next day alertness.

Next slide, slide 14. So skip this slide, it's about Zopiclone. Next slide, results so no new evidence for the comparison of Zolpidem to Eszopiclone, so our original conclusions don't change. And those were that limited indirect evidence shows that the two drugs are similar for subject sleep latency and number of awakenings, but Eszopiclone more effective for increasing sleep duration.

Next slide. There's no new evidence for the comparison of Zaleplon to Eszopiclone. The quality of the overall body of evidence for this comparison is still poor.

Next slide you can skip, and go to slide 18. And this is a summary of the direct comparative evidence for short term efficacy. So as you can see we're unable to add any new information about comparative efficacy, either direct or indirect for Zolpidem extended release, although two placebo controlled trials showed improvement over placebo, the way the outcomes were reported as posters made indirect comparisons to other drugs impossible. For ramelteon, we added indirect evidence that ramelteon is similar in efficacy to Zolpidem and Eszopiclone for objectively measured sleep latency.

Next slide. Moving on to long-term effectiveness and efficacy.

[end side A]

Susan Carson:

A six month placebo controlled trial of Eszopiclone. It's been published as a poster only. And this trial confirmed the efficacy of Eszopiclone over six months that was first reported in the CRYSTAL study, which is in our original report, and [inaudible] a six month trial. So the poster reported that there was no evidence of rebound insomnia or discontinuation effects. This is shown in a graph only. And in the original, or the first six month study, rebound insomnia was not assessed. So this study does add new evidence that Eszopiclone over the long term didn't cause rebound insomnia.

Next slide. We identified no new evidence for long-term safety this update. And there's still no comparative evidence. The evidence for long-term safety is limited to one year open label extension studies of Zolpidem

and Zaleplon. And the two six month studies of Eszopiclone. There are no studies of the long-term safety of Zolpidem extended release or ramelteon as of yet.

Next slide. Subgroups. New evidence for efficacy in older adults comes from the two placebo controlled trials that I discussed over key questions one and two. The one in Zolpidem extended release and the one in ramelteon.

Next slide. We do have some new evidence about safety in older adults. A new systematic review and a new observational study of hip fracture, the risk of hip fracture. The systematic review didn't compare the individual newer insomnia drugs, and it also included benzodiazepines and over the counter medications such as antihistamines, so it doesn't provide comparative evidence. Combining studies of Zaleplon, Zopiclone, and Zolpidem versus benzodiazepine there was no significant difference in cognitive adverse events or psychomotor type adverse events. For all sedative hypnotics combined, including the benzodiazepine, the number needed to harm for all adverse events for the placebo was 6 and the number needed to treat for improved sleep quality was 13. So based on that, a lower number needed to harm than number needed to treat, the [inaudible] concluded that in older people the benefit of sleep aids may not outweigh their risk. But again this combines benzodiazepine.

So the next slide, more information in older adults. An observational study that's already included in our original report concluded that Zolpidem use was associated with a similar rate of hip fracture as users of benzodiazepine. In this update, a new observational study used data from a survey of Medicare beneficiaries to determine if the increased risk of hip fracture might be due to confounding factors that are not available from [inaudible] data. And the concern is that perhaps people at higher risk of hip fracture might be prescribed the newer drugs. So the potential confounders they looked at were BMI, current smoking, ADL score, cognitive impairment, and a physical impairment score. And they found that ADL score was the strongest confounder. And it caused an overestimation of 10% comparing Zolpidem users with benzodiazepine users. They did conclude however that the magnitude of the effect of unmeasured confounders was unlikely to explain completely the elevation in hip fracture observed in older sedative hypnotic users. So taken together, these observational studies suggest that the newer sedative hypnotics may not be a safer alternative to benzodiazepine regarding the risk of hip fracture in older adults.

Next slide. We added no new evidence to our overall conclusions for subgroups this update. There's no evidence to suggest that one newer

insomnia drug is safer or more effective for any subgroup based on demographics or comorbid conditions.

In the last slide, in conclusion, the main new evidence consists of placebo controlled trials in newer drugs, and they provide either no or limited comparative evidence. There's some new evidence from observational studies confirming existing evidence about safety. And there are no studies available for the new included population of children.

Dan Lessler: Great, Susan. That's a really, very nice review. I'm wondering if any P&T members have questions.

Vyn Reese: Susan, hi this is Dr. Reese. Rozerem seems like it's a totally different type of drug than the others and it doesn't use benzodiazepine receptors, so it's very difficult to compare it to the other drugs, it's almost like in a class by itself. Do you want to comment on that?

Susan Carson: Yea, it's the only one that's not a sedative hypnotic, and it's the only drug that doesn't, is not classified as a controlled substance. And we did find that it may be a little bit less effective, but it may be a choice when there are concerns about substance abuse.

Vyn Reese: Thanks for those comments.

Dan Lessler: Other questions?

Alvin Goo: Hi Susan, it's Alvin. In your, I know you didn't report anything but are there any comparative trials with these newer agents in cognitive behavioral therapy that you're aware of?

Susan Carson: There's not. At least according to the update scan we did in November. The only study of cognitive behavioral therapy we found was versus Zopiclone, the drug that's not approved in the U.S. But nothing versus the newer drugs, the other newer drugs.

Alvin Goo: Okay, thanks.

Susan Carson: I was supposed to do the update scan which I forgot.

Man: Oh, okay.

Susan Carson: Should we do that now or after.

Dan Lessler: Why don't we just finish getting clarifications here and then we can do, then let's do the update scan. Patti.

Patti Varley: This is Patti Varley. Was there any studies that compared any of these agents to over the counter melatonin?

Susan Carson: No.

Dan Lessler: Other questions? So, okay. Why don't we do the scan.

Susan Carson: Okay. So this should be pretty brief. This was conducted in November 2006. We found no new drug and no new indication. There were no new safety alerts at the time we did this update scan, but since then there was a FDA alert in March that you probably know about, it's for all of the sleep agents, including the benzodiazepine sedative hypnotics and also ramelteon. And it's a warning about behaviors such as sleep, the risk of behaviors such as sleep driving. And the FDA encourages manufacturers to conduct studies to look at the magnitude of risk for the individual drug for these behaviors. So our update scan found seven potentially relevant trials. We found no head to head trials. And one publication is a full text publication of a trial of Zolpidem extended release that was previously available only as a poster. The poster's already in our report. And then again there's a report of Zopiclone versus cognitive behavioral therapy that I mentioned.

For Eszopiclone, there are two new trials. One looks at the combination with Fluoxetine in patients who have insomnia associated with depression. And then there's a two week placebo controlled study in older adults. For ramelteon there's one new study, and it's about the potential for abuse and cognitive and motor adverse effects versus Triazolam. So that would be the first comparison of ramelteon versus a benzodiazepine.

There's also one new study of Zolpidem compared to another benzodiazepine, rotizolam, which I don't think is available in the U.S. This study's from Japan. And this study looks at next morning effects.

And then the last study someone asked about melatonin. There is a study which looked at the effects of a cocktail of Zolpidem plus melatonin and its effects on performance tests. I think the study might be in healthy volunteers though, not patients with insomnia. So on closer inspection it probably wouldn't meet our inclusion criteria. But the abstract is in your report if anyone would like to look at it. So that's the new evidence.

Dan Lessler: Great, thanks Susan. Any questions about the scan? Maybe, I'm just thinking whether or not we should accept the scan as an update and then go on from there, since [inaudible] asked that we sort of do that.

Man: Let Jeff take over.

Dan Lessler: Okay. So we'll move to stakeholders here. Susan are you available to stay on the phone just for a bit?

Susan Carson: Yes.

Dan Lessler: Thank you. So, first is Dr. John Tran. And again I just would remind people to let us know if you're being sponsored and limit your comments to three minutes please.

John Tran: Good morning. Yea, my name is Dr. John Tran. Thank you for giving me the privilege to speak to all of you today. Actually I am currently working in a community mental health center. My clinical responsibility includes outpatient, health clinic, nursing home, assisted living, CCF, and adult family home. I'm a board certified general and geriatric psychiatrist. I am on the [inaudible] bureau for Lunesta however today, I am here on a voluntary basis and I do not receive any payment from a company.

What I would like to request is that the P&T committee would consider having Lunesta as one of the options for the state formulary. I'm impressed with the medication on several levels. The first is their six months controlled double blind placebo controlled studies where a follow up with six months open label where the efficacy for sleep onset and sleep maintenance continue throughout that period of time almost up to a year. And then on top of that, there doesn't seem to have any development of dependence, tolerance, or rebound insomnia at the end of the trial. So that's very impressive.

And translate that to clinical practice. I have patients who I've treated and fail on traditional pharmacotherapy where, which includes sedating, antidepressant, antipsychotic medications, as well as some benzodiazepines doesn't have good results. And when I put them on Lunesta they seemed to have very good results both for sleep onset and sleep maintenance.

One patient come to mind quickly was a lady that I treated for bipolar affective disorder also had chronic insomnia problems. I treated with the traditional means that I mentioned as well as on Ambien. The Ambien also helped her but only for sleep onset or falling asleep. But as far as for maintaining sleep didn't work very well. I switched her to Ambien CR, she did well for a month for both falling asleep and staying asleep, but then the staying asleep effect went away. So now I put her on Lunesta afterwards, and this is like a half a year later and she's still doing well and falling asleep and maintaining sleep.

So [inaudible] in conclusion I just want to mention that I, most of my patients are the indigent population and they suffer from mental illness. So

they would not have the opportunity to come here and express their voices to you about, you know what would be most helpful. But I do want to request that the P&T committee at least consider putting a good, hypnotics on the formulary, at least for physician who may be similar to myself in helping the similar population may have a chance, an option to you know for better treatment and help our patients better so. I just wanted to request that Lunesta may be considered on the formulary. Thank you.

Dan Lessler: Thank you. Any questions of Dr. Tran? No, thanks. Next is Dr. Jon Sonoda.

Jon Sonoda: Hi good morning, my name is Jon Sonoda I'm the medical scientist for Sanofi-Aventis. And I'm basically here to testify for Ambien CR for possible inclusion to the formulary. I guess the question comes is Ambien CR more effective than Ambien. And what you may not have known is you know Zopiclone was an isomer for Sanofi-Aventis. And Zolpidem was actually licensed out to pharmacy [inaudible]. So if you remember those bottles used to say [inaudible] on those purple bottles. Neither of them were indicated for long-term use. Just like benzodiazepines which have an indication for seven to ten days.

Now most patients that have insomnia according to the world health organization, if they have insomniac episodes for two weeks, it's considered chronic. The NIH says four weeks. What this means is that the majority of patients that go to see a physician for insomnia are chronic. How are we going to treat this? This is why Sanofi came up with CR to treat chronic insomnia for sleep maintenance.

We do have trials to show superiority over Ambien, we have a high [inaudible] trial that actually took patients, put them on Ambien, and [inaudible] patient population of 24 was crossed over to Ambien CR. When you do a crossover, the study becomes very powerful. What we found is that exposing these patients to traffic noise, they've actually slept through the night better on Ambien CR. So we decrease wait time after sleep onset. Which is how the FDA looks at treating sleep maintenance. This is very important, because this is how you determine whether or not a drug can be used for long-term.

There's different kinetics have done a lot of things. The patients aren't exposed to the whole 10mg dose. By [inaudible] there is some safety benefits due to lower therapeutic levels at peak times. We also increased the duration from hours three to six in the morning that took over sleep maintenance. In our [inaudible] trial, which was mentioned in the poster. This trial was six months on Ambien CR. And it's the first time we re-looked at looking at drug tolerance. Because patients were allowed to take as many tablets as they wanted to. We wanted to see if they took it three

times a week, seven times a week, and after months would they take more tablets. And the answer is no. None of the patients increased their tablet dosage. An N of 700. The placebo group did start to take more tablets. After six months the trial was stopped and what we did is we looked at adverse effects and withdrawal symptoms. After one day of rebound, the Ambien CR group went exactly back to placebo on total sleep time and wake time after sleep onset. We had 20 criteria for doctors to look at. Things like was there increased anxiety, did they have fatigue, headaches, loss of appetite upon discontinuing the medication. None of which was significant. So this is important because now we have a trial to say there was no tolerance, and when we stopped it there was no withdrawal symptoms on Ambien CR.

The NIH also had a consensus statement that looked at different drug therapy. And they actually go over stuff like Trazodone and the tricyclic antidepressants. Both of which are commonly used, which have no data. In fact tricyclics and Trazodones are rarely used for depression due to lack of efficacy and adverse effects. In that consensus statement they go and say that the non-benzodiazepines are the most effective with cognitive behavioral therapy. That's their recommendation. This is important because rarely do you see drug disease states where some of the primary first line drugs are not even approved by the FDA for treating chronic insomnia. Ambien CR does have that indication and can be used for long-term use. Any questions?

Dan Lessler: Thank you. Next is Cari Creasia.

Cari Creasia: Good morning, my name is Cari Creasia and I am a psychiatric patient. I have been taking Rozerem for over three months now. And I noted in some of the comments I was listening to, this gentleman over here mentioned that benzodiazepines. I have tried just about every drug there is for sleep disorders. I'm treated for ADD, depression, and anxiety. I'm a difficult person to put to sleep. When I'm suffering from any kind of stress at all I virtually get no sleep. On Rozerem, I can tell you that I sleep through the night, fall asleep easily, I can't even tell you when I fall asleep because it happens so easily and it, I wake up virtually with no symptoms. No headache, no grogginess.

And prior to being prescribed this drug, my sleep patterns were so disruptive I could not drive. I didn't even trust myself to drive. I was treating my children poorly. And I'm going through divorce right now. Sleep disorders are chronic and debilitating. I'm finding that a lot of my depressive symptoms and a lot of my relationship issues are no longer a problem.

This is the first sleep aid that I have been able to take continuously and see the type of results that I have. My behavior prior was like that of a child going through their terrible twos. If I didn't get my way I threw a fit, I couldn't function in relationships, I was not easy to tolerate. Now that I'm sleeping regularly and through the night, I do not have those problems anymore.

So I wanted to make it clear today that that drug has helped me immensely. Rozerem, because of its safety. I also successfully battled an addiction to prescription pain medications five years ago. So I have to exercise extreme caution when using any medications. And Rozerem is in a class that does not expose me to any danger. I'm functioning at a much higher level now, and Rozerem has afforded a safe, effective answer to my problem. It has enabled me to face my future with renewed hope and a smile instead of barely audible grumbling in the morning wearing a frown. I've renewed friendships and I'm happy to say I sleep very well. So obviously I'm here to [inaudible] Rozerem and would hope that maybe other people can have the same satisfaction that I do. Thank you. Does anybody have any questions?

Woman: I have a question. Are you enrolled in one of our plans? Medicaid or a Uniform medical plan?

Cari Creasia: No I am not.

Woman: And are you being paid to speak today?

Cari Creasia: No I am not.

Woman: Okay, thanks.

Dan Lessler: Thank you, thank you. Next is Dr. Gene Felber.

Gene Felber: Morning, I'm Dr. Gene Felber with Takeda. I'm a clinical and outcomes manager, epidemiologist, and biostatistician. Thank you for taking, allowing me to speak today. And for my three minutes of [inaudible]. As you well know, Rozerem is a MT1 and MT2 receptor agonist. It does not bind or have any affinity for GABA. It is shown to be consistently safe and efficacious in reducing sleep latency. It also increases total sleep time as measured by polysomnography. And I also wanted to point out based on the scans that subjective sleep latency and objective sleep latency are two different things and they don't correlate particularly well.

One of the studies that was mentioned in the update of the update was the, I think was that by Griffiths. Roland Griffiths and he is used by the FDA, I'm sorry the DEA to examine the abuse potential, abuse liability of drugs.

And in that study what he does is he takes subjects, he randomly allocates based on whatever, there could be placebo, in this case it was ramelteon. And he looks at the abuse potential at doses up to, in this case 20 fold the recommended dose. So up to 160mg of Rozerem. The subjects were asked how much they like the drug if it has any perceived value other than what it's indicated for. So off label or abuse potential. If it's, has any street value and can be sold for such. And in those studies that he does with ramelteon there was no statistically significant difference, and also effects measuring sedative anxiolytic effects of cognitive and behavioral performance. As it pertains to abuse potential, Rozerem was not found to have any abuse potential, not have any street value, and not to be a drug that was well liked by people who have an affinity for that type of behavior.

We have five well established randomly, sorry, placebo controlled trials that are, you know up to I think the end is 2,400. We have short-term, we have long-term studies demonstrating safety and efficacy. There are again only a couple of those have made it to publication, but given the uniqueness and the method of action as it differs from the benzos, we ask that the committee carefully consider Rozerem for their, on the PDL.

I also wanted to comment briefly on.

Dan Lessler: Sorry but you're out of time here.

Gene Felber: Oh, okay.

Dan Lessler: So thanks. Are there any questions?

Gene Felber: Okay.

Dan Lessler: Thank you. So next is Dr. Larry Cohen.

Larry Cohen: Larry Cohen, I'm on the faculty at WSU, associate director of psychopharmacology research and training for WimiRT and I should disclose I'm on the USP psychiatry expert committee. A couple comments I wanted to make and I wanted to suggest that the newer benzodiazepine, these are actually selective benzodiazepine BZ1 receptor agonists be considered as preferred agents. So I'm speaking positively about all of these agents. And also wanted to make a comment about the limitation. The ten day limitation on the, or the ten dosage limitation on the number of dosages that can be given for patients that receive these drugs. In a lot of states there's a limitation and in chronic insomnia consumers that obviously is problematic. The older benzodiazepines and other agents have true limitations and I just wanted to really quickly go over the treatment goals for an ideal sedative hypnotic agent are to restore normal

sleep architecture, have little or no rebound insomnia on discontinuation, little or no abuse potential to prevent intermittent or short-term insomnia from becoming chronic insomnia, and last, have little or no impact or improved daytime performance, which is an active area of research in sleep today.

There are comments in the report that you all received from 2006 from the Oregon group about only case reports in the literature about substance use and abuse of these agents. And they cited Zopiclone and Zolpidem in that report. It's interesting that only case reports out of millions of people that have been treated with these drugs is what we find. There's very limited abuse in the literature and they also commented and just for your information this is on page 35 of the report.

In the UK there was a study looking at people that were admitted to addiction treatment sites and of those about 300 people in their study, about 80% were using these drugs for sleep and about 20% were using them recreationally. And interestingly in the community, the way people abuse them is to force themselves to stay awake after they take them. Which is pretty bizarre behavior you have to admit.

Another thing that's really key to this class of agents is the quality of life issues. These drugs improve daytime performance, meaning people's sleep quality is significantly improved, and it was found in the studies that were cited in the report. They also have limited or no impact on cognition which is a serious problem with the benzodiazepines, older agents, and also Trazodone, which is very frequently used because it's so inexpensive.

And the last is neuromuscular response time. People driving having a reduced ability to stop in time, they've also used a number of neuro-cognitive tests including the digital symbol substitution test. And there are serious problems associated with memory, so it's clear to me that these agents and the three considered, Sonata, Lunesta, and Ambien. All three of those agents should be preferred agents compared to the older agents that have serious limitations. Thanks for considering my comments.

Dan Lessler: Thank you. Any questions or comments? Okay, thanks.

Larry Cohen: I should have said I was not here speaking on behalf of any company by the way.

Dan Lessler: Are there any, Susan are you there?

Susan Carson: Yes.

Dan Lessler: Yea, I was just going to ask committee members if there are any last questions for you in light of stakeholder input.

Man: Susan did you hear the last speaker?

Susan Carson: I did.

Man: And what are your comments?

Susan Carson: Well, our report was not designed to look specifically at the older benzodiazepines compared to the newer drugs. But we did look at active controlled trials and in summary we did find that the evidence comparing the two classes of drugs was very limited. There's no studies directly comparing Eszopiclone, ramelteon, Zolpidem extended release to a benzodiazepine. So the only evidence is for Zolpidem and Zaleplon. And in the limited head to head studies, compared to benzodiazepines, they were similar in efficacy and short-term adverse events. The issue of abuse and dependence and what the speaker mentioned would be seen in other than short-term trials which is what we looked at regarding the benzodiazepine, so I couldn't comment on that.

Alvin Goo: Hi, it's Alvin. I'm trying to get a grasp on these studies with compared to placebo. Can you give me a range in minutes on the improvement that you generally saw in sleep latency and duration?

Susan Carson: Yea, let's see. I think on one of the slides.

Alvin Goo: That was with ramelteon.

Susan Carson: Okay. So on slide ten, this was objective sleep latency measured in a sleep lab. And the mean difference from placebo for the different drugs ranged from 13 minutes up to 21 minutes.

Dan Lessler: So I think the 21 minutes.

Susan Carson: So between ten to 20 minutes.

Alvin Goo: Oh okay, I thought that was just for the ramelteon compared to [inaudible].

Susan Carson: It's also, there was a study of Zolpidem compared to Eszopiclone also versus placebo.

Alvin Goo: Okay, thanks.

Susan Carson: And they used the same outcomes.

Dan Lessler: Okay, other questions for?

Ken Wiscomb: This is Ken Wiscomb. Are there, is there any literature that looks at the interaction between this class and SSRIs, SNRIs, and or atypical anti-psychotics?

Susan Carson: I think there are some new, there was one newer study comparing the combination of Fluoxetine with one of the, I think it's Zolpidem in patients with depression and insomnia. But nothing in our current report.

Ken Wiscomb: Thank you.

Dan Lessler: Okay, are there other questions or comments? Okay. Thanks Susan, that's helpful. I think we can let you go now. We appreciate your staying with us here.

Susan Carson: Okay thank you, bye.

Dan Lessler: Yea, bye. So maybe we could begin just with the scan, the update to the update in terms of just accepting the scan as an update and would ask if there's a motion to do that.

Vyn Reese: This is Dr. Reese. I move that we accept the scan update on the newer sedative hypnotics.

Ken Wiscomb: Second.

Bob Bray: Second.

Dan Lessler: Okay. Actually I think Ken beat you to it there Bob. All those in favor say, "I."

Group: I.

Dan Lessler: Opposed same sign. Okay, so we can accept the update. Next maybe we just could begin with some observations about this class of drugs.

Vyn Reese: This is Dr. Reese. I have several thoughts. And I sort of just want to, I'm going to think out loud with this class. It's a real question as to whether to add it. I think that there are some softer, there's some soft evidence that they may be better than benzodiazepines but it's very soft. And it's, these drugs also have had, clearly have adverse events associated with them like sleep driving and other serious problems that though they are quite rare.

This is a heterogeneous group and Rozerem, ramelteon really needs to be taken out of this group. It's not a benzodiazepine receptor agonist and it's not, it's in a totally different class, it's a melatonin drug. And it doesn't have the same abuse potential clearly as this class or the benzodiazepines. So it's not in the same group. And it may have different indications. And it's probably going to be more rarely used for special populations who have chronic insomnia. So I don't think it belongs in this class.

I think Ambien CR, the evidence is pretty weak that it's any better than Ambien, and usually companies come out with long acting preparations when their previous drug is going generic, which is the case here. So I'm not sure there's really a huge difference between those two groups, those two drugs. And though one is generic now.

And the rest of them, you know there are pluses and minuses for each one, but they're pretty similar. So I mean it's, I could be talked into adding, you know one of the drugs in this group, but it's very soft so I'm sort of struggling with it as to whether really to do that or not. I think that there are some patients who tolerate these drugs better than they do benzos. And so it's nice to have that, them available. And there are patients with abuse potential where these drugs may be better, although they probably have some abuse potential themselves as was noted, however bizarre that might be. So those are my thoughts in this class.

Dan Lessler: I think those are helpful comments to think over. Other observations or responses to Vyn's comments?

Patti Varley: This is Patti Varley. I would say that it would be difficult for me as well to pick one as being necessarily that outstanding or better than another. So in your comments that there's something that I agree with is that whether we need to just approve them as a class, and I agree about taking that one out because it is a different, so that's what I would say.

Dan Lessler: Alvin?

Alvin Goo: Hi, Alvin. Yea, a note about ramelteon. I think you know I agree it is a totally different mechanism, but I sort of like the way that the group summarized these agents as newer sedative agents, so I don't know, I kind of think that ramelteon is, has a limited use and I would argue that it should just be put in the same class and we should just vote on it as a class. But that's just.

Dan Lessler: Carol.

Carol Cordy: Carol Cordy, I, maybe we could do the same thing we did with the calcium channel blockers. You know if people felt strongly that it's a

different kind of drug then just say the GABA and the non-GABA sedative hypnotics. Would that?

Vyn Reese: Yea, this is Dr. Reese. It's not really, it's not as effective as the other drugs. It clearly is not. In the studies you can't say, if you [inaudible] in with the others it's not as effective in most patients with insomnia. And so it's really, it's a different, it's in a different class. It's sort of more like a chronically, chronic drug. And at sleep latency and everything else it's just, it doesn't really stand up to the others. So you'd either say that it's less effective, but it may be safer. So I mean, it just doesn't fit. And that's my, that's how I struggle with it. I mean we could say it's in a different, we could put it in a separate subclass within this class but again, I struggle with it because it's just not, it's like an apple and an orange.

Dan Lessler: I think Carol's point though, if you just, sort of looking at how to classify them is just a newer set of sedative hypnotics, you know GABA versus non-GABA and have, sort of deal with it that way might be a, it would seem to address your, everybody's issues. Bob.

Bob Bray: Question for Siri. Excuse my thick headedness, but I always have to reorient myself as to, since all these are on prior approval currently.

Siri Childs: And they're on EPA.

Bob Bray: Okay, so by, if we move to do this in place, and they're on the PDL does the EPA continue? Or does that go away?

Siri Childs: We can do it either way. We can continue the EPA even though we have preferred and non-preferred drugs. So you tell me what you want us to do and we can do it.

Dan Lessler: I guess on the EPA, what do you look for now in terms of criteria?

Siri Childs: It's basically the FDA labeling.

Dan Lessler: Other comments or questions? Yea.

Janet Kelly: Janet Kelly, Alvin was kind of discussing this as well. I'm trying to look at these as one table that talks about the mean difference in latency. I look at that and I'm like 13 versus 21. Is that really clinically significant? I lie there at night a lot longer than that, and I'm not really sure that means a whole lot of difference. And then I don't see where the duration is. I mean when they talk about, but how much, I mean what are we talking about. They get an hour more sleep at night? They get two hours more sleep at night? That's the kind of piece that I think would be helpful to have and I don't really see that. And I think the studies don't report it that way,

maybe for good reason. Because those of us that have insomnia that aren't [inaudible].

Dan Lessler:

Alvin.

Alvin Goo:

Yea, I agree. Thanks for bringing that back up. And my other concern is that by putting an agent on a PDL sometimes that gives representative sort of advertisement, and by us putting on this PDL I'm not sure that we are recommending this as a first line agent, although in some cases it might be appropriate, but I think the evidence is, as far as safety is not out there and it needs to be done, and I just would like more information. So I just want to make sure that if we are going to put these agents on a PDL that we are not endorsing this agent as a first line, this class.

Dan Lessler:

Okay, I mean I think first and foremost our comment is to safety and effectiveness about, across the class. And then it goes from there.

Siri Childs:

This is Siri Childs again. If you're struggling you can always say that this is not a drug class that you would like on the PDL also.

Vyn Reese:

This is Dr. Reese. I'm not sure that we shouldn't have it on the PDL though. I, you know, I think there are some advantages, but the data is soft. So it's like, if we're going to be really evidence based I don't think we can consider this hard evidence that these drugs are better than the benzos. But there's some soft evidence that they are and there's, I think addiction potential is less. So it's a hard call.

Carol Cordy:

I'm curious, the benzodiazepines that are sleepers are not, there's no limit on number per month, but it looks like all of these there's a limit to ten a month, and I'm just curious how that decision came about. Because on the other end, you know there are some people that need medications every night. Whether it's these or whether it's benzos or Benadryl. Does anyone know?

Man:

About the.

Carol Cordy:

About the ten day.

Dan Lessler:

Siri do you want to comment?

Siri Childs:

I really am not prepared to address that issue. I think that it's beyond the scope of this discussion.

Dan Lessler:

Okay. Jeff.

Jeff Graham: Well I just wanted to support Siri that I think if that wants to come forward, you need to do that in your DOR portion of a meeting and ask that to come forward.

Dan Lessler: Any other? So, I'm wondering if there is a motion here. Maybe that'll help us crystallize our thinking.

Vyn Reese: This is Dr. Reese. I'll go ahead and try this that I mean I'll accept with happiness anybody who wants to help me out. After considering the evidence of safety, efficacy, and special populations for the treatment of insomnia, I move that Zaleplon, Zolpidem, Eszopiclone, and Zolpidem extended release are safe and effective. No single drug is associated with fewer adverse events in special populations. These drugs can be subject to therapeutic interchange in the Washington preferred drug list for the treatment of insomnia. Ramelteon is another sedative hypnotic that's not a member of this class and can't be substituted for the others.

Man: Would you like to add if it's safe and efficacious and so forth.

Dan Lessler: Right, with respect to Ramelteon.

Man: What did you say?

Dan Lessler: Want to add that safe and efficacious. Same as we have on the other.

Vyn Reese: Is another, okay. Is another sedative hypnotic that is safe and efficacious and is not a member of this class. That cannot be substituted for the others. Ramelteon is safe and efficacious, is another sedative hypnotic that is safe and efficacious. It is not a member of this class and cannot be substituted for the other medications for the other agents. And cannot be substituted for the other agents.

Carol Cordy: Carol Cordy. It is a member of this class.

Woman: That's what I was going to say. Yea.

Carol Cordy: As stated, it is a sedative hypnotic drug. So I think we have to word that.

Vyn Reese: I'll just say is not a benzodiazepine receptor agonist.

Woman: That would be more specific.

Carol Cordy: Well and if, I was looking back at how we worded the calcium channel blockers. We said I move calcium channel blockers may be considered two subclasses. So I'm wondering if we can.

Vyn Reese: That's fine. [inaudible] wordsmith that.

Carol Cordy: Yea, put it up in the main part. Because we're not saying that, that we're saying they're safe and efficacious, but we're not saying they're equally safe, or equally efficacious, which was your concern I think.

Janet Kelly: Janet Kelly, back to the practical stuff here, I'm not sure what we've accomplished by saying that last sentence down there about the ramelteon, how are we going to use that? Who could, who can't, I'm confused. I thought the idea was that we would want that for someone who had, you know a drug abuse potential or something to that effect, but we haven't said any of that.

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Man: Chronic insomnia, it's not a short term agent, it's you know it can't be substituted for the other drugs easily. So you know, but it is, it may be safer, and it may be efficacious in subgroups. So it's you've got to put it in there somewhere.

Dan Lessler: Is the point that you would want ramelteon available for special populations then, is that the distinction we're trying to make? To actually specify that? Which would be people with, whenever there's concerns about substance abuse or chronic insomnia? I mean I sort of agree with Janet. I mean it's hard to know.

Vyn Reese: I think that would. This is Dr. Reese, I think that would be better addressed by a special request for that agent. I mean it's not like the others and I think it would be not in this class.

Alvin Goo: Hi it's Alvin. I think ramelteon, another complication is that it hasn't been studied in patients with abuse.

Dan Lessler: Right.

Alvin Goo: And so I, even though I think that's where it should be, I can't. I don't have any evidence to say that's where it should be. So that's the other complication.

Carol Cordy: Carol Cordy again. Can I give a shot at trying to put all the drugs in the same class and then separate them out. If we say, as we did with calcium blockers, I move that the newer sedative hypnotics way up at the top, the first I move that, before listing the names. I move that the newer sedative

hypnotics be considered two subclasses, and then what you put down below the benzodiazepine two subclasses and then the benzodiazepine receptor agonists and the non-benzodiazepine receptor agonists.

Man: [inaudible] melatonin.

Carol Cordy: We want to call it, what is it called?

Man: Melatonin receptor agonist.

Carol Cordy: And the melatonin. Well but I mean to leave it open, if there's something new that comes down. Either way. And then you can, well.

Vyn Reese: This is Dr. Reese, I'm not moving that they be divided into two, I'm moving that they're already two, okay. Recognizing that so you can't, the motion is not, it's just not correct.

Carol Cordy: Well, but they're, they haven't been divided into two, unless I mean. It, unless we want to have, change the name to newer sedative benzodiazepine agonist hypnotics.

Vyn Reese: What we did before with the calcium channel blockers we just said, calcium channel blockers are divided into two classes, the non-dihydropyridines, and we listed those, and the dihydropyridines and we listed those. We just separated them by an and, and I think that's probably a better way to do it.

Dan Lessler: So just after the benzodiazepine receptor agonist here put the specifications.

Vyn Reese: Yea that's what I would do. I move that the newer sedative hypnotics, the benzodiazepine receptor agonists, and list those, and Rozerem, a non-benzodiazepine receptor agonist. Rozerem.

Woman: So you don't want the benzodiazepine receptor agonists listed.

Vyn Reese: No I want the, I mean they're the first one. I move that the newer sedative hypnotics be considered as two subclasses, benzodiazepine receptor agonists listed, and ramelteon, which is misspelled, a non-benzodiazepine receptor agonist.

Jeff Graham: This is Jeff. Again, consistency, why don't you say, "And a non-benzodiazepine receptor agonist, parentheses."

Vyn Reese: And at the end I would just say ramelteon is another sleep [inaudible] that is safe and efficacious, and cannot be substituted for benzodiazepine receptor agonists.

Woman: Just, I think the last sentence can be removed, the very last one, since we repeated that above. And then say, I'm just adding to what you're saying, that I think you need to say that they're all safe and efficacious. And then qualify it later on. So to end this big long sentence, are safe and efficacious, after ramelteon. So go back up to the listing, the sentence. And a non-benzodiazepine receptor that is ramelteon are all safe and efficacious.

Woman: You could just, you could put, no newer sedative hypnotic is associated with fewer adverse events in special populations.

Man: But that's not true. It is not true. I mean basically ramelteon is not the same as the others. The other ones have you know sleep driving, amnesia, all sorts of other side effects ramelteon doesn't have. And it's not true that, it's safer than the others but it's probably less effective. So you can't put it, you can't state it that way.

Woman: Well we're not saying they're equally, we're just saying they are safe and efficacious.

Man: Well that's the presumption when you read it that way.

Dan Lessler: So, maybe no newer associated with. Would this then also specify that ramelteon cannot be therapeutically interchanged?

Man: Well yes.

Dan Lessler: Right, okay.

Man: Right, because it has to be, you have to say no benzodiazepines.

Dan Lessler: So, but I think.

Man: [inaudible] fewer adverse events in special populations.

Dan Lessler: Right.

Man: The benzodiazepine receptor agonists can be subject to therapeutic interchange.

Dan Lessler: Right.

Man: Rozerem cannot be substituted for other drugs in this class.

Dan Lessler: So, I mean the essence here is that we're saying that these are across the board safe and efficacious, that I think we're moot to the point of comparative efficacy and safety because, I mean I think in total, looking at this from what I'm hearing from the committee is that there's just, there's not a lot of good data. I mean there's some general indication, but we're acknowledging that one of the agents works through a different mechanism of action and therefore it should not be substituted.

Man: Right, except the problem I see is like about the third sentence. No newer sedative hypnotic is associated with fewer adverse events in special populations. That's not true when you list ramelteon with the other two. You're acting as if it's the same, and it's not. And it has fewer adverse events. Also it's less effective.

Alvin Goo: You know, I guess just to split hairs here a little bit. I don't think we have evidence that that's the case. I think we have rationale that that is the case, there's probably ways that people would use those that do make rational sense, but based on the evidence I don't think that we can say that there is any drug that's better in or fewer adverse populations, adverse events in special populations.

Man: It has not been associated with, as far as I'm concerned, there's been no reports of ramelteon causing amnesia, sleep driving, other things that are associated with this other group. So it has not been associated.

Alvin Goo: Those are case reports though.

Man: I know but.

Alvin Goo: Those aren't, you know I think if we're looking at comparative efficacy there's no comparative efficacy or comparative side effects that we have evidence for.

Man: That's in short term trials, again for risks you have to look at the general population and case reports are the best way to do that in big populations, not in small controlled trials. So risk is not assessed that well.

Woman: But haven't these drugs been available for different lengths of time as well, so therefore your case reports are going to be influenced by the number of people treated and the number of, and length of time it's been available.

Vyn Reese: Yea this is Dr. Reese. And ramelteon may have a whole bunch of different side effects we don't even know about yet because it hasn't been out that long. So we can't make that statement.

Woman: I would agree with, it sounds like deleting, the highlighted sentence. But I still think to be consistent with what we generally do, we want to say after you have the parentheses ramelteon, that they are safe and efficacious. And that's what we say. We don't say they're equally safe and efficacious, we don't say they're equally safe, equally efficacious, but that they are safe and efficacious, and that's what we always, you know are looking at. Is to compare these. Because this isn't. Or somewhere we have to say that, don't we?

Dan Lessler: Yea. So, I mean. Go ahead Al.

Alvin Goo: I'd just go back to ramelteon and I'm not quite certain I agree that it's weaker and I just don't think it should be even on the PDL. I don't think there's much of a role and if there is, then they can write DAW.

Dan Lessler: Okay, you know what I'm going to ask, could you scroll down so we can see this again? And I'm alright because this is different than what you originally proposed and I know. And I'm wondering if people could read this and if somebody would be willing to put this forward as it is right now as a motion.

Vyn Reese: This is Dr. Reese. I think it, when I initially you know voted I had ramelteon at the end. And you know separate totally from the others. And not even saying it was, it should be, that it could be substituted for the other agents. So I mean I'm, I think Alvin is right in that ramelteon may be just, you know it doesn't fit here at all.

Donna Sullivan: I have a question. Are you? This is Donna. Are you, is your intent to make ramelteon included on the preferred drug list? Or are you trying to say you want it to be non-preferred?

Woman: You know I want to clarify this a little bit. The preferred drug list is different from the preferred drugs on the preferred drug list. And my understanding of what we've been talking about is that we maybe don't want any of these as preferred drugs. It doesn't mean that they won't be available with prior authorization is what they are now. So I think that's a decision that kind of which is separate from this in a way because we're not necessarily saying that these are going to be preferred drugs on the PDL. We're just saying how, you know whether we want them to be or not and I sort of got a feeling we don't. We want them to stay PA as they are, right?

Vyn Reese: Yea this is Dr. Reese. I think that's not in our [inaudible] here. We can let that be decided by the powers that be. But actually it's not that bad the way it's written. You know it really isn't. And I think it gives a lot of flexibility to whether they're, you know, and how they're managed. There's one problem with spelling. It's right before ramelteon, it should be agonist instead of, leave the off of agonist. There you go.

Dan Lessler: Okay, so would you want to read this and put it forward?

Vyn Reese: [inaudible]. I mean that's fine. I'll go through. I think this is, even though it's sort of vague and sort of inclusive, it probably will work. Okay.

Man: [inaudible]

Dan Lessler: Siri do you have a, you have a comment.

Siri Childs: I just think that we need to have a little more direction. I don't know if we know what to do from what's there now so, please give us more direction.

Patti Varley: This is Patti Varley. My only concern about that is that the review didn't give us much more direction, so we're struggling with the fact that the data is lacking in regard to making a more specific statement.

Dan Lessler: Siri, help me in understanding why you need more direction and in what way.

Siri Childs: Well because I hear Carol Cordy saying that she doesn't think that any of these drugs should be a preferred drug, but when we go through the process of establishing a preferred drug list, it's understood that the drug, there will be something that's preferred and something that's non-preferred. So are you really talking about adding this as a preferred drug class? Or would you just consider saying that this isn't a preferred drug class because all these drugs are a little bit different and there may be special uses for this drug and just leave it up to expedited prior authorization in our regular program.

Vyn Reese: This is Dr. Reese. I think these drugs should be on the PDL. At least one representative of them. I think that that's, there's relatively good, that's an arguable point. That's my personal belief. I think they need to be, they're commonly used, you're going to get tons of, you're going to just get swamped by these drugs. And as long as you have one drug in this class where you can say let's use this one.

Dan Lessler: And one drug in either, under either mechanism of action.

Vyn Reese: And then and ramelteon you can handle separately because we said it's not interchangeable, and we're not sure whether it should be on the PDL or not. I mean that's sort of my view of the way we've written it here. I mean, and is that. I mean is there any other way we could phrase this?

Dan Lessler: Actually the way I would interpret this is saying that these, all of these medicines should be on the PDL, but you know and which one actually becomes the preferred agent would be left up to you. Up to HRSA. And then if. No is that?

Duane Thurman: This is Duane Thurman. I think that the kind of guidance we need is that the next step here once you save it, like for instance let's leave off the ramelteon and just say the others. If we look at what you've got up there what we, what our next steps are is to look at the rebates that we've received, the rebate offers and then to make a selection based on the cost analysis that we do. And the problem that this presents to us is that by saying that you've got this second class, this leaves the potential there where we could leave that drug out completely. And so you either, what you're either saying is you need to have one of each, you need to have something representing you know the ones we can interchange and then you also want us to have the availability of this different drug. So essentially it seems like you're almost calling out that we need to have one of each, and any other drug that comes in the future, you know that you'd have the two subclasses.

Dan Lessler: Okay, so what if we were to say that there's evidence that all of these agents, be they you know benzo receptor agonist or not are safe and efficacious, and then just said specifically that, I guess I suppose that ramelteon can't be substituted. I mean the others can, but ramelteon cannot. That would do it.

Alvin Goo: Or would it be better just to say the PDL must contain one benzo receptor agonist. Because I don't know if it, I don't know if we really want only ramelteon on our PDL.

Dan Lessler: No but, it would not be only ramelteon. I mean if you said they're all safe and efficacious.

Donna Sullivan: It, Dr. Lessler this is Donna. It could end up that way. If you were to say in our cost analysis and ramelteon became, was the cheapest agent and there was a huge cost break between the rest, it would be selected and then we wouldn't be able to substitute it for the other ones because you're telling us we can't interchange.

Vyn Reese: And they way we've written them now, at least one benzodiazepine receptor has to be on it.

Donna Sullivan: Right.

Vyn Reese: Okay, and we're not saying anything about ramelteon. It may or may not be depending on you know what's decided. I mean we're not saying it has to be on right now.

Donna Sullivan: I think I've captured what you were trying to say Dr. Reese about you wanted it, ramelteon may or may not be on the list but you wanted something else available.

Vyn Reese: Exactly. I think that's what.

Donna Sullivan: It's captured right here in the way it's written.

Vyn Reese: It's captured now.

Dan Lessler: Okay.

Vyn Reese: Should I read it again?

Dan Lessler: Hold on. Do you have a?

Man: Yea. So going back to, there's been lots of discussions about EPA. And in the past, you know that has been our privy. We have recommended that medications be part of an EPA process. So one of the comments was, well that would be too onerous, I mean it would be too cumbersome. So the question that I have is how does that process work now. Is it too onerous of a process that's in place, does it work well, if it were to remain, this category were to remain part of an EPA type situation, is that doable?

Siri Childs: This is Siri from HRSA and it would certainly work for HRSA because it's worked for what, five years. You know as new drugs come on and this, you know that are sedatives and hypnotics, they go on EPA with FDA labeling.

Man: So I guess the comment that I'd make is, if it's working and our concerns are that the data's a little lacking, there are some safety issues here, and we want them to be used appropriately, is that not an okay avenue to ensure that? I mean is, I guess that's what I ask of the committee.

Dan Lessler: Which is to, what's.

Man: Is to recommend that they remain part of an EPA process. If that's what the committee thinks should happen.

Dan Lessler: Hold on.

Man: I don't think it should happen. That's why I'm.

Dan Lessler: Okay, okay, well then that.

Siri Childs: This is Siri again. You actually could have both. You could have it both ways for HRSA. You know just like we do have some drug classes where both the preferred and non-preferred have EPA criteria, you could have that in this class too. And then we could take the, we could honor the supplemental rebates you know and select a drug based on your recommendations. But even the preferred drug would be, would have the criteria.

Dan Lessler: Okay. Carol.

Carol Cordy: In terms of, let's say there's two patients that need to get a medication. And one patient needs, I'm saying if this were part of the list without EPA on everything. They need a benzodiazepine receptor agonist. And there's one, say whatever the first generic is, is easy to get, so they would get that. I guess my first question is would they still only get ten a month, but that's another issue. But and let's say there's another patient who needs the ramelteon, and if it's in the same class I would assume that they would then, it would not be a preferred drug, but it would be available through EPA the way it is now. Is that right? That those two patients, one that needs a benzodiazepine receptor and one that needs the one non-benzodiazepine receptor, they both would get their medication. One might get it substituted because they'd maybe prescribe something else, they'd get the Ambien.

Woman: [inaudible] too complicated.

Carol Cordy: I mean it's just, you know if I'm the patient I need to get one of these drugs, what is sort of the easiest way to get that. It sounds like if this is part of the PDL, it would be a little easier if it were as Vyn suggests, if this were part of the PDL, not a non-PDL class.

Dan Lessler: So.

Vyn Reese: I'm just going to make the motion as it stands.

Dan Lessler: Yea. So let's do that.

Vyn Reese: I think it's okay. It's not perfect. After considering the evidence of safety efficacy in special populations for the treatment of insomnia, I move that the newer sedative hypnotics be considered as two subclasses.

Benzodiazepine receptor agonists, Eszopiclone, Zaleplon, Zolpidem, and long acting Zolpidem, and a non-benzodiazepine receptor agonist ramelteon. Newer sedative hypnotics are safe and efficacious. The benzodiazepine receptor agonists can be subject to therapeutic interchange in the Washington preferred drug list for the treatment of insomnia, ramelteon cannot be substituted for other drugs in this class. At least one benzodiazepine receptor agonist must be preferred.

Dan Lessler: Is there a second?

Patti Varley: Patti Varley, I'll second it.

Dan Lessler: Okay. I'm going to ask that we just vote. All those in favor say, "I."

Group: I.

Dan Lessler: Opposed.

Group: Nay.

Dan Lessler: Okay. Did you get that? So there's one, one opposed. And the motion carries. And we're going to adjourn for lunch. And what should we do in terms of being a little bit late here.

Jeff Graham: Well I'll try to get a hold of our next presenter and see if we can delay it about 15 to 20 minutes.

Dan Lessler: Okay.

Jeff Graham: And get back here.

Dan Lessler: Okay try and get back by 1:15 or.

Jeff Graham: 1:20.

Dan Lessler: 1:20, okay so we'll re-adjourn at 1:20. Thanks.

Roger Chou: This drug class review on pegylated interferons for chronic Hepatitis C. Can you guys hear me or is there a weird echo or something?

Dan Lessler: No echo, we can hear you fine.

Roger Chou: Okay, great.

So next slide. Literature searches. We just did our standard literature searches. I'm not going to go into those in detail. But we looked at

MEDLINE, Cochrane, and DARE records list. And we solicited dossiers from the manufacturers of the pegylated interferons.

Next slide. In terms of our data collection and analysis, we looked at study design and population characteristics. Really our main outcome ended up being virologic response. Sustained virologic response as well as a sustained biochemical response. We did have to look at early virologic response for some of the head to head trials because they were very short-term. But those aren't as good a predictor as sustained virologic response which is what we really wanted. We also tried to look for quality of life and other clinical outcomes. But that data was very sparse, especially on really important clinical outcomes like cancer, and cirrhosis, and need for transplant or those kinds of things. The trials just aren't long enough and pegylated interferon hasn't been used long enough to assess those kinds of things. We assessed all of the trials we included and we performed a meta-analysis which we'll talk about on the next slide.

So for the meta-analysis, we did a, we pooled relative risk, we used a random effects model. There was quite a bit of diversity between trials, we didn't think a fixed effect model was appropriate. We assessed heterogeneity using the Q statistic and the I^2 statistic and we did subgroup analyses based on the presence of HIV, the type of hepatitis C genotype as well. We performed sensitivity analyses, looking at study quality, effects of unpublished data, effects of outlier studies. And because head to head data was very sparse, really none for even sustained virologic response, so we did perform some indirect meta-analyses each of them comparing pegylated interferon alfa-2a or 2b plus Ribavirin versus amount of pegylated interferon plus Ribavirin.

Next slide. In terms of the key questions, the first key question is kind of the standard comparative effectiveness question. Looking at pegylated interferon alfa-2a plus Ribavirin versus pegylated interferon alfa-2b plus Ribavirin. And we also looked at whether, how duration of treatment or dosing protocols affected estimates of comparative effectiveness. Key question two looks at comparative tolerability and safety. Same comparison. And key question three assessed effectiveness as well as tolerability and safety in subgroups. So demographic subgroups including age, racial groups, gender, hepatitis C genotype, markers of disease severity, use of other medications, or presence of comorbidities such as HIV.

Next slide. The populations we were interested in were non-pregnant adult outpatients with chronic hepatitis C. And we included subgroups with HIV co-infection, non-responders, or relapsers including patients being retreated. Subgroups based on gender, race, or age, genotype, markers of disease severity, and other comorbid conditions, including obesity which

is important because one of the pegylated interferons is a weight based dosing and the other is fixed dosing which has been postulated as a potential advantage of one over the other.

Next slide. [inaudible] of the intervention. So pegylated interferon alfa-2a, or Pegasys. This is one with fixed dosing, 180mcg per week. Pegylated interferon alfa-2b is PEG-Intron, which is dosed by weight, 1.5mcg per kg per week. Both are approved for a separate, a different brand name of Ribavirin, but the Ribavirin is actually chemically identical. The pegylated interferons vary in terms of the molecular weight and the peg part stands for polyethylene glycol, so those molecules are attached to interferon molecules. So it's, the size of that molecule also varies and that affects the half life of the drug and other pharmacokinetic properties.

Next slide. So I mentioned the outcomes that we talked about before. Really, most of what we ended up getting was the same virologic response and biochemical response. There was almost no data, or none I should say on cirrhosis, rates of hepatocellular cancer, a need for liver transplant, very little on quality of life. And then we looked at early virologic response for the head to head trials. We look at a number of adverse events including withdrawals, depression, suicidality. The most common with the interferons are kind of flu-like symptoms. So the myalgias, fevers, chills, etc. We also looked at hematologic stuff.

Next slide. Just an overview of the included studies. We included a total of 41 randomized trials. Two were rated good quality, nine were rated poor quality, the remainder were fair. There were only two head to head trials. They were very short term. I think they ranged from about four to eight weeks. One was rated fair and one was rated poor. 15 other trials looked at dual therapy with pegylated interferon either alfa-2a or alfa-2b versus non-pegylated interferon. And then there were five trials that looked at dual therapy with pegylated interferon versus pegylated interferon monotherapy. There were 19 dose duration [inaudible] trials and two trials that looked at dose ranging for the Ribavirins specifically. We included five systematic reviews but only one was actually comparative. All the others just reported you know the results of the different trials. And they all only included the same two or three trials, so the systematic reviews weren't terribly helpful. We also looked at 40 uncontrolled and observational studies. They were not comparative and also not terribly informative for this review.

Next slide. In terms of the quality of included trials. None of the trials included were considered effectiveness trials. They all utilized numerous inclusion criteria, they were conducted in specialty settings, they used rigid dosing regimens, and most of them evaluated relatively short-term intermediate outcomes. In terms of the quality criteria, 34% of the trials

described adequate randomization methods. About the same percent described adequate allocation concealment. 12% masked patients and providers, 12% masked outcome assessors, and 85% reported intention to treat.

Next slide. So this is for key question one, the comparative effectiveness question. So first looking at direct evidence. As I mentioned earlier there were only two head to head trials, they only looked at early viral response, and there was no significant difference in the two trials. The two trials were very different in terms of their study design. So Silva was eight weeks, 36 patients, what this trial did was it started patients on monotherapy, and then added Ribavirin for the second four weeks. So it's not a standard use of these drugs. And it found no significant difference in viral response, though alfa-2b you know was, there was a trend towards favoring alfa-2b. For Sporea 2006, this was a longer trial, and it used dual therapy from the beginning. And it also found no difference in viral response, but the trend was in the opposite direction. We didn't think we could make much of these two studies. One of them only included patients with genotype one, and I actually can't remember which one that was, so. But like I said there was quite a few differences between the two trials.

Next slide. So we went to the indirect evidence, because the direct evidence was not in any way conclusive. So we looked at trials that compare dual therapy with pegylated interferon, either alfa-2a or alfa-2b versus dual therapy with non-pegylated interferon. So for that comparison the pegylated interferon dual therapy was superior for sustained virologic response. For alfa-2a there were five trials and the relative risk 2.14 with a 95% confidence interval of 1.32 to 3.47. For alfa-2b there were more trials, ten trials. And the relative risk was 1.28, the confidence interval was 1.10 to 1.49. In patients without HIV infection you can see those results. The relative risk for alfa-2a was 1.55 and for alfa-2b was 1.12. The estimates for sustained virologic response were stable in subgroup analyses based on study quality, genotype, and when we included, or when we added the results of one unpublished trial. So because it looked like there may have been differences in the, you know with each of those with the pegylated interferon dual therapy with alfa-2a or 2b compared to non-pegylated interferon therapy, we performed some indirect analyses.

So this is the next slide. Which says that SVR rates in adjusted indirect analysis. So we have two rows there. The first row compares pegylated interferon alfa-2a plus Ribavirin versus pegylated interferon alfa-2b plus Ribavirin with the common comparative non-pegylated interferon alfa-2a or 2b. So this was, so most of the trials of dual therapy with peg interferon alfa-2a used non-pegylated interferon alfa-2a and most of the trials of pegylated interferon alfa-2b compared it to trials of non-pegylated interferon alfa-2b. So the comparators were slightly different. For the first

analysis we just pooled everything, and we found a relative risk of 1.67 with very wide confidence intervals. So again even though the previous analysis suggested that there might be some differences, the adjusted indirect analysis it really drops out. You can't really make much with that wide of a confidence interval. We also repeated the analysis just using the common comparative non-pegylated interferon alfa-2b. There was one trial that looked at peg interferon alfa-2a plus Ribavirin versus non-pegylated interferon alfa-2b plus Ribavirin. Even though it was only one trial it's actually the biggest trial of alfa-2a out there. It was about half of all the total patients there. And if you look at that the relative risk is actually 1.00. I've actually never seen that before where you get a relative risk of 1.00. Again the confidence intervals are wide, but not quite as wide as with the previous analysis. It again just shows that there's no clear differences, I just thought that it's interesting that the relative risk gets closer to zero when you only look at a common comparator, a true common comparator, not just any non-pegylated interferon dual therapy. We suggest interpreting these results with some caution. There's clinical diversity among the trials in terms of the populations studied, the dosing of interventions, and like I mentioned earlier the comparator treatments. And you see wide confidence intervals. So the estimates aren't precise, and that's actually expected with the indirect analyses. With these analyses you actually add the very variance together from, because you're adding separate sets of trials, so you need, so they're a lot less efficient in terms of the analysis than when you have direct head to head evidence.

Next slide. For sustained biochemical response, this was reported in fewer trials, about half of the trials that, compared to the one that reported the same virologic response. For dual therapy pegylated interferon alfa-2a versus non-pegylated interferon alfa-2a, there was one trial. And it found a relative risk of 1.98. For dual therapy with pegylated interferon alfa-2b versus non-pegylated interferon alfa-2b, the relative risk was 1.17. There were too few studies to perform adjusted indirect analysis there so we did not attempt it.

Next slide. For other clinical outcomes we tried to look at histologic response but there were only three trials and all of them looked at pegylated interferon alfa-2b. Those trials found no differences between dual therapy with pegylated interferon alfa-2b and dual therapy with non-pegylated interferon. For quality of life there is really only one trial, and they didn't give much input, it found small differences between dual therapy with pegylated interferon versus non-pegylated interferon and scores returned to normal 24 weeks after the end of treatment. No studies looked at long term clinical outcomes, we mentioned that earlier.

Next slide. In terms of the effects of dose or duration of treatment on comparative effectiveness, there were 19 trials that compared different

doses, varying duration, or standardized versus tailored treatments, so this means stopping therapy or adjusting therapy depending on early virologic response. There was no direct evidence meaning that all of these trials only looked at either pegylated interferon alfa-2a or pegylated interferon alfa-2b. So very little that you can extrapolate that in terms of comparative effectiveness. For the dose ranking trials of which there were eight, they were all for pegylated interferon alfa-2b. In summary, the trials found that no dose was more effective than 1.5mcg per kg per week for achieving an SVR. The optimal dose in non-responders or relapsers was unclear. And again they didn't really provide useful information on comparative effectiveness because they were all on the same type of pegylated interferon.

Next slide. For duration-ranging trials there were nine studies. They found for genotype one 48 weeks was superior to shorter courses. For genotypes two or three, shorter courses were as effective as 48 weeks particularly in early responders. Again, they didn't provide useful information on comparative effectiveness because they looked at each of the pegylated interferons in isolation. There was no, there was substantial clinical diversity. Indirect analysis wasn't possible because the trials were really designed so differently. They all used different doses and different regimens.

Next slide. There were two trials that looked at different Ribavirin doses and both of them found that the higher doses, 1,000 to 1,200mg weight based were superior to lower doses which were 800mg.

Next slide. So key question two is, addresses safety and tolerability. We only found one small, short-term head to head trial. The other one didn't actually report safety outcomes. It found no differences in withdrawal due to adverse events, flu-like symptoms, or hematologic side effects. In terms of indirect evidence, we looked at withdrawals due to adverse events for dual therapy with pegylated interferon alfa-2a or b versus non-pegylated interferon for alfa-2a and 2b, you can see the relative risks are pretty close. 0.80 and 0.94 with a lot of overlap.

Next slide. Other comparisons. We also looked at rates of neutropenia. So there was only one trial for alfa-2a dual therapy and four trials of alfa-2b. And again the relative risks are quite close, 2.33 versus 2.58 with a lot of overlap. There were similar trends [inaudible] anemia. We found no significant differences in rates of depression or flu-like symptoms and other adverse events were less consistently reported so we didn't attempt to pool data for those.

Next slide. We did look at uncontrolled and observational studies. 40 studies, most of them were non-comparative and they really weren't,

provide useful information beyond the trials. So because they were non-comparative, the quality wasn't great, they weren't less highly selective, I mean they were, they didn't provide better effectiveness information than the trials. They really weren't terribly helpful. There was one study that found no difference in rates of withdrawals due to adverse events directly comparing pegylated interferon alfa-2a versus 2b, so it's the only other head to head evidence. But the rates weren't reported in that trial. If you look at the rates of withdrawal due to adverse events they range widely. 0 to 10% for alfa-2a, 0 to 47% for alfa-2b with almost very, with very similar medians. So again we didn't think you could make much from the non-randomized trial data.

Next slide. So for key question three which addresses subgroups. First race, gender, and age. In general there's some evidence of poor response associated with older age of black race, but we found no comparative evidence comparing effects of pegylated interferon alfa-2a versus 2b based on demographic factors. The majority of patients in the trials were male in all but one study. The average age ranged from 34 to 54, and the race was reported in four of 15 trials. The proportion of black enrollees ranged from 5% to 33%.

Next slide. So we did also look at the effects in different, for different HCV genotypes. So genotype one is the most common in the states, genotype two and three are less common. And so you can see that we stratified the analyses based on the pegylated interferon types. So for pegylated interferon alfa-2a there were three trials of genotype one with a relative risk of 2.24. For pegylated interferon alfa-2b there were five trials with a relative risk of 1.32. Again those overlapped in terms of the confidence intervals. And you can see the other results. There all of them are overlapping. And again, probably can't make too much of that. If you do formal indirect analyses they're going to be non-significant. So we found insufficient evidence to conclude that dual therapy with one pegylated interferon is superior to the other for hepatitis C virus genotypes one, two, or three.

And we also performed a separate analysis for hep C genotype four, remember I mentioned there was one systematic review that tried to look at this, and it actually found that one of the pegylated interferons was superior to the other for SVR, but it was an implicit indirect analysis meaning that they looked at the relative risks of comparative dual therapy with non-pegylated interferon and they concluded that there was a difference because one was significant and the other wasn't. So we basically repeated the analysis, we added one trial that day that had been published since they finished it and you can see the direct results on the first two rows. So for pegylated interferon alfa-2a the relative risk is 2.33, for 2b it's 1.19. And then you can see when you do the indirect analysis,

the results totally drop out. The confidence intervals are very wide, and it encompassed one. And this is just an illustration that you need to look at the, you know inputs and indirect analyses should be interpreted very cautiously because this is often what happens when you start trying to combine different data sets.

Next slide. For HIV co-infections, no direct evidence. So the sustained virologic response for dual therapy with pegylated interferon versus non-pegylated interferon for alfa-2a was 3.22, and for alfa-2b was 1.63. Again the confidence intervals overlap there. For withdrawals due to adverse events similar rates, 0.86 versus 1.17. So we thought insufficient indirect evidence to draw conclusions for HIV co-infected patients.

Next slide. For other subgroups, other comorbid conditions. These were generally excluded from trials. We found comparative evidence. Obesity was looked at as a subgroup analysis in three trials. They found pegylated interferon alfa-2a and pegylated.

[end side A]

Roger Chou:

To be less effective in patients over 75 to 80 kg. Weight based dosing again has a theoretical advantage, but we found no comparative evidence to actually look at whether that plays out in real life. For severity of baseline infection we found no comparative evidence in patients with higher viral loads, more severe fibrosis or inflammation, or other markers of more severe baseline disease.

Next slide. I want to mention a couple of unpublished and upcoming trials because this is, there's a couple of trials that may inform these results substantially. So first just wanted to say that we did find some abstracts that were submitted by, you know the pharmaceutical companies. When we included those in our analyses they didn't change any of the conclusions. There's a couple of large trials that haven't been published yet. So the IDEAL study is the big one, this one has, we just checked about a month ago, no results as far as we can tell have been released yet. But it's going to be by far the biggest trial. It looks at almost 3,000 patients. It directly compares pegylated interferon alfa-2a dual therapy versus pegylated interferon alfa 2-b dual therapy. One of the big issues with this trial though is that the Ribavirin dose varies in the, between the two drugs and also the way that adjustments are made varies for the two drugs and the sponsor of the study had to do some of these things because the FDA required it, but this has already generated a lot of discussion about you know how to interpret, how are you going to interpret the results. The company that did not sponsor this trial has basically made statements to the effect that they're not going to, they may not believe the results because of the Ribavirin issue and some of the other study design

issues. So they've kind of positioned themselves already. But we don't, we haven't seen the results yet. It is only in genotype one patients, so that's the other issue. So it may not answer the question about which is the best pegylated interferon kind of in genotypes two or three. The WIN-H trial is another large trial so some results have been published as an abstract. It's a very large study, almost 5,000 patients. And it compared dual therapy with pegylated interferon alfa-2b with fixed-dose Ribavirin 800mg versus weight-based dosing. So it actually might help inform interpretation of the IDEAL study once that comes out. It did find that the weight-based dosing was superior for sustained virologic response. That was statistically significant, but it's really a pretty small absolute difference. So 44% versus 41%, because the numbers are so big, the number of patients in this trial is so large, you know you can get statistical significance even when the absolute differences aren't real big. So like I said, I think these two trials are going to inform this question more when they're released. And wanted the, everyone to know about those.

Next slide. So for some re. Overall the quality of evidence was fair to poor. Many of the trials were open label. There are a lot of issues about not describing, you know randomization adequately and things like that. We found insufficient evidence to determine whether dual therapy with pegylated interferon alfa-2a, difference from dual therapy with pegylated interferon alfa-2b in either efficacy or safety. The only head to head evidence is short-term and very sparse. Like I said two small trials. The estimates from indirect analyses suggest no clear difference, but the estimates are very imprecise and should be interpreted cautiously due to clinical diversity. Again most of the trials had methodological shortcomings and we're waiting for this IDEAL study, but as I've said before there are already some issues in how those results will be interpreted when they come out.

So, next slide. That ends the summary.

Dan Lessler: Great, thank you Roger. I was going to ask if any of the committee members have questions for you about the presentation.

Roger Chou: Sure.

Dan Lessler: Does not look like there are any questions. So we're going to, Roger can you stay for a few minutes? We're going to get stakeholder input here.

Roger Chou: Yea I can stay 'til about 2:15 or 2:20 or so.

Dan Lessler: That'd be great, thanks. So I have a list of people who signed up to speak to the hepatitis C meds. And first is Dr. Vandana Slatter.

Woman: Inaudible.

Dan Lessler: Yes, please. So and again, wanted to ask people to limit their comments to three minutes if you would, and just identify who you're representing and, that'd be great.

Vandana Slatter: Okay, thank you. Thank you, good afternoon. My name is Vandana Slatter. I'm a medical liaison with Roche Virology and a Pharm D by training with a background in infectious disease. I am also a member of the Washington state board of pharmacy, however today I am not here to represent the board, but rather the company in which I work, Roche Laboratories. The CDC estimates 3.2 million Americans are chronically infected with hepatitis C, HCV in Washington. And in Washington state, HCV is currently the leading indication for liver transplant. In HIV infected patients, HCV is a major cause for morbidity and mortality. Since FDA approval in 2002, Pegasys with Ribavirin has become the most prescribed treatment for patients infected with chronic hepatitis C, we believe for five main reasons.

First, Pegasys is the only pegylated interferon approved alone or with Ribavirin for the broadest range of [inaudible] indications, including the following unique indications to Pegasys. In patients with compensated liver disease and histological evidence of cirrhosis, for chronic hep C infected patients with clinically stable HIV disease, as monotherapy in patients with chronic hepatitis B including E antigen positive and E antigen negative patients.

Second, a wealth of clinical data supports the Pegasys label, and has set new treatment standards such as combination therapy for Ribavirin, with Ribavirin 800 mg for a shorter duration of 24 weeks in genotype two and three patients. Pegasys copegus therapy has achieved the highest reported [inaudible] trial SVRs in patients overall at 63% and also in those most difficult to treat. Seven key studies with Pegasys and hepatitis have been published in the New England journal of medicine.

Third, Pegasys offers durability of response and tolerability. Recent data presented shows that greater than 99% of patients who achieve an SVR following Pegasys alone or with Ribavirin remain HCV RNA negative for a mean of 4.1 years. And this study is ongoing. Pegasys plus Ribavirin had significantly less incidents of depression and flu-like symptoms than the standard non-pegylated interferon Ribavirin. And further safety information is outlined in the package insert, but I'm happy to give an overview if needed.

Fourth, Pegasys is easy to use. It is administered as one standard dose for all patients, except for hemodialysis patients and both pegylated

interferons are administered at fixed dose in patients greater than 85 kg as per the package insert. And Pegasys is packaged as a ready to use pre-filled syringe.

Fifth, Roche's commitment and support to optimize therapy for HCV patients includes research to improve response rates and advance HCV therapy in special populations such as cirrhotics, prior treatment non-responders, and African Americans. Pegasys, a comprehensive support program is also available 24/7 to patients and providers to help manage hepatitis therapy.

Overall, multiple FDA indications, wealth of clinical data and experience, with Pegasys ease of use and tolerability offer patients infected with HCV, including the most difficult to treat the best chance for treatment success. Thank you.

Dan Lessler: Thanks, are there any questions? No, okay, thank you. Next, Dr. Isaac Lloyd.

Isaac Lloyd: Good afternoon, my name is Isaac Lloyd. I am a medical science liaison with Schering Plough, virology division. And I'd just like make a couple of points regarding treatment with hep C in PEG-Intron. The following information supports the use of PEG-Intron by demonstrating effective therapy, predictable response rates, and low relapse rates. The overall response rates for PEG-Intron is 54% based on the registration study with Dr. [inaudible], 52% based on the package insert. In the registration study, PEG-Intron demonstrated a low relapse rate of 18%. If you look at the FDA briefing document table 12, Pegasys demonstrates a relapse of 30%. At a recent AASLD, Dr. Ira Jacobson presented final results from the largest U.S. community based study ever reported. The WIN-R study which I think was a typo, it's the WIN-H study. Just recently the OHSU report. PEG-Intron and Ribavirin known as the WIN-R trial had relapse rates of 15% weight adjusted Ribavirin arm, and 19% in the flat dose Ribavirin arm. Now regarding positive predicted values and early virological response rates, it is not within PEG-Introns label and is from the AMCP dossier. Positive predictive value of early virological response is defined as a reliability of early virological response as a clinical indicator of sustained virological response. Predicting which patients will not benefit from continued therapy will reduce the need for extended treatment. In a retrospective analysis of the PEG-Intron registration trial, Dr. Davis and colleagues evaluated the accuracy of utilizing early virological response at week 12 at predicting treatment response rates. In a cost, efficacy, and analysis of the registration trials of PEG-Intron plus Ribavirin, and Pegasys plus Ribavirin, Dr. Malone and colleagues reported the positive predictive value for genotype one patients. The positive predictive value for PEG-Intron and standard dose of Ribavirin of 800 mg

was 63% and 65% with the unapproved dose of 10.6 mg per kg of Ribavirin. The positive predictive value for Pegasys was 57%. Although the Pegasys cohort reported a higher early virological response, a higher relapse rate was also reported in this group. Therefore more patients in the Pegasys cohort continued treatment from four to eight weeks, even though they never achieved sustained virological response. PEG-Intron is unique in that it has the ability to weight based dose. PEG-Intron is dosed giving 1.5 mcg per kg per week. In published studies, weight based PEG-Intron and Ribavirin demonstrated similar response rates, regardless of patient weight. Pegasys is given at a fixed dose of 180 mcg for all patient weights. In fact, the FDA briefing document states, the heavier the patient, the lower the response rates for Pegasys. Although not approved for co-infection in hepatitis B virus, there is published data with PEG-Intron in these patients. So in summary I'd just like to say that PEG-Intron provides effective therapy across all weight categories, predictable response rates, and lower relapse rates. Because there is differences in two products that would suggest that both products be allowed on the Washington state Medicaid formulary. Thanks.

Dan Lessler: Thanks, are there any questions? Okay, thank you. While we have Roger on the phone I'm wondering if there are any other questions in light of stakeholder input for Roger? No, okay Roger thank you very much. We can let you go.

Roger Chou: Thank you.

Dan Lessler: Take care.

Roger Chou: Alright, bye.

Dan Lessler: So, why don't we just begin. I'm wondering if there are any general observations or comments just on the presentation by way of getting some general discussion here. Bob.

Bob Bray: Well, it seems to me that the evidence is not there to distinguish these drugs on either safety or efficacy. And so, that seems, the [inaudible] information there sounds clear.

Dan Lessler: Other observations or comments. So, can't really say much comparatively.

Patti Varley: This is Patti Varley, I mean, my concern is that this is a pretty serious problem, and yet the data doesn't indicate clear evidence of what is the best at this point. And there's at least some indication that depending on the individual's response there is some response. But I think some of these longer term data collections looking will give us clarification but I agree. I

don't think at this point we have much data to say one's better than the other.

Dan Lessler: So, I'm wondering if, does anybody think they could make a motion based on what we've seen so far?

Man: Sure.

Dan Lessler: Okay.

Bob Bray: After considering the evidence of safety, efficacy in special populations for the treatment of hepatitis C, chronic hepatitis C I should say. I move that PEG interferon alfa-2a and PEG interferon alfa-2b are safe and effective. No single drug is associated with fewer adverse effects in special populations. And they can be subject to therapeutic interchange in the Washington preferred drug list for the treatment of chronic hepatitis C.

Vyn Reese: This is Dr. Reese. I would just make sure you just add PEG-Intron alfa-2a plus Ribavirin and PEG-Intron alfa-2b plus Ribavirin.

Patti Varley: And, this is Patti Varley, wasn't there a comment about it having more negative effects, one of them, in the black population? Is that in the data set?

Vyn Reese: Yea, this is Dr. Reese. It was less effective. It says that both were less effective with older age and black race.

Dan Lessler: Some evidence.

Jeff Graham: In the, this is Jeff Graham, in the P&T brief, there's at the end of question three it says, there are almost no data to determine whether comparative efficacy or safety varies according to race, gender, age, presence of obesity, severity of baseline disease, or other comorbid conditions. I think the evidence is still pretty weak.

Dan Lessler: Yea. Any other comments on this draft motion. So the, I guess Bob's put the motion forward. Is there a second?

Vyn Reese: Dr. Reese, I'll second it.

Dan Lessler: Okay. Any further discussion? Okay, I'll, why don't we go ahead vote. All those in favor.

Man: Just, one thing we talked about was having the term chronic hepatitis C. And there'd be two places, second line and last line.

Dan Lessler: Right, right, thanks.

Jeff Graham: Chronic hepatitis C infection. I didn't make the motion.

Group: Dr. Bray.

Dan Lessler: Oh, I'm sorry. Okay, I'm sorry. Okay, so Dr. Bray made it, Dr. Reese seconded it.

Man: Formerly.

Dan Lessler: We have a second. So, is there any other comment? Okay, why don't we go ahead and vote then. All those in favor say, "I."

Group: I.

Dan Lessler: Opposed same sign. Okay. So the motion carries. And I think that concludes our business as the P&T committee [inaudible].

Jeff Graham: There's just one typo, there needs to be a capital T in front of these drugs.

Dan Lessler: Yea, that's correct. Okay. So we are going to adjourn as the P&T committee and reconvene here as the DUR.

Man: I think we have a scheduled break now, but we could take it a different time. I don't know.

Dan Lessler: I'm wondering if.

Jeff Graham: Because we just sat down a short time ago.

Dan Lessler: So why don't we. Is it okay if we move forward and then take a break in a little bit since we just. Are people okay with that?

Woman: We need a couple minutes to get set up here with the other.

Dan Lessler: Okay, so maybe five minutes?

Woman: Yea, just a couple minutes.

Dan Lessler: Okay, so why don't we reconvene at 2:15 then. Just a very quick break.

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Dan Lessler: Is to approve the last DUR minutes and actually, since I'm extensively quoted but I actually was skiing. I don't think, so. Vyn actually was chairing, so it seems like they're, it's just an attribution problem. And I don't know Vyn, do you, were the things that were attributed [inaudible].

Vyn Reese: I don't remember everything I said but some of them I did say that Dan said. So. But Dan, that Dan is quoted saying I said actually. And I don't remember all the comments, so I can't swear to the fact that it must have been, could have been misattributed to someone else, but I know I did say quite a few of the things that Dan was quoted as saying.

Man: [inaudible].

Dan Lessler: That's right.

Siri Childs: You know, this is a really good example of why we have to always say our name before.

Vyn Reese: Exactly.

Dan Lessler: Right.

Siri Childs: Because this was done by the transcriptionist, so.

Dan Lessler: But.

Siri Childs: Do you want to try to do, go through and scratch through when it's been. I mean you weren't there at all.

Dan Lessler: Right, so right. I was, I actually left at noon that day. So I'm actually, and since it is a transcript, I mean I think we can be fairly assured of the content. It's just a matter of the attribution. And I'm not.

Vyn Reese: If you could just you know write that I said it instead of Dan. It may have just been the chair who said it, but it's possible I said those things. So I guess I could take credit. Or you could just put man again like it's on every other attribution. It could just be man instead of Dan.

Siri Childs: Regina can we take care of that?

Regina Chacon: [inaudible] can do that.

Siri Childs: Okay, thank you.

Dan Lessler: So then should we formally approve them next time or should we just say that's going to be taken care of [inaudible]. How about we just approve with a correction, with corrections as indicated. So is there a motion to accept the minutes from the last UR?

Vyn Reese: This is Dr. Reese and I will move to accept the minutes as corrected.

Dan Lessler: Okay, is there a second? Somebody was here. Ken, okay. All those in favor, I.

Group: I.

Dan Lessler: Alright, we can move on. So next, Siri should I, or Jeff should I turn it over to you in terms of the agenda for this afternoon?

Siri Childs: This is Siri Childs again and what we're going to do this afternoon is we're going to talk about the erythropoiesis stimulating agents, and we have the pleasure of having two of the drug marketers with us today that are going to do presentations. And then we're going to follow up with a presentation by Elizabeth on behalf of both UMP and HRSA which will, we will present. Elizabeth will present the criteria. But I'd like to lead off with our drug manufacturers if we could please and call Amgen first and then Ortho Biotech second.

Tim Clark: Hell, I'm Tim Clark and I'm a regional medical liaison with Amgen and as the original developer and manufacturer of all the currently marketed erythropoiesis stimulating agents, Amgen is, like this committee, has the safety and well being of oncology and [inaudible] patients as a primary concern. I think to make this presentation a little bit easier if you don't mind, instead of saying erythropoiesis stimulating agents all of the time, I'm just going to say ESAs and since this is a class effect, this will include all of the marketed product so that'd be Aranesp, which is darbepoetin alfa, and EPOGEN and PROCRIT which is epoetin alfa. And unless something is specific to one of the unique products, consider it to be across the board for all three of them.

Basically we think that the ESAs have been studied extensively and that, Amgen believes that when they're used in the FDA approved indications they are both safe and effective. This past March Amgen along with Ortho Biotech and the FDA revised the safety, the package information based on new and existing data for these products. And part of the outcome of this was a black box warning. And I'm just going to summarize the black box warning briefly. Basically clinicians were advised to use the lowest dose possible to avoid red blood cell transfusions. If you remember in the past, we had a target of hemoglobin across our indications of 12 g per dL. So this target was changed to avoid red blood transfusions, red blood cell

transfusions. Additionally it was noted that these products can increase the risk of death or cardiovascular events when the hemoglobin was, exceeded this 12 g per dL. Specifically within cancer patients, the ESA shortened the timed tumor progression in patients with advanced head and neck cancer when they were receiving radiation therapy. Especially when their target hemoglobin again was greater than 12. They shortened the overall survival increased deaths attributed to disease progression of four months in patients with metastatic breast cancer who were receiving chemotherapy. And again the target of hemoglobin was greater than 12.

Then there was an increased risk of death when patients who had anemia of cancer. And even though the target was 12, these patients were not receiving chemotherapy or radiation therapy for the malignancy. And this is not an approved indication for these products. Additionally there was, the last warning had to do with patients receiving prophylactic erythropoietin alfa for pre-surgical means and not receiving anti-coagulation therapy because of the potential for thrombotic events.

Now I've mentioned that there were new studies as well as older studies. And I'm just going to briefly mention the new studies that were reflected in this package update. If we look at oncology, the warnings had to deal with increased mortality and/or tumor progression. And this was based on three studies. The first was Amgen's 103 study, that's kind of the short term for it. This was with darbepoetin alfa, and these, this study was in patients with anemia of cancer and they weren't receiving either chemotherapy or radiation therapy. The target hemoglobin at this point was 12 and this was an unapproved indication. The other study was DAHANCA and this is the Danish study, and this was in patients with squamous cell carcinoma and this was for patients who were receiving radiotherapy. And here the target hemoglobin was about 14.5. The third study that went into the overall package change was a meta-analysis of 57 clinical studies. And this study was published in the journal of the national cancer institute last year. While this study, this meta-analysis demonstrated that there was not a, there was a slight increase in change in overall survival, it was not statistically significant. However the thrombotic, thromboembolic events was greatly increased with these products.

If we look at nephrology there was one study, and this was published last year in the New England journal of medicine. That was the CHOIR study. And in this study the target hemoglobin was either 13.5 or 11.3. And then lastly there was epoetin alfa study that was done in patients having surgery. And this had to do with increased thromboembolic events. Amgen has widely communicated the safety information and I'll specifically review what we did within the state of Washington. It's

important to note though that it wasn't unique to just this state. All of these efforts were duplicated throughout the United States.

In January we voluntarily issued a dear healthcare professional letter. And this had to do with the 103 study, this was the anemia of cancer study in which we saw, you know an increase in risk for mortality. And this occurred in January of this year. And we also published the results of the study on publicly accessed websites such as clinicaltrials.gov and clinicalstudyresults.org. The FDA updated the product label on March the 9th. And Amgen immediately put this on our website. On March the 12th we issued a dear healthcare professional letter. And this was sent to 100% of the oncologists and nephrologists within the state of Washington. Other individuals that received this were state officials with state Medicaid, the Medicare carrier, and fiscal intermediaries. Additionally, the field force contacted 100% of the physicians with regard to this updated information. In addition, professional organizations, membership rosters for organizations such as the academy of managed care pharmacy, the American society of clinical oncology, national kidney foundation, American society of hematology. All of those membership rosters were used to, as recipients for this information.

There was a face to face meeting with Washington state Medicaid officials on March 29th and all of this data was reviewed with them at that particular time. The entire body of evidence is still under review. Last month the FDA had a public meeting of the oncology drug advisory committee and Amgen actively participated in this meeting. The FDA has not issued any new directives subsequent to this meeting. Following the oncology meeting, committee meeting, CMS issued a proposed national coverage decision on the ESAs. There was a public comment period, and that closed last week. At this particular time CMS is reviewing those comments and the expected deadline for the final policy is some time in mid-August.

To continue their review, the FDA has scheduled a cardio-renal advisory committee meeting on September the 11th. And here they'll look at the body of evidence concerning all of the nephrology indications [inaudible] clinical trials. Amgen will continue to serve the best interest of patients by communicating data and information as it becomes available. And this will be sent to healthcare professionals, to policy makers, as well as the regulatory agencies.

Prior to this meeting, we reviewed the proposed PA criteria for this class of drugs. And we found it to be consistent with our package label indications and Amgen supports the appropriate use criteria and will help support Washington Medicaid as they implement the criteria. If you have any questions I'll be happy to address them.

Dan Lessler: Thank you.

Tim Clark: Thanks.

Dan Lessler: Are there any questions from P&T members? Okay, thanks. Siri did.

Siri Childs: We now have Ortho Biotech, who is the other marketer of the drug. And they'll, again talk about what the problem is, how they've addressed the problem in Washington state. And we're [inaudible].

Roxanne Meyer: My name is Roxanne Meyer. I'm a Pharm D by background. I work for Ortho Biotech on clinical affairs. I work in the outcomes research group. Thank you for the invitation to speak. Because we are basically marketing the same products, I don't want to belabor all the points that were made by my predecessor here so, I will just kind of continue on and try and speak to the points that Dr. Childs asked me to speak to.

Obviously we've kind of identified what the problems are and he did a great job articulating as well as what as in your handout as far as what the studies are that are newly available. Some of the studies are from '04, '03 and then there are the newer ones which he talked about just a few moments ago. That's the identified problems and the associated risks that are with that. On May 10th of this year, ODAC which is the oncologic drug advisory committee for the FDA met to review this data as well as the previously published data in the public domain regarding these safety changes. Out of that meeting, ODAC made some recommendations to FDA. FDA has not yet decided what they're going to do with those recommendations, but we are currently in discussions with FDA about what those recommendations, what the next steps are for those recommendations. The recommendations that did come out of the ODAC was possibly looking at some additional label changes from 2004. Their recommendations was not to change the current target hemoglobin level of 12 or below. And also they recommended that some more trials that were adequately designed to assess survival would be done. We currently do have one study that is ongoing and this speaks to breast cancer, because the BEST study, which is one of the studies in your packet, did show a safety signal with reduced survival in metastatic breast cancer patients. So currently we are accruing patients for stage four metastatic breast cancer who are receiving first line therapy. And the primary endpoint of this study is progression free survival. But unlike the BEST trial which showed a negative safety signal and targeted a hemoglobin of 14, this study will target a hemoglobin of 12, which is our label.

In addition to participating in the studies that the FDA and Ortho Biotech will be conducting, not unlike Amgen we also did a dear healthcare

professional letter that went out also on March 12. We targeted all specialists. So all nephrologists, oncologists, and hematologists, which make up the [inaudible] share of the folks who prescribe these drugs. In addition to, not unlike Amgen, if you go to our homepage, our whole homepage is dedicated to our safety message and update on our package label. So it has the dear healthcare professional letter, it has the link to the FDA website along with their advisory statement from March 9. It has our PI and the update to the label with the black box warning. In addition to that we also did the same thing with respect to our field force. Our sales force have made every effort to contact 100% of prescribing physicians, hospitals, and clinics either directly face to face with the physician through nursing access or, and of course pharmacies and pharmacists as well.

Our clinical field, we have a very comprehensive medical information safety packet that includes all the studies that are in your packet as well as some others that is available through our med info department as well as folks like myself out in the field who do face to face safety updates to practicing physicians as well as clinicians. With respect to guidelines we Ortho Biotech have always supported guidelines. We support and recommend ASH/ASCO as well as NCCN with is the national comprehensive cancer network guidelines, as well as other evidence based consensus guidelines that are out in the public domain. We do support your effort to implement guidelines and we will assist you in any way possible. We do hope and recommend that you will continue, or consider including Procrit's compendia listing, which is a little bit different than our label. In addition to our labeled indications we have to compendia indications which would be MDS which is myelodysplastic syndrome, as well as hepatitis C. And there is data to support utilization of those.

And in conclusion I would just kind of like to kind of summarize. And I'm sure our Amgen counterparts would agree. There is a wealth of clinical studies that are available that show that this class of drugs is safe and effective when used for FDA indications and on label. And we hope that you will continue to make that available so that all patients may benefit from that. Any questions?

Dan Lessler: Questions? No, okay. Thank you.

Roxanne Meyer: Thank you.

Elizabeth James: Thank you both for introducing this topic. I feel like I don't have much to say now, you guys did such a great job. Thank you. So I'll try not to duplicate anything that was already said, but I guess. Basically what as a group of agencies what we sort of feel is that the ideal today is to look at the products in the patient populations to look at the recent FDA and manufacturer activity. And just to simply highlight the recent safety data,

this is not a place to review a drug class or to critique study methodology so I'm totally not going to go there. And then also just to consider what we need to do here in Washington state.

So here are the products, and most of them should be familiar. There are a couple investigational drugs listed here and there are many other formulations. There's like a epoetin omega and several others, but these are the main ones and the Eprex, I don't know if I'm saying that correctly, and then also the pegylated epoetin beta are both considered in some of the studies that I'm going to bring up which are mostly the studies that the Amgen and Ortho Biotech folks already mentioned.

So these are the FDA approved indications. You can see that for both the Epogen/Procrit and the Aranesp that the first two indications are the same, or sorry, treatment of anemia of chronic renal failure patients, and cancer patients on chemo are the same, and then the shorter acting agents also have the treatment of anemia and Zidovudine-treated HIV infected patients, and also reduction of allogeneic blood transfusion in surgery patients.

So here are the populations that we need to consider. And these are patients that are included in the labeling, and also patients that are included in some of the studies that I'm going to present. Patients undergoing surgery is one that was brought up a little while ago. So here's the alert. And again not to belabor anything that's already been discussed. There are certainly increased risks, increased incidents of death, and this is a preliminary analysis that the FDA has put forth on March 9. They have not reached their final conclusion, but this alert does follow the May 20, 2004 ODAC committee report, as well as the FDA's November, 2006 alert. So this is sort of like an updated alert. This is not the first of its kind with these drugs. And what they're basing their alert on are the studies that were presented briefly already that are based in cancer, kidney disease, and patients undergoing surgery. And in the back of your packet that you were handed out with the slides, I have included, which I know is also in the package inserts that you've received from the Amgen and Ortho Biotech colleagues. But also I have included exactly what's on the FDA website as far as the box warning, the updated warning, and you can also see the website at bottom if you're interested in going there.

So here are the studies that I'm just really briefly going to go through and most of these have already been referenced today so I will not go into too much detail. What I do want to point out in each one is the target hemoglobin levels that were included in the study, and also the many early terminations of these studies.

So this one was already mentioned, this is the Danish study. And the interim analysis was reported to the FDA by Amgen in the summer. This is radiotherapy alone or with Aranesp. Their target hemoglobin for the study, they were looking at 14 to 15.5. And I'm sure all of you are aware that this is because there was a perceived benefit in increasing hemoglobin in patients undergoing radiotherapy. Potentially that they would have better outcomes. And their primary outcome in the study, and again I only included primary outcomes just for simplicity's sake in these slides. Local-regional disease control. And there was actually worse control in the [inaudible] group. And there was a non-significant trend toward mortality and all of my statistical training tells me I'm never allowed to talk about trends, but these are things that were also stated in the FDA's alert so I'm going to try to bring those forward. This was terminated early as a result of these findings.

Another head and neck cancer study and if I recall any facts from the studies wrong you guys feel free to point out and let me know. Don't want to get anything incorrect. This one was again a target hemoglobin that was 14 or 15. They were also looking at progression free survival. And progression free survival was worse than the treatment group. And there was also a greater percent of non-cancer related adverse events and vascular adverse events in the epo group.

The BEST study which is the metastatic breast cancer study that was mentioned earlier. This is an agent that was used, the agent used in this study is not one that's used in the U.S. But again you can see a high targeted hemoglobin level. And we're looking at 12 month survival. And you can see there is again a greater percentage of disease progression related deaths etc. in the treatment group. And this also was terminated early as a result of the increased mortality in the epo group after just four months of data.

So the pegylated epo, epoetin beta study, which again this is investigational, it's not yet marketed here. These are cancer patients receiving chemotherapy which is an indicated, an FDA approved indication for these, this class of drugs. Targeted hemoglobin of 11, 13. And this one was actually halted by the company because of safety concerns just a few months ago.

Another phase three study by Amgen, and this was just mentioned a little while ago. The new indication for Aranesp. A target of hemoglobin of 12. And there was an increased mortality in the treatment group compared to the placebo. And these were cancer patients not receiving chemo.

And then the last two studies, or sorry there's three more. This study and the following study were both looking at chronic renal disease. Patients

not on dialysis. Again you can see the targeted hemoglobin and the primary outcome composite death. And that was, the composite death outcome was the only one that was shown to be statistically significant. And it was in the higher hemoglobin target group. And this was also terminated early. And this was a data safety and monitoring committee decision to terminate this early. They said that no benefit would be seen. And no significant findings as far as primary outcomes were found in this other chronic renal disease study. However, there was a significant difference in hypertensive adverse events in the treatment group compared to the placebo. [inaudible] care. And only trends were found in the study otherwise. But the FDA determined that these particular trends did support the study findings from the previous study.

And this is the surgery study that was also mentioned. These patients were undergoing elective spinal surgery. They did not have prophylactic anticoagulation. And you can see that they were required to have a pre-treatment hemoglobin of 10 to 13 to even be in the study. These results were reported just a couple months ago. And there was a higher incidence of deep venous thrombosis in the epo group compared to the standard of care.

Some major study limitations and again this is not a methodology presentation. These are the major study limitations pointed out in the FDA alert. Just wanted you to note that the study dosing regimen in many of these were not approved and I didn't go over dosing regimen. The treatment groups include populations for which these ESAs are not approved. As we've already talked about, such as patients undergoing surgeries. The outcomes relied on high hemoglobin targets which I mentioned, and perhaps the study was evaluating a new, unapproved ESA.

Just for perspective I wanted to bring forth the CMS proposed policy that was also mentioned. And it's really long and really involved, so I sort of just left the first two points as there's a list of conditions that ESAs cannot be used, and there's a list of cancers that are appropriate. And there's a long list, it's on the website, that all the references are at the back of the packet as well. So I'll leave that part at that. And then the next slide explains in a little more detail some of their proposed policy specifics. And I'm trying to think if there's anything I want to go really in detail in. They are only allowing 12 weeks a year of covered treatment. They're giving a four week dose trial period to determine if the hemoglobin is, if it's working. This four weeks of treatment, is the hemoglobin or the hematic rate going to rise appropriately. They don't want increased fluid retention because that can lead to some of the adverse events. I think those are the main things to go over here. So just to kind of let you know for perspective, this is not where we're going, this is not what the agencies are

recommending to the DUR board, but just to let you know what else is going on around the country.

So the future activity. The FDA is awaiting many trial results. Many of the studies are ongoing, there are new studies that have been started that we don't even have preliminary results for yet, just a long list of studies that are ongoing. The public comment as was mentioned earlier, that time has closed. And the decision from CMS will come this, some time this summer. And just like we're doing here, there's going to be a lot of likely new or strengthened restrictions in this drug class.

So what's the goal here today. I mentioned the goal earlier about what we're trying to do as a DUR board or what you guys are going to be looking at. The key is to balance the risks and benefits. And this is just what we do every time we come together. And we want to avoid the need for transfusion because we don't want to deplete the blood supply if we don't have to, but we also want to prevent, again we want to prevent use of excessive transfusion by avoiding ESAs when they're actually the most appropriate place to go. And we also don't want to use ESAs in an attempt to improve quality of life or increasing patient's energy level because that doesn't have any substantial documentation or evidence yet.

So here are the criteria we're suggesting. And in your packet and also in your notebook you can go. And the main things are at the, you can see at the bottom of the page number one and then on the back number two. And these both will be required. And these are drawn right out of the FDA alert. This is nothing that we jammed up on our own, this is exactly what's being called for. So they have to be, these agents need to be used in managing anemia in one of the disease states that's labeled, that's indicated in the package insert. And we've gone over those already.

And the second thing. And here are the objective measures. Now at Uniform Medical Plan of course we don't actually have access to these, so these are going to be on a prior authorization phone call basis. But these are the things that the FDA put forward. We want hemoglobin less than 12 that's monitored monthly. We want adequate iron stores so that we know we, we're actually going to be putting these agents to use where there's something to use them with. And adequate blood pressure control because the hypertensive adverse events are some that are leading directly into the other adverse events, all the cardiovascular disease and death.

So, one other caveat I just wanted to throw out and there is this long list of disease states on the back that, this isn't hard and fast. And I think the goal really, and I don't, I'm speaking on behalf of the agencies but I want to make sure that I'm speaking accurately so please correct me Siri, Donna. [inaudible] I don't think you guys use these products. So we don't want to

limit. Obviously we want to give good patient care. We want to make sure we're getting these agents to patients who need them. We want to prevent transfusions when applicable, when appropriate. But this list for now is going to be only made more lenient unless there's more severe data brought in that means that we need to close it down. And specifically, the myelodysplastic syndrome which was just mentioned. That's one that there is good supportive evidence. And if we need to address that, if there's more discussion that needs to be had, if more studies need to be brought here, specifically to talk about. Anything that needs to be done in the future. You know we'd be glad to do it. But this is at least a starting point, and it is based on the FDA's alert which is based on data that the companies who make the drugs and market the drugs are saying yes we agree. So we figure like this was a, this is a good place to start. So, and if you guys have anything to add to that. Okay, great.

Dan Lessler: So, I was just wondering how you, if you could comment on how this guideline or policy is implemented. Is it a prior authorization process across the agencies.

Siri Childs: When we're able we have a point of sale implementation that we're going through right now. But when we're able, we will apply prior authorization to these drugs, and this will be the criteria that we will approve these drugs for. So it won't happen overnight though because we are going through an implementation with our prior authorization program. I'd look for it to happen before the end of the year if everything goes well with our point of sale implementation.

Dan Lessler: And do you expect a considerable decrease in utilization then based on the.

Siri Childs: I'm hoping with the help of our drug manufactures who are you know going out as you heard with their great marketing, you know letting all of the prescribers know what the side effects are and how to manage those side effects that the prescribers will, you know be compliant themselves without you know a great deal of prior authorization requests, so.

Alvin Goo: Hi, Alvin, do you have a sense of what percentage our process through point of sales. Because isn't it majority in clinic administrative drug.

Siri Childs: Right Alvin, we're only talking about what's going to be processed through point of sale. So we need to address this on our provider administrative side also. But, you know we haven't done that yet. So right now it'll go through on the position administered side, we haven't, we just haven't caught up with them yet, but we hope to do that. I can tell you that from the Medicaid perspective, we only have about 900 patients that were receiving this in calendar year 2006. And I might also say that as

disappointing as this was, we did see that over half of them were for off label use.

Dan Lessler: Other questions or comments? So it sounded just looking at the agenda that you'd like an endorsement of.

Siri Childs: Right.

Dan Lessler: This direction, this policy that you're taking. So, if there aren't any, if there isn't any further comment or discussion, I'm wondering if somebody would be willing to make a motion to, I guess it would be to endorse the ESA policy. Is that?

Siri Childs: Criteria.

Dan Lessler: Criteria.

Patti Varley: This is Patti Varley. I'll try to make, I'll make a motion that we approve the appropriate criteria use for ESAs and support that.

Dan Lessler: So, appropriate use criteria. I just.

Patti Varley: Yea.

Dan Lessler: For ESAs. Is there a second?

Alvin Goo: Second.

Dan Lessler: Any other discussion? Okay. All those in favor say, "I."

Group: I.

Dan Lessler: Opposed same sign. Alright, so the motion passes. Thank you very much that was an excellent presentation all around. Very informative.

Siri Childs: I thought it might be kind of interesting for you to see that when there is a problem that comes up, that our manufacturers are so willing to work with us to get the word out and to, you know provide the right guideline.

Dan Lessler: Yea. It's good to see. So, I guess Jeff now we're going to move to the ADHD update.

Jeff Thompson: Yea. I'll just give you an update where we are at with the ADHD and then I also wanted to give you some heads up on some new legislation that came out during the [inaudible] session that's going to stem, that's going to take us into the anti-psychotics. And it'll be the same drill, you know

working with you, working with the community. So, just a history here of what we've been doing. It may not seem this long, but it's [inaudible] to me. I mean we've been working this for almost four years now with the mental health drug workgroups starting out with narcotic review, you know the ten or more prescriptions, asking you the providers whether you know the 12th or 15th script is medically necessary. And that's generated a 25% reduction in narcotic use in those clients. And then if it takes 25 scripts and you guys say it's okay that's then fine with us but the good news about this kind of program is it's actually generated about 25% of these clients are now in alcohol and drug treatment. Because we've combined that not only with your medical necessity but also with the outreach to look at whether there's an alcohol or drug problem.

Neurontin use we worked with you on those guidelines. That's actually I think been a very big success story with both you and the department of labor and industry. With appropriate off label use. Second generation antidepressants where the people were on two or three SSRIs at the same time at low dose, probably not the best use of our pharmacology budget. 1,500 clients, a million dollars that we moved over to I think more appropriate treatment.

Sedative limits in children, that was the five in 30 days. I'm going to ask you, you did the sedatives today, I'm going to assume, and when we talked with the mental health drug workgroup and the consultants they wanted to keep that restriction so that children could get a preferred sedative, but no more than five every 30 days. Obviously if there's a unique circumstance we'd be willing to make an exception. But when we talked with the consultants they thought that was a good safety restriction to continue on.

And then I'm going to talk about the sedatives, talk about prescription information sharing, which has actually we changed the law in this state that now we can actually give you mental health drug information across providers. In this state, I was not allowed to share with you the fact that one client was being prescribed anti-psychotics from two providers because those anti-psychotic prescriptions were considered a mental health treatment record. So we've changed that statute now where we can actually do information sharing. And then I'll talk about what's going on, [inaudible] for a little bit more here.

You know real quick, it's a big issue, we have 537,000 children in Washington state Medicaid, that's the majority of them. And one of the reasons why, and I was talking with the mental health nurse practitioners the other day. One of the reasons why you feel like we, you know we work probably too closely together, is the other side of the equation is we have some of the sickest clients in the state. And that's the reason why

Medicaid is always being looked at you know with mental health drugs because we take care of most of the most vulnerable clients in the state.

Next slide. And then obviously the reason why you're talking to Siri and I all the time is most of those clients are [inaudible] for service, even though it's only 40% of that million clients. Because most of the clients that are HO are in, are the moms and kids. Not the SSI, aged, blind, and disabled. So, and then just real quickly remember that there's a mental health contractor in between there and we're going to be doing a lot of work with Mr. Kellogg to probably straighten out some of the pharmacy issues that happen when a Molina client shows up but it's in an RSN with a contractor who we're not sure is an RSN contractor or a fee per service contractor. So you'll see a lot more work with that. Ms. MaryAnne Lindeblad's actually looking at working the contract with the HO so it's going to be very clear what's here, and what's over there as far as mental health drugs are concerned. So we have built a very complex system in this state, and now I think we've got some really, people very interested in trying to make sure that the contracts work appropriately and more transparently.

[inaudible] it is about medical necessity, and it's about evidence based medicine, we're going to, this is how I like to run at least my thought processes if it's, if you can show me that it's reasonably calculated to do all these things, prevent, [inaudible], diagnose, blah, blah, blah. Why wouldn't we pay for it? But, I'm always going to ask, is there a least costly alternative, or no treatment at all. Because that's part of the reasonable calculation. And in the reasonable calculation, you know it is looking at the evidence. And it's not just about randomized trials. That's not what evidence based medicine means for us in our administrative code. If there's randomized trials and it's indicative that's an A level consistent, why would we pay for it. If it's B level evidence where you've got good consistent type one through type three trials, why wouldn't we pay for it. But if you've only got type four evidence, which is case series, and we're talking about you know high risk issues, whether it's a technology or drug, then we've got to talk in the level C evidence here. And if you can document less risk, less cost, next step in reasonable care, why would we pay for it. But if you can't do that, you know how are we spending our money on this valuable resource called Medicaid. And a lot of this happens here. I mean I was, I'm actually on the phone just back here trying to figure out [inaudible] ship a kid off for a D level evidence phase one trial because they're so unique we're trying to work with children's on that. Or that we're going to ship somebody down to UCSS or we're also paying for D level evidence. But no more experimenting on our kids, and SSI clients. They have to be in an IRB, or it has to be humanitarian device exemption. And quite frankly I want to keep talking about that when it comes to off label, because that's experimentation. If

there are no studies then we're experimenting. It's not any different than taking something out of your white coat and putting it into a kid's heart or lung. Off label drugs, and I know that's pretty harsh, but that's just, what my thought process is. Yea.

Woman: Are you taking questions?

Jeff Thompson: Yes, why not?

Woman: [inaudible] said technology or drugs. Don't you include other things like therapy?

Jeff Thompson: Therapies also. And you're going to see that. We actually just finished our first technology assessment with the state looking at standing MRIs. Is that an appropriate, something we should pay for, for the diagnosis of any number of skeletal diseases. When you [inaudible] load them while they're in the MRI. And the answer is there's no evidence to support, you know a three times more cost for somebody to stand up in an MRI versus to lay in the recumbent position. And so we just actually, there was another, there's another group of you just like this, actually out there that made that decision for us. And we're going to be doing pediatric bariatric this summer and we're also going to be talking about lumbar fusions in clients with chronic back pain in the fall. So this is the operational definition that we're really working on in the state as far as therapies, drugs, devices, procedures.

Woman: I mean I guess I was asking about you know like CVT and [inaudible] that kind of thing.

Jeff Thompson: It's something that you know in mental health we haven't really talked about. You're talking about cognitive behavioral therapy and that. This actually really applies to more med [inaudible] issues. And we're just now starting to talk about how does that apply you know in the mental health. Because you know what everybody's done now is they've said, everything is evidence based medicine. Evidence based preventiveness, and evidence based mental health, evidence based this. But nobody will actually put on paper what do you mean by evidence based medicine. Where are you on the hierarchy of evidence, how well is the evidence been presented and done. And where are you in this you know whether it's type one or type five evidence. And so working on mental health with Mr. Kellogg. It'll be interesting.

Next. So, again just to give you the baseline, you know we started looking at children on ADH therapies, ADHD therapies. Obviously an on label indication, a very good set of documentation that these are good for children who have attention deficit disorder, but asking the question

should be they on two, or three drugs, or four sometimes as well as a sedative. And this is the prescribing practices here. Not saying yes or no, or bad or good, but let's start taking a look at it. And this started drawing the attention, you know where is the evidence that combination use is more effective than monotherapy. Or that when you use combinations you can cross over between the methylphenidates or the dextroamphetamines and Strattera or all three. And then this is just only one snapshot because many of our kids, especially our foster kids, not unusual to see them on two anti-psychotics, two mood stabilizers, two ADHD drugs, lithium and something else. That's not a rare event. From usually three or four providers.

And so, next slide.

Dan Lessler: Jeff, would you explain that? I mean you had dots all over the place.

Jeff Thompson: Sure, go back. So basically it's a multiple Venn diagram. So we have 7,000 children that are on methylphenidate, we have 5,100 on amphetamines, and 565 on dextroamphetamine, and where you see the overlap, these are people that are on both of these drugs, both of these drugs, both of these drugs, or a combination of all three drugs at once. And then we've had some sedative use and we were starting to see actually an increased use of Ambien and Lunesta and other sedatives in these children that were taking the stimulant drugs. And that's where we came up with the five in 30 days. And obviously if there's, there is something that's dealing with a PTSD event in children where they might have had a mother or father die or something like that we can always make exceptions. But as a general rule, the workgroup agreed that five of a sedative in 30 days would be ample enough to take care of you know some issues here.

Next slide, sorry about that. Call me on it any time. So we established some dose limits. Looking at, we had children up to several hundred mg of all the different agents. And so we looked at over the age of five, we established the limit of 120 mg of methylphenidate, three to five nothing over 30, and less than three, you know we've got to take a big deep breath. And so you can see the number of clients that are on the methylphenidate agreed upon dose limit. And the good news is these percentages are small. I think that's the good news. But I think don't be fooled by just small percentages. Remember Medicaid, five percent of the population generates 50% of the cost.

[end side A]

Jeff Thompson: Costly clients because, and I'll show you some evidence to this effect, these are the people that go in and out of the emergency rooms, in and out

of the hospitals that chew up a huge amount of resources. And we want to make sure that they're on the most appropriate psychopharmacology so that we actually eliminate the downstream effects and not potentiate them. And the same is true for the amphetamines. 60 and 15 were the limits. In less than three and we talked about what should we do about this, and we set up a second opinion process. So Mary Bridge, Spokane, Sacred Heart, and Children's Seattle do second opinions when they exceed these dose limits, the combinations, or the age limits. Yes Carol.

Carol Cordy: How are those doses determined? I mean it sounds like sometimes it's just an expert panel. Like with five per month of sedatives.

Jeff Thompson: Siri do you want to go through the particulars?

Siri Childs: Well Carol we brought this, the recommendations of the mental health workgroup to the DUR board last year and we asked for your input and your authorization for us to use these dosage guidelines. But they were developed by our mental health workgroup which was comprised of M.D. psychiatrists and a pediatric psychiatrist specifically was brought in to consult on that.

Carol Cordy: So it sounds like that falls into the expert opinion.

Jeff Thompson: It is, which is part of evidence based medicine. Because there are no studies on this. And so that's where the experts and when I presented this actually at a Medicaid conference this week where I had all the medical directors from around the country looking at these numbers, I saw a few states going, "Oh my God, you've set them that high?"

Siri Childs: Yea, that's what I was thinking.

Jeff Thompson: So, but there were other people that said this is too low. You know, and so it is expert opinion but that's part of evidence based medicine. Is if there's no studies we'll go down to expert opinion. And the drug companies were at the table when we talked about this as well as the RSNs and the advocates. And is it the right? Yea, it's the right place to set these because that's what the community and the agency agreed to. And now we can show the outcomes.

Next slide. So we did the same thing for combination with Strattera and set the limit at 120 mg of Strattera. And then any combination of any of the three is something that would drive a second opinion because it's only now that some of the studies are coming in on combination use. A lot of it is this sort of trial and error or experimentation. Whatever you want to call it, or clinical judgment. But when we actually throw it through the mill.

Next slide. This is after about 800 consultations now, over the course of almost a year isn't it Siri? A year I think this. Yea, and so the good news is that we're allowing 40% of [inaudible] to go through and it's an appropriate therapy. I think that's the good news when you look at the second opinion. But 57% of the time, the modalities are changed. Typically to less drugs or less dose. And I think you can see that sometimes the outcomes, sometimes the outcomes can actually be a referral for psychotherapy, or just we need to touch the kids not just a record review. And those are happening and we try and make that happen. Some of the times there are other outcomes which means that, you know the client moved off of our status of eligibility or moved out of the state. Many of the times they're adjusted by the consultation with the second opinion and the do, mostly they do phone calls. So the second opinion doc, the pediatric and adolescent psychiatrist, will call up the primary care doc, and they'll have a discussion about the treatment protocols. And so that's one of the things that we're paying for and we're going to improve on that. And then some of them, actually I think it's the Hawthorne effect, and we are looking at those 147 that were denied with no response because the physician you know just changed his or her mind rather than going through the second opinion process. And it's our commitment that we will look at that and making sure that that's not just, you know they gave up. I think mostly when we looked at this they actually are going with our guidelines, and just re-looking through their notes. Any questions on this one? More pie charts, Venn diagrams. One more?

So when we look at what is the type of denial. You know it's on, pretty much on duplication and dose limit and then the no response is those ones where the doctor after we send that we want to see the records, the doctor doesn't respond for a second opinion. And we are checking those to make sure kids get their medications. So that is a Hawthorne effect. The interesting thing about this is that the kids over on the east side of the state are different than the kids over on the west side of the state. Because over on, the doses are actually more on the east, sometimes than they are on the west. And I won't tell you where the combinations are, but they're different. And so is that variation in Medicaid appropriate. And we're going to, we've had one meeting with all the second opinions and we gave them sort of a report card. And then we're going to have a follow up meeting in the next couple months to talk about that. And my idea, as always you want to reduce the variation to move the mean. Which means you don't want to bring the best down, regression, but what you want to do is move everybody towards the best, which is move the mean but reduce the variation in care. Just as you expect your automobile, your financial industry, or anything that you purchase, you expect that. We should expect that in medicine, but we have to do it in a more complex manner with engagement and getting experts to work on this.

Next slide. So real quick you know, we're set with some age dose and combination for children and adults with the anti-psychotics and there is a legislative bill, I'll talk about it here where we're going to repeat the second opinion process. Probably do it a little bit differently for better customer service, but we are set now with some dose limits and we'll come back to you when we start this up on both the anti-psychotics for the adults and again, some people feel this is too high, some people feel it's too low. It's very differential even by our state institutions, eastern and western state. But again, why is that? We're not taking care of any different clients, they have the same diagnoses, and yet there's very huge opinions, very large variance in whether we should be dosing them at these beyond FDA dosing limits or beyond FDA indications.

Next slide. The same is true for children. There are only two of the anti-psychotics that have been studied. There is only evidence in two drugs, and yet we have children in all age groups on all of the anti-psychotics here in this state. And it's quite a number of them. We probably, you know I believe we probably have about 5,000 children if you do the combinations, the types, the dose, that are on these medications that are, you know outside the studies. And I understand that some of these children have some really, very extreme behaviors as well as some extreme, some diagnoses that we need to have a discussion about. But what I don't want to see is what happened in Massachusetts where there was a daughter that died and now the parents are being [inaudible] up on homicide charges because there was excess dosing. And that's driving policy in Massachusetts. I want to prevent that here. But I want to work with you on that limit. So we have doses for children established, which is all the drug classes. But we have combinations and ages, you know ways to look at this. But this is our prescribing practice here, with the preferred drug list where it's wide open when it comes to the anti-psychotics. When we have a preferred drug list, and we have DAW, and we don't distinguish between off and on label, this is what we have. And I think we need to talk about this, is this appropriate you know for our children.

Next slide. And you can see that there's even differential in the FDA maxes when we look at eastern and western states. But these are the maximum doses for adults that we're looking at.

Next slide. We'll come back to you and show you we did an education opportunity on dementia and the use of anti-psychotics. That we had a number of our over 60 year olds had a diagnosis of dementia. Now some of these clients could have dementia and schizophrenia that's burned out, so this is why it was just education making a recommendation that they at least not exceed 1.5 times the study dose. But you can see many of these clients were getting multiple anti-psychotics from multiple different providers, yet there's a black box warning on this. And we do see this

where the dose climbs in an 80 or 90 year old and then it falls down because they die. Is that [inaudible] related? Or is that just because they're escalating their behavior as their disease progresses. So this was an education that we did out to the community on the black box warnings and. Did we do an analysis of whether there was any change in prescribing on that?

Siri Childs: We don't come back and look at it.

Jeff Thompson: Okay, might be something we might want to go back and look at. Next slide. So, one of the things that the drug companies have constantly said, and I agree with them, that what we need to do is not just concentrate on, you know too much, and too young, with too many combinations, but is this the right dose, are they taking their medications, are we actually improving outcomes? So actually I'm going to show you some new data that we just came out with and started and we are presenting. So when you look at experience down in California, down at Calmed or you look at some of the veterans' experience, we all know and from the CATIE study, we know that most people don't take their anti-psychotics religiously. As a matter of fact from the CATIE study it's about 75% non-compliance. And we see that in our, in actually in our medication histories. You can look at people that are on monotherapy and they religiously take their medications from January through December. But when they go on, beyond one drug in this drug class, it's random events that I see. Sometimes they're on, sometimes they're off, sometimes they're in double, triple, quadruple amounts of medication. So we looked at, in about 10,000 clients who had the diagnosis of schizophrenia, we looked at their hospitalization rates, we looked at their ER rates, and we looked at their placement rates in skilled nursing facilities. So we ranked, we did an analysis on their gap in therapy, used a study that was done out of Calmed and there are multiple ways of looking at that, but just replicated their analysis of gap in days. And then we [inaudible] it whether they had RSN or non-RSN care by the number of hours of care. So if it's less than four hours it's non-RSN, if it's over four hours it's RSN care and they're in the [inaudible] contract. Does everybody understand that? And we looked at polypharmacy, the number of drugs, and we looked at the number of prescribers. And in 10,000 clients with a diagnosis of schizophrenia, and this is what we see.

Next slide. So when you look at these 10,000 clients and you look at adherence, so where they have good compliance, zero to ten days gap, all the way to over 41 days of gap, it is either predictive or it is, it's telling us a story that as they have more gap in therapy, they are more likely on admits per 100 to go into a mental health hospitalization. That's EMT, that's state hospital, and community hospital. So, and that's not a big surprise, but one of the things that I've heard over and over again with the CATIE study was that the CATIE study didn't have case management,

and obviously that's why they were not adherent. But if you compare over four hours versus less than four hours of RSN care, you can, and now I'm not saying it's bad, it's likely we're dealing with more severe clients, but yet note that relationship holds. And so we need to go in and understand that. We need to not just use claims, we need to go in and do record review. And I've talked with Sharon Farmer, and Rick Reese, and Mark Avery and what King county would like to go in is do a record review of these type of clients in King county RSN and find out what is driving these re-hospitalizations. Because in the red, these people right here, this represents and the highest, this represents about 1,500 hospitalizations and in one client, that's 29 hospitalizations in three years. And these clients typically cost Medicaid, they cost you the taxpayer between 60 and 100,000 dollars per year. And so, what is the value of anti-psychotics in these clients because they're not taking it and they're going to the hospital more often. So we need to understand that. Not in an accusation, not in a report card, but let's dig in and understand it, because if you look at all the studies, everybody's got their idea, but there's no toolkit to actually bend that curve down. Any questions on this one? Yes.

Man: Well, when you say up there, so if the people down at the bottom don't adhere to their drug, right?

Jeff Thompson: That, it's just an increasing gap of therapy.

Man: But they don't get hospitalized.

Jeff Thompson: But they don't get hospitalized. This less than four hours, if people remember, the ability to get in to RSN care means that you have to meet the access to care guidelines. The access to care guidelines are not based on a diagnosis, but a severity of illness. More psychosis, more delusions, more positive, more negative symptoms.

Man: So those people down there, even if they're not taking their medication they're not as ill, right?

Jeff Thompson: They're probably not as ill.

Man: Okay.

Jeff Thompson: And these people are more ill. But in addition to being more ill, they're not taking the medication that will help them stay out of the hospital.

Man: So [inaudible] people down below are actually the same as people up above?

Jeff Thompson: I think it's something that we need to understand as a control group and do a chart review and figure out. Are these people homeless? Do they, is it because of homelessness they're not taking their meds or is it because what the CATIE said, that they don't like their anti-psychotics because they're not getting rid of the positive symptoms or they're giving them more symptoms that they don't like, the weight gain or other things. And everybody's got an opinion on it, but nobody's got a methodology to figure out how do you get the person on the right dose, the right drug, and maintain their therapy so we keep them out of the hospital.

Man: So you're saying here then, the people that always say well we need case management, what you're saying there's a bunch of people down there that don't need any management at all, that never show up in the hospital, they don't even take their medicines.

Jeff Thompson: Right, and these people get more case managing.

Man: Okay, so.

Jeff Thompson: And they get up to 200 hours of case management.

Man: So I'm, so we're trying to figure out why those people have.

Jeff Thompson: Yes.

Man: That would maybe include some homeless people.

Jeff Thompson: It probably does include homeless people, it probably includes what the CATIE study talked about, that people don't, are not satisfied with either the reduction in their symptoms or they're not satisfied with the side effects of their symptoms, or there's drug and alcohol abuse that goes along with this, or that they're not in, you know the appropriate social setting. There are some studies that say if you're in a family, or a group home you're better off than if you're alone. But, you know if the idea that case management is the solution to adherence, we're not seeing it here. And with a lot of questions. With a lot of caveats. And that's why a record review is the analysis that needs to really.

Dan Lessler: Alright, I mean that's not what you have there Jeff, because I mean you don't have the non-case managed people. I mean you.

Jeff Thompson: Well these are the non-case managed.

Dan Lessler: But by definition they are less severe.

Jeff Thompson: Right.

Dan Lessler: So in severe group, you don't have, you've got a case managed group but you don't have a not case managed group.

Jeff Thompson: And basically if you look at the distribution curve over four hours, okay. It's basically almost 80% of the clients are getting less than 20 hours. And then there's a small cadre of 20% that are going all the way out to 100s of hours. And we will do that analysis and we'll do, we're going to do a regression analysis on it. But I don't think the answer lies in analysis of claims data. I think the analysis relies on us doing, taking these and actually diving into the records and looking at what is the actual cause and effect here. And then developing tool kits and a reporting mechanism. Because this is like a lab test. I can tell you within a month whether somebody picked up their anti-psychotics. You need to know that. At the very least that's what we've learned is we can share with you, because we've changed the legislation, I can now tell you whether they didn't pick up their anti. I can't tell you whether or not taking it, I can just tell you whether they didn't pick it up. But that's what's happening here. And the anecdote, or the inference was the CATIE study didn't answer that because people were getting case managed. [inaudible] they're case managed. So now we need to go on. But it's not going to be in the claims file that the answer is.

Next slide. The same applies for as they get more drugs, we see more hospitalizations. Again, you know I'm just pointing out.

Woman: It just seems like those are the sicker people.

Jeff Thompson: It is the sicker people. And what's interesting is you know the relationships are kind of all over the place. This is in a [inaudible] by polypharmacy. But remember, it's not, it's a multidimensional problem. Many of these people that are on polypharmacy are not taking their meds too. And if you were, I think I showed you a slide a long time ago where I can track the peaks and valleys of their use by their different drugs over the course of a year and you will find that these people that are taking two, three, or four drugs, have abstinence periods where they're not taking any drugs or they're switching between drugs who are being prescribed by multiple providers.

Woman: And that was going to be my question is. When you look at greater than four hours, there's no data saying whether that's with a good case manager or a bad case manager or a consistent one, or 15 of them. Because we know in the mental health system, the turnover is incredible. So the quality of that case management isn't just per hour.

Jeff Thompson:

But see what we're saying here is before it was, well no case management versus case management. Now we're saying well maybe the quality of the case management. All I'm doing is bringing the data and causing a dialogue about the questions and with Rick and Sharon and Mark and I agreed that it's a record review that will actually solve this issue or at least explain this. But until the data is brought forward, and you know and I can't make huge claims on this one, and Dan you're absolutely correct, you know. But before I brought this forward this didn't happen here in the state of Washington.

Next slide. And so, and then you remember, we need to start looking beyond just the anti-psychotics when Ken Stark and Doug Allen started looking at people who had both mental health issues and drug and alcohol issues up in Snohomish county, that the more likely they are, the more that they go to the emergency room. And I'll show you what that looks like here in our data, the more likely they are to have dual diagnosis issues. And when they exceed 31 times or more to the emergency room, they are 99% likely to walk out with an opiate. That's a problem. I think you'd all agree to that. And so when we look at these people with, that have the diagnosis of schizophrenia that are going to the hospital, we need to also look at what other drugs that they're taking. And I'll guarantee you we're going to find, unfortunately a lot of narcotic use and substance abuse issues. And we all know that. But now what we can do is start sharing that data and start giving you some idea of what's going on out there beyond your office when you see them.

So next slide. So the same relationship holds, albeit now that the less than four hours, when you look at emergency room use. So here it is by the number of prescribers. And this holds true. So if you look at number of prescribers, the number of drugs, or the abstinence period, you see you know a climb in the amount of either hospitalizations or emergency room use, or placement into skilled nursing. I didn't, I'm not going to show you that slide. The same relationship holds. It's dose dependent, so you know. So this is not a randomized trial, but as you see increasing doses of either, of any of those, you start seeing relationships. So that starts to say that there's something going on that we need to look at. And so in this case, you know case management and some of these people here, you know whether it's four or more prescribers in continuity of care, are going to the emergency room a total of 5,700 times, you know over a three year period. Some of these people actually go 100 times a year to the emergency room. So it is what it is, it's not, you know it needs to be explored and we'd like to actually work this up with the RSNs to understand this and then publish it with a toolkit and get into a process where we can share this information with the prescribing provider with the new legislation so that we can make sure that at least we can bend this curve down a little bit. With all the caveats that this doesn't explain.

Next slide. So this is in essence 5773 the new bill before we had this new bill the mental health diagnosis contained in the medical treatment record as well as the mental health drugs constituted a mental health treatment record. And as a matter of fact if you were to look at the actual law, and then if you were doing this at Harborview, or Group Health, or Spokane, they were in violation of a law. But nobody really knew it because, you know. So now what we've done is we've said that medical billing information which includes a mental health diagnosis in the medical billing information, or a mental health drug treatment constitutes a HIPAA protected adventure into care continuity that we can share amongst prescribing providers. And now the law allows us to share that information in that circle. And actually Group Health just changed this a year ago. Where they broke the ceiling and actually they're doing what we're going to do now. So it doesn't happen even though we thought it was happening, a lot of times you weren't seeing the entire picture of what's happening to your clients on the med [inaudible] side.

Dan Lessler: So what does that mean practically? Jeff, I mean does that mean a psychiatrist at a community mental health center can now, because it's part of continuity of ongoing care contact me and say, "I want you to know that Mr. Smith has XYZ diagnoses and is on ABC medicines?"

Jeff Thompson: What it means for me is that what I can do, I mean you could always do that. And it would depend upon whether the mental health provider would disclose to you that information. And most mental health providers, if they were strict by the rules they would have, you would get a confidentiality statement before they would ever talk to you. What this means for us is that Siri and I can now share with you any diagnosis in the medical claims, which can include everything from appendectomy to schizophrenia, I can show you that information as well as I can show you, if you the prescriber of record the other prescriptions they're getting, including mental health drugs. So I can give you a full portfolio of what's going on, excluding mental health counseling, inpatient psychiatric, and title 41 protected which is alcohol and drug screening and treatment. So, it is what you're supposed to be able to see in the EMR, but we had a law that actually restricted that whole green section. Does that make sense?

Dan Lessler: So it's administrative data that you [inaudible] now.

Jeff Thompson: So if every single one of you are prescribing an anti-psychotic to me, in the old rule I couldn't tell you amongst you all that you were prescribing to me. I can now do that.

Man: And we get names.

Jeff Thompson: And you get names.

Man: I would get [inaudible] prescriber.

Jeff Thompson: And you get doses. Yes. But I couldn't even tell you the names. I couldn't, I would have to totally exclude that. Yes.

Woman: [inaudible] have to ask for it?

Jeff Thompson: What we're going to do is we're going to build a system where we're probably going to identify the highest risk and I'm going to push it out to you in paper form, and then we'll develop it in some of the web based form. And hopefully within a decade we'll have an EMR but that's going to be a decade. Yea, Patti.

Patti Varley: I thought there was some law, as a mental health person that if I was coordinating care, I didn't need a consent to talk to their primary care. Is that not true? Yea, isn't that true? I get one anyway, but the law I think protects me that if it's in the safety of my patient, I have a right to talk to the primary care about my psych treatment.

Jeff Thompson: I believe that an interpretation of the mental health statutes could be read either way, it depends on how much you're disclosing. I believe that most more conservative people would read it that you need to get, other than I'm seeing [inaudible] or something like that, you need to get a release for you to tell him a diagnosis or a medication.

Woman: A signed release?

Jeff Thompson: A signed release. And I'll shoot you all the law. And it's a little bit ambiguous on that side, but I would say you should consult your lawyers and have them. And I can probably pretty well tell you what they're going to say. Get a release.

Woman: Well, that's always the better way, but I actually, because the releases are only now good for 90 days and then you have to have them re-sign them that I've been told by my administration that if it's to their primary care, I don't absolutely have to have it signed. Now I try to get them whenever I can.

Jeff Thompson: So, but now what we'll be able to do for our high risk clients, I'll be able to tell you whether they're picking up their meds. And that's where I think we start with our highest risk.

Next slide. So health bill 1088, basically has a number of things on improving mental health care for children. We've expanded the number of

visits, [inaudible] Carol here you are. So we've expanded the number but you can't do it. You have to be a mental health professional. You cannot be a pediatrician or a primary care. But we've expanded the number of visits for from 12 to 20 for contracted mental health services and fee per service, but you have to have mental health credentials. So a psychiatrist, an ARMP can now do up to 20 visits before it was 12 visits. Only a psychiatrist.

So then there are four wrap around programs we're going to try and duplicate Oregon's work with wrap around which means that you go out and do education with the family and the client, in a very intensive way around the mental health treatments.

We're going to do primary care education very similar to Massachusetts, where we do outreach and look at tools and guidelines and materials that we can give to both primary care and mental health professionals.

Second opinion processes for AAP. There's 900,000 dollars to run a second opinion process for children on anti-psychotics. And you will be engaged in what the thresholds are and how that will work. And we'll be working on that over the next few months.

As well as Eric Trupin has an evidence based practice center now to look at what is the evidence for off label use, or education, or CVA, or you know, yet to be determined on the scope of that evidence based practice center.

As well as now the house bill 75, or 5773 where it's the sharing of information. So we're going to concentrate on kids first, we're going to use, try and wrap it all around so it's not just about drugs, it's about improving outcomes, outreach education, and see if we can't make this hum here, because there's just too much variation in the system right now. Yes.

Carol Cordy: Well, I know everybody else [inaudible] but there just aren't enough providers to see kids [inaudible] therapy.

Jeff Thompson: And it is what it is, I mean even if you wanted to put out you know double the amount of children psychiatry, you still wouldn't meet the need. I mean, and.

Carol Cordy: But I'm wondering if some of that is the reimbursement.

Patti Varley: Exactly Carol. This is Patti. There are several of my colleagues who will not take the kids because they get, they don't get reimbursed. So part of

the access is that we need to pay people appropriately for taking care of them.

Jeff Thompson: And there are actually increases in a number of E&M codes for both primary care and pediatrics in other additional legislation that will be included here. But the evidence is not there that pay equals access. As a matter of fact if you look in Medicaid [inaudible] reports that say even if you bump the rates up 20% you only buy 5% access. I'm just telling you.

Woman: Has anybody looked at whether 20% still equates out to them taking some other insurance. I mean that's my question is that if they have six appointments open and they get paid a certain amount, if they're going to get paid less, and that's their overhead cost of living it's a problem.

Jeff Thompson: And I'll just push it back on you. If we were to pay 80% of UMP rates that would be an additional quarter billion dollars to the state. So either you raise B&O or you take it out of education. So, we're engaging you in the solution, there are increases in both the pediatric and primary care fee schedules that go along with this, we've expanded the benefit, now we're going to work with you on you know how do we reduce the variance, how to do it in an education and evidence based manner. It doesn't get much better than this. And then you know I mean if you look at what you guys have done a phenomenal job you know with the preferred drug list. The preferred drug list is actually a very liberal drug list. It is the most liberal in this state. And Patti and I had a discussion with [inaudible]. I mean if you look at all the other health plans and you look at what you've created, it is the most liberal. And that is a public input process and that's great. And then we've worked on safety and we're going to continue working on safety. So I think it is working, probably not as fast as everybody wants, probably not as much as everybody wants, including me, but you know it doesn't get much better than this. It's up to Medicare right? Jim you're, you go ahead.

Man: How are you guys going to determine what it is you're going to look for in the chart reviews that you're talking about doing to drill down into those books.

Jeff Thompson: We'll convene a group of experts again, some pediatric, Chris Varley, Jack [inaudible], Bryan King, Bob Hiltz. Probably try and get some of the other people from Mary Bridge and then get them together and talk about from an expert, is there evidence to say that there's a limit by which you want to take a big deep breath before you step over. Age, dose, combinations of a single drug class, or combinations across drug class, or when they're not taking their meds, or when we can show excessive amounts of, I mean you will an engaged in where the threshold is.

Man: I guess the point I was making is the, you know if you only look for certain information that'll be the only information you get. So it's good that you're trying to figure that out ahead of time because you might find out something that you didn't anticipate. And I, and the converse is just because people that are on high doses or lots of medications don't do well, does not equate to well then we shouldn't give them as much.

Jeff Thompson: I never said that.

Man: I know, but that's why I said, I think you have to be very careful about the information that you look for, so that you can really drill across all of that stuff.

Jeff Thompson: The right drug, the right time, for the right reason. I mean that's really what we've got to hit on. And we've got to hit on why aren't they taking the right drug for the right reason at the right time. Yea.

Vyn Reese: It's Dr. Reese. I think one of the things you're going to find is going to be disease severity is the driver behind number of prescriptions, number [inaudible] and admissions. I mean the patients are seeing lots of people that are not, they're not getting consistent care, they're desperate, each provider is giving a different drug, they don't tell them that they just saw somebody else, and it's just, and that's just a marker of sort of, a progression or exacerbation of their illness. And then they go to the [inaudible] hospital [inaudible]. And so it's like, that's the sort of thing that you'll see, you know in the outpatient setting, not uncommon.

Jeff Thompson: And that's why information sharing is important, so you know.

Vyn Reese: It's important but the patient is, there's very disorganized, it's hard to regulate them, and there's not a lot of inpatient settings here too. [inaudible] inpatient settings at an earlier place and that sort of escalation. But I think that that may be what you see.

Jeff Thompson: Right and remember we have other tools that are available to you that you don't have in your practice. We have lock in program. One provider, one narcotic provider, and limited access to hospitals.

Vyn Reese: Yea, well narcotics are different than mental health drugs so there's a.

Jeff Thompson: Well no, but if you are engaged and you want to say that you've got you know somebody that continues to go to 20 different providers to get their mental health drugs, and you tell us that they should be on lock in program so we have one prescriber, one primary care provider, and we're limiting you know who gets access to narcotics, and hospitalization that's coordinational care and that's allowed under the federal rules. So that's a

tool that we can make available to you. Or we can put them on narcotic restriction where we can basically stop a narcotic prescription and ask you whether it's medically necessary when they're going to the emergency room and getting that.

So all these tools we made available and I think you know the, what is absent. What is absent is if I got, I don't, maybe you're smarter than me but, if I have somebody with schizophrenia that's diabetic, and is an alcohol and drug abuser, I don't know how to take care of those people. I used to be a pretty good internist, but I still, I don't even think in my prime I would know how to do that. So unless we're working together, which is really who we're talking about, you know it has to be an integrated system.

And we just spent two days with all the Medicaid medical directors and mental health directors from around the country talking about what is integration. How do you connect the body to the mind. How do you talk about integration. And I think it goes beyond just medical home, I think there needs to be some more dialogue and some more interaction between the state and the providers. Because there are tools that we have that we can give you, and I think there is also information we can give you to make it, you know more and better care. Questions? Comments?

I know the data is descriptive, it is not peer reviewed. It is what it is. It is not a sample, it is the entire universe of what prescribing here. But it offers us I think the opportunity to use the data and to not use anecdote or personal opinion, but to actually use data to drive in and discover what's going on. And if you look at the literature on adherence it's really very interesting. Much of the literature on adherence is basically based on a patient's questionnaire response. Very little of it is actually based on, did you do pill counting. And so a lot of what we think is the problem with adherence we don't really know.

And I actually, what's interesting is I've not seen the study and there's a meta-analysis of, it's not really meta it's a descriptive analysis of 164 reports on adherence and they, and I don't think they've nailed it yet. Because none of them have really gone in and done chart reviews and really strived to identify you know cohorts or combinations that can lead to non-adherence. And then these excessive amounts of re-hospitalizations. And I think that's what we have the opportunity to do, is really understand these people and how to get them the best therapy and treatment. Alright, I'm done. Thank you very much.

Dan Lessler:

Great, thanks. Any other comments or? So I, and I don't think there's anything in terms of, it was really just discussion in terms of this last agenda.

Man: Well what I think [inaudible] clear is I think, just because he did the sedatives is maybe, you know are you agreeing to continue the five in 30 day rule for children. For the sedatives and just put it on the record.

Siri Childs: Jeff, I've got to confess something to you. The way we brought this to the board for children is that we were going to deny it for children unless there was an extreme circumstance and then we were going to allow five for 30 days. And that's how, what was brought to them, and that's what they approved. So most of the requests that come to us, if the child is less than 17 and there's not, you know a compelling reason or a medical justification we're denying it straight out.

Dan Lessler: So that, thanks.

Man: So I think, I mean just to be you know transparent, I mean is that your instructions as the DUR to the state to continue, you know that practice.

Man: Do we ever have input in this before?

Siri Childs: Yes you did.

Man: Was it one time?

Man: We presented this and.

Man: It was quite a while ago.

Siri Childs: Dr. [inaudible] did a presentation for the mental health group and there was age limits, there was dose limits, and then there was the combination drugs, and then there was the sedative hypnotics in children under the age of 17. And we agreed that unless it was, you know compelling in medical justification, we would deny. And if we would approve it would be just five in a 30 day period.

Dan Lessler: Was it just the mental health subcommittee that did that?

Siri Childs: No, well they created the recommendation and we brought the recommendation to you.

Dan Lessler: And we just, and we said five in 30.

Siri Childs: Yes, yea you said.

Dan Lessler: And then we said five in 30 after it was denied initially across the board.

Siri Childs: Right.

Dan Lessler: Okay.

Patti Varley: And this is Pattie Varley. My recollection is that because if you looked at the data, there was no data available of any evidence of the use of those medications in children or adolescents. There was absolutely no data.

Dan Lessler: Bob did you have a.

Bob Bray: Well I guess it would make sense to me that if that's the recommendation of the mental health subcommittee and they've upheld their opinion about that and we haven't seen any evidence to say we should do something different then I would say the DUR should just say yes we should honor the recommendation of the mental health workgroup.

Man: Which we've already done.

Bob Bray: So we're right. So we're, you're asking us again and we're not hearing anything different from the mental health subgroup. So I would say in the absence of any other information that we're upholding what we already upheld.

Woman: Can I ask, and that includes all sedative hypnotics, is that right?

Group: Yes.

Woman: Not just the new, right.

Man: I just want to be transparent about that because you did review that class and make sure that there's no surprises.

Carol Cordy: This is Carol Cordy. Was this the same process as happened to get the ten for adults? Of the new ones or was that something different?

Siri Childs: No, that's something different.

Carol Cordy: Okay. I was asked to bring that up at this meeting, so I just, I'm interested to know how that occurred.

Siri Childs: Again, I'm not prepared to talk about that at this meeting. We can talk about it at a future meeting when we can bring all of our evidence, you know to support that. But I didn't come prepared.

Dan Lessler: Okay, so could we, I mean maybe we could just put that on the agenda for the next time in terms of looking at.

Vyn Reese: So [inaudible]. This is Dr. Reese let me clarify it. So for adults it's ten in 30 and for children it's five in 30 if they get it at all.

Siri Childs: Right.

Man: And that's only for prior authorization drugs. That limit is not there for PDL drugs. For other benzodiazepines.

Woman: PDL [inaudible].

Woman: For adults it's.

Siri Childs: It's for sedatives and hypnotics. Yea, this is the way it has been prior to our discussion today on the preferred drug list.

Woman: But for adults it's just the newer sedative hypnotics. For children it's all.

Siri Childs: Right, yes.

Man: So the same limit as for Temazepam, ten per month.

Siri Childs: For children, yes.

Man: Children only.

Siri Childs: Yea.

Man: Okay, not adults.

Man: Five per month.

Siri Childs: For children yes, for adults no, but only because we've been in a freeze. We haven't been able to go ahead and [inaudible] do the same thing for the, for all of the sedative hypnotics.

Jeff Graham: Maybe we should review this whole [inaudible]. It sounds confusing to me as to what, how we set this policy. Maybe at another meeting we could discuss that.

Siri Childs: Yea, I think that we have a consensus of what we should do in children, but we need to bring back with evidence what we do in adults.

Dan Lessler: In adults, right. That sounds good.

Siri Childs: And make it consistent across the board.

Dan Lessler:

Right, okay. Alright, I want to think, there being no further business we can adjourn.