How to do clinical trials in the chronic and acute framework are clearly needing additional input, improvements in design, styles, and methods, and methods for inference. I will be very brief now because I have some time to talk about the acute setting, so now I just want to say one brief word about doing research in the chronic framework.

[Slide.

Right now there are precious few, if any, I am not aware of any clinical trials that have really answered the question about what to do about the fact that placebo patients in a chronic framework drop out very rapidly, and statisticians have developed both crude and very sophisticated methods for imputing data, the crudest being the last observation carried forward and variance thereof, and the more sophisticated using methods of multiple imputation developed by some quite credible and rather brilliant statisticians.

In my view, none of those satisfies the criteria needed to draw valid causal inference because there is some form of informative censoring going on in these trials, in particular, placebo patients are dropping out because they are not getting adequate relief, and adverse effects are

coming into play, so the censoring mechanism may very well be informative.

A design has been used in other areas of medicine, appears to me to be potentially very relevant in this arena, and that is the so-called withdrawal trial. The withdrawal trial is an enrichment trial in which patients stay on the trial for the 12 weeks, as Lee proposed, for example, and dropouts are taken note of and there is some kind of inference on the dropout rates done, but the only patients who are relevant are those who have stayed on and had satisfactory response from the test treatment by the 12th week.

Those people, I believe should have a criteria, for example, the one I described, at least some X percent of the patients who started the trial have to be around for the 12th week for the drug to be considered a chronic medication.

At the end of that week, patients are randomized into one of two groups. Half remain on the trial that they started with, on the treatment that they started with, they remain on the drug, the other half go off the treatment they started with, and go on to a placebo, and proof that the drug works is contained in demonstration of placebo

treatment superiority during the subsequent period of time. Depending on the drug, it might be a week or two weeks thereafter.

This particular approach does away with the need for imputing the values of dropout patients to the end of the trial, and when patients are dropping out in the first and second and third week, the imputation really looks quite silly.

This is a proposal that I think needs some time and attention, and hopefully will allow us to draw better inference about the treatments we wish to investigate.

Thank you.

DR. FIRESTEIN: Thank you.

The next speaker is Mason Diamond, pharmaceutical consultant.

DR. DIAMOND: Thank you. My name is Dr. Mason Diamond. I am independent consultant, pharmaceutical consultant from the Boston area. I am also Vice President at Engenium [ph] Research, which is a contract research organization based on North Carolina.

I am speaking today on my own behalf and I paid my own expenses to attend this meeting. At this moment, I have no financial arrangement nor

financial interest in any company or CRO currently involved in the development of analgesics.

Before I begin, I wish to thank the FDA and the Arthritis Advisory Committee for giving me the opportunity to address this group. Furthermore, I would like to commend CDER, Division 550, and specifically Dr. Simon and Dr. Witter for taking this much needed initiative. To my knowledge, no other regulatory authority has done this.

My purpose in speaking today is to highlight some concerns regarding the needs of the elderly population. I strongly believe that these concerns should be addressed in analgesic drug development.

There are over 34 million Americans over the age of 65 that are affected by pain. Research has shown that at least 62 percent have taken prescription medication for more than six months to treat their pain.

More disturbing are the estimates that as much as 80 percent of nursing home residents suffer from painful conditions that go untreated.

Arthritis has been identified as the single most common cause for chronic pain in the

elderly, however, it is not uncommon to see more than one indication requiring analgesic therapy. In addition, most elderly persons have multiple medical problems that require multiple medications.

Many drugs used to treat these concomitant conditions have not been sufficiently evaluated for co-administration with each other, let alone with many analgesics. As a result, the comprehensive guidelines necessary to deal with the complex safety issues in this population are not available.

It is the fear of possible serious and life-threatening side effects that is often the barrier to adequate pain treatment in older adults. The situation is further complicated by progressive cognitive and emotional difficulties encountered in this population.

This makes medical evaluation and management even more challenging. The net result is that while in many cases the pain management with drugs and other treatments are possible, each year millions of older people are forced to endure unbelieved suffering.

The elderly represent the largest number of pain sufferers and purchasers of analgesic products, yet, they remain in the greatest need of

innovative therapies.

In an effort to address this need, I would like to offer some points to consider as we move forward in our discussions of analgesic pain models and clinical study designs.

First, inclusion/exclusion criteria. In order to minimize response variability in our clinical studies, it is common for us to enroll as homogeneous a population as possible. While scientifically sound, this approach tends to exclude those individuals who may be most representative of the target population.

For example, in arthritis trials, the actual effectiveness and safety profile common to a more frail elderly population may not be reflected in the Phase III study results. My recommendation would be to ensure a more representative patient cohort in our pivotal clinical trials or conduct separate studies specifically in this population.

Second, the pharmacokinetics and pharmacodynamics of drug interactions significantly complicates pain management in older adults. The resulting side effects from polypharmacy, coupled with the underlying medical conditions, can be daunting to deal with.

It is not uncommon for the elderly to be on five or six medications at a time and often more. Although these issues have been discussed in the FDA and ICH guideline documents, and drug companies do go to great lengths to evaluate drug interactions, these studies need to include more older adults who are being treated for multiple medical conditions since they represent the ultimate beneficiaries of these new therapies.

Third, the duration of evaluation. The most common pain problem in the elderly are chronic and patients often take analgesic medications for long periods of time, if not for the rest of their lives.

Many adverse events become evident only after long term use. Evaluations of 12 weeks or even 12 months may not be sufficient to capture the long-term risks and benefits of a particular drug. I am sure that everyone here agrees that we are all committed to bringing safe and effective medications to the public as rapidly as possible, however, we must also ensure that our research provides the necessary information to enable practitioners to better manage their patients especially those on complex treatment regimens.

This could be accomplished by blinded studies of longer duration or by employing longer open-label follow-up extension studies, which would provide this much needed information while not impeding the drug development process.

Finally, outcomes evaluation, I think on everybody's mind. In a search for better methods to evaluate pain, we are focusing on objective measures to incorporate into our study designs, mechanism-based assessments, determination of biomarkers for underlying diseases, and levels of pain modulating biomolecules are some of the options under discussion.

I feel that all these options should be actively pursued, however, these approaches will take some time to validate. Also, in many cases, the objective evidence for underlying disease may not correlate with the symptoms, and symptoms may wax and wane spontaneously.

One solution is the utilization of multidimensional pain outcomes. This includes pain assessment, functional assessment, psychological outcomes, and quality of life measures.

New assessment tools designed for both cognitively impaired and unimpaired elderly adults,

such as the geriatric pain measure developed at UCLA, are in the process of being validated. In addition, there are very many well-established and highly validated tools dealing with each of these areas that are currently available, however, since pain affects so many aspects of people's lives, no one measure can adequately capture the overall effect of any therapy.

For example, in an arthritis trial, it is possible to show no change in pain level, but a significant impact on the patient's ability to function. This is due to an individual's ability to adapt their level of activity to the level of pain tolerance.

So, if a patient takes an analgesic that enables them to climb stairs, walk a greater distance, take care of themselves, or play with their grandchildren, but continues to report pain, I would still consider this a clinically significant outcome.

In addition, the impact of pain on an individual's psychological state and overall quality of life is no less relevant than pain level or functional status. Therefore, until we have one system that measures all of these parameters, we

should evaluate efficacy based on more than one outcome.

It is clear that the treatment of pain in older adults is an enormous undertaking. No less so is conducting clinical trials in the elderly population. We must remember that the information captured during drug development provides guidance for practitioners in addition to satisfying regulatory requirements.

Therefore, I believe that by addressing the needs of the elderly during the drug development process, we will enable the medical community to more effectively treat the millions of elderly patients through a need and bring them the benefits of these new drugs.

Thank you.

DR. FIRESTEIN: Thank you very much.

The next speaker is Daniel Carr from Tufts University.

[Pause.]

DR. FIRESTEIN: While we are waiting to sort out our technical difficulties, why don't we move ahead to the next person that is not using slides.

Dr. Abraham Sunshine from Analgesic

Development.

DR. SUNSHINE: Thank you. I am Abraham Sunshine, Professor Clinical Medicine at NYU School of Medicine. I am President of Analgesic Development. I appear here on my own, and I have not received any compensation from pharmaceutical companies to appear.

I was asking myself why did I want to speak, and I think I can contribute in giving some historical perspective on the analgesic guidelines.

The 1993 Guidelines, which we well described by Dr. Fang and her associates, really began in the eighties, and it took 10 years to get a document that went through all the hurdles, first, to get a consensus and then to get it through the FDA.

So, that document is over 20 years old. I want to acknowledge the work of Lee Simon and his associates for initiating this conference, and also the work of Ray Dionne who ran the consensus meeting at the NIH.

The 1992 Guidelines really were driven by investigators and industry who just didn't know what to do to get an analgesic approved, and the ground rules were changing with each drug that was

approved, so to move forward, it was thought that a consensus would be helpful.

Now, the guidelines served us well. The drugs that were being developed at that time were acute analgesics. There were no drugs for chronic pain, and the last thing a pharmaceutical company would be interested in is developing a treatment for neuropathic pain.

So, there was no discussion, as Dr. Firestein pointed out, about how to conduct chronic trials because there were very few chronic trials or drugs being considered, and opioids for chronic nonmalignant pain was a no-no. People didn't use opioids for chronic nonmalignant pain.

I think advances have been made now, as we saw fentanyl being used, patch being used in low back pain, but we also know about the OxyContin story, that anybody that had a backache was put on dope and got into trouble.

The guidelines did permit us to develop many of the NSAIDs both for Rx and also to define an OTC dose. The technology was developed, so that one could pick up the effects of 12.5 milligrams of ketoprofen, and even 100 milligrams of ibuprofen, and dose-response work was done using these

guidelines.

The guidelines also helped avoid pseudospecificity, and I think this is an important point because we are at a road where I think as I hear rumblings, that we are going to pseudospecificity. For example, dysmenorrhea was understood to be a drug, recycled oxygenase was involved, but in order to get a claim for treatment of dysmenorrhea, one had to show that the compound work as a general pain medication, and then, in addition, in dysmenorrhea.

I was on the web site that Lee talked about, and it really is a good web site and I see that Google has helped you get this web site working, and yesterday morning I came across CDER's policy on OTC analgesics 1994, signed by Dr. Woodcock, who clearly points out that to get a claim for menstrual cramps, one needed two positive clinical trials in appropriate pain models, and in addition, positive clinical trial in an OTC dysmenorrhea model.

I don't think these guidelines are being followed at the moment, and now we are getting pseudospecificity where drugs which really have a broad implication in terms of pain management, are

brought labeled for dysmenorrhea, and not for general pain.

The other that was important to emphasize in the eighties and nineties is that small sample sizes of 30 to 50 patients per treatment in a single center generated important data, and data where you got dose response to the NSAIDs. Ketoprofen, from a dose of 12.5 milligrams up to 100 milligrams was clearly defined.

Today, and I don't know the reason, one needs hundreds of patients per treatment arm and then there is a lot of deliberation is the drug better than placebo.

One of the problems, I don't know that it was discussed so far, is combination therapy. Very few combination drugs have been approved. I mean there are combinations of ibuprofen with opioids, and there is a combination of tramadol with acetaminophen, so polypharmacy didn't get ahead.

One of the reasons, it was extremely difficult to show the contribution of each of the ingredients. Although we know that codeine works, and we know ibuprofen works, put them both together, and the results were not convincing, so there is no ibuprofen-codeine product even though

it was attempted many times.

I think as you move forward with the guidelines, it is clear that polypharmacy is here to stay. The other thing, polypharmacy was discovered by patients, not by CDER, not by the industry, but if you look back, there was Empirin compound, acetaminophen, and aspirin--Dr. Brandt talked about that--and caffeine. Then, there was Empirin with codeine, and these were drugs that just over time were found to be helpful, but when pure science came to play, combination therapy was a no-no, and you had to prove the contribution of each of the compound.

When Burroughs-Wellcome took caffeine out of Empirin compound, the sales of Empirin compound plummeted, much like the stock market is doing today, and that compound is off the market. I think that caffeine has a role as an analgesic adjuvant.

DR. FIRESTEIN: Dr. Sunshine, could you please wrap up? Thank you.

DR. SUNSHINE: Okay. I think as we go ahead that we have to develop tools to explore all the contributions of the neuroscientists that Dr. Woolf discussed today, so that we can utilize the

information to develop better drugs. Time does not permit me to go into that aspect, but in five minutes I couldn't answer the question, so I think it is going to take maybe not 10 years, but a couple of years.

Thank you.

DR. FIRESTEIN: Thank you very much.

I believe now our information technology problem has been solved, and we can now go back to Dr. Carr's presentation.

DR. CARR: I thank the committee very much for having invited me down here. In particular, I think Lee and Jim Witter, and as did the prior speaker, I thank Ray Dionne for having organized a preconference and also Ms. Reedy for getting me down here.

As I was listening to the erudite and complex discussion earlier today, I wonder what might there be that hadn't yet been said. So, I titled the title of this 10-minute presentation "What might still be said, that hadn't yet come across," and I am speaking from a rather distinctive point of view of a clinician, but I would like to call attention to a great resource that I think has yet not been tapped, and should be

tapped, which is that the evidentiary body upon which clinicians seek to make recommendations for therapy and to treat their patients, insofar as analgesics are concerned, in large part, derives from approval trials.

So, I would say that there is an opportunity to render this very robust data-generating process much more useful to clinicians and therefore, their patients.

[Slide.

Now, to try to lighten the postprandial stupor, I thought I would begin by posing four simple questions. The first is--and these are reasonable questions--who won the last presidential election? Did X Corporation make money or lose money? As Dr. Sunshine mentioned, we are all interested in that.

What kind of pain does my patient have, and what is the most effective treatment for my patient's pain? In the interest of time, I am not going to cover the first two questions, but I will say that in try to cover or provide mustering of evidence to answer the third and fourth questions, I have had the privilege to be involved with some wonderful individuals over the years, with Ada

Jaycox for the old AHCPR acute and cancer pain guidelines, and more recently with Joseph Lowe and Leo Gudis and others for work with AHRQ.

So we have actually made an earnest effort to try to muster the evidence. This report, which can be cited or traced through the AHRQ web site, on cancer pain, involved screening over 18,000 titles. A couple of weeks ago, there was an NIH State of the Science Conference held here in Bethesda, as well, just down the block, and for that we screened an incremental 6,000 titles relating to cancer pain.

So, we have made an effort to try to muster the evidence.

[Slide.

At the same time, and I am sorry if I repeat what you have heard before, but I am just putting things that I think clinicians might tend to focus on, is that recent insights, much of them accomplished by individuals in this very room, to my mind have blurred the boundary between acute and chronic pain.

Pain is itself a widely distributed process, and I am not sure we have mentioned the brain yet, but the brain and imaging of the brain

are both very important factors to consider in understanding pain.

I think we have heard, although perhaps not in these words, that chronic pain is itself a disease, and a theme that has popped up again and again amongst different speakers is that the field itself has arrived at what you might term combination analgesic chemotherapy, much as one uses combination chemotherapy for other conditions.

In fact, the onset of the disease of chronic pain is potentially very rapid. If one looks at epidemiologic data from the 1999 IASP book on Epidemiology of Pain, edited by Crombie or the 2000 Review in Anesthesiology by Perkins and Kehlet, it is quite clear that many patients who undergo operations of any kind will develop persistent pain.

I think this is an under-recognized epidemiologic factor, but it is very, very important, and I am actually surprised that this market opportunity hasn't been seized upon. There is also much insight into the long- and short-term benefits of aggressive therapy, although in the preemptive analgesia area, it is clear that a single drug is unlikely to make an impact.

We have also had evolving understanding of drug pharmacokinetics and pharmacodynamics in particular appreciating the diversity of individuals according to gender or ethnicity or even as far as interpretive aspects go, culture. There has been tremendous insight into understanding the mechanisms of opioid tolerance, and we are just beginning to see the emergence of insight into disease-specific mechanisms, such as in cancer.

For example, I refer to work by Debar and colleagues on identification of endothelin-1 as a cancer-specific mediator. Nonetheless, as one has tried to consolidate all these published trials, and by the way, I think the efforts to consolidation are themselves an advance through Cochrane or evidence-based practice centers, the fact remains that the vast majority of most pain treatment is empiric and generic.

In other words, one starts with acetaminophen, perhaps switches to a nonsteroidal, perhaps has a so-called weak opioid, or perhaps changes the weak with a strong opioid, which is the same algorithm you might follow for a badly sprained ankle, as cancer pain.

[Slide.

One of the big problems in trying to organize the evidence is that the evidence itself is quite flawed, and I think the FDA can help future generations. Randomized, controlled trials are a tiny fraction of the pain literature. It is quite shocking, but when we did the acute pain guideline in '92, we pulled 13,000 titles, of which 675 were randomized, controlled trials.

Last year, when we did the cancer pain, roughly 20,000 titles screened, as you saw, about 180 were randomized, controlled trials, and for the interim State of the Science NIH Consensus Conference, we got another 6,000 titles. We boosted that figure from 180 to 216.

What are all these other trials? The vast majority are observational or describe a technique. Because of the nature of the literature, so many different types of diagnoses, patients, and outcome measures, it is impossible to do a quantitative meta-analysis for most of the clinically important questions.

In fact, for the State of the Science Conference two weeks ago, of the 218 retrieved pain trials in cancer pain, there were 125 different

pain-related instruments that were employed.

Now, granted, some of the differences were in a 3-point scale versus a 4-point, versus a 10- or 11-point scale, but the fact of the matter is there could really be a great service done to insist upon some standardization for pooling of this colossal, but difficult-to-combine body of knowledge.

The generalizability of the trials, as you have heard before, is limited by inclusion and exclusion criteria. The clinician is treating an individual who has comorbidity, who may be elderly, who is taking other drugs, and these are not represented in the data upon which the evidence is based.

A very important factor is the relatively small amount of focus placed upon side effects. Side effects, including adverse events, but even predictable side effects are what keep many patients from achieving good pain relief, such as with opioids, and it would be wonderful if there were a non-punitive shift in the process, so that side effects could be monitored prospectively and with greater precision than in the past without penalizing the sponsor of the trial.

One has a sense from the literature that previously, there was a process set up which encouraged actually underpowered trials, that is, few patients per trial. If one looks at the actual retrieved trials for cancer pain treatment, for example, these are on the orders of dozens of patients per trial, but if you look at cancer treatment, such as primary chemotherapy, through collaborative groups, these number hundreds or thousands.

In fact, if one were to calculate the number of patients, let's say, with cancer pain versus the number of patients enrolled in trials, these are a tiny, tiny fraction of those with the condition.

[Slide.

Well, what about that question, is this treatment helping, well, to translate efficacy data into effectiveness is the mission of a clinician, and thus far I have called attention to some gaps in the literature and what FDA can do to help.

I would say that to patients and their families, the primordial outcome is low pain intensity. On the other hand, particularly with the treatment of chronic non-cancer pain, quality

of life often trumps the pain intensity on a visual analog scale. Very often the approach to treatment of chronic non-cancer pain is to encourage patients to do more even if their visual analog scale does not go down, and as you have heard, very commonly in the clinical setting, patients self-titrate to a visual analog scale, which may be moderate pain, but they are able to do more.

We need standardized consensus instruments. Right now there is an effort underway that I am privileged to be involved with. It's a tripartite collaboration of the Joint Commission AMA and NCQA to try to develop performance measures to evaluate the implementation on site of JCAHO guidelines, but this is a bit of a struggle.

We will get the job done, but is not helped by the proliferation of instruments. Obviously, you have heard a lot of erudite comment about the need for generic versus condition-specific instruments.

One caveat is that coarse instruments, and the SF-36 is a coarse instrument, may overlook benefit, which is actually done to patients. I guess it's a disclaimer, I have been involved in the development of the Treatment Outcomes of Pain

Survey from Tufts or TOPS scale, that is essentially an augmented condition-specific SF-36 validated for patients with chronic pain.

Of course, we are aware that we can't just administer endless questionnaires because of the burdens on patients and clinicians. I have already mentioned that side effects seem to be approached very differently in the literature, in a much more cavalier haphazard way than are the desired outcomes, but they are often the thing that stops the patient from getting better. They just can't increase the dose.

So, are there things one do towards an answer?

[Slide.

Well, I personally believe that to frame compartments about acute pain or chronic, to say when does acute become chronic, it is a little bit of a misleading question because it equates a time course with a mechanism, but we all know there are many instances of prolonged acute pain, such as labor pain or arthritis, a sunburn or if someone comes in with an obstructed viscus, which are cured, and they never become chronic pain, or even repetitive pain like muscle bruises or soreness in

athletes, for instance.

Therefore, one must infer that nociception itself rarely induces chronic pain except perhaps when there are psychosocial factors. These are the small accidents that evolve into disabilities.

On the other hand, the progression of acute to chronic pain is well documented clinically, and as I have mentioned, is a big problem in epidemiologic terms.

DR. FIRESTEIN: Dr. Carr, would you wrap up. Thanks.

DR. CARR: The last slide, I think, but I will wrap this up in a minute.

[Slide.

I would submit to you that we have to look at the evidence and apply logic and distinguish between intense nociception, which most of us imply by the phase acute pain, versus the rapid onset of peripheral and central nervous system reorganization, that Professor Woolf spoke to you about.

There seems to be a clue that if you have concurrent nerve injury and intense nociception or inflammation, that increases the risk, so in an ideal world, if we all did our jobs, there would be

prospective identification, planning for patients at risk, individualized anti-nociceptive and behavioral interventions, effective treatments chosen according to evidence, and combined, these would be titrated, we would monitor standardized outcomes to validate and calibrate our practice.

In so doing, we would accomplish our mandated continuous quality improvement, we would meet JCAHO standards and identify best practices. Then, we would follow up people and we would assess long-term cost and benefits.

Thank you very much for your attention.

DR. FIRESTEIN: Thank you.

The next speaker is Dr. Ann Berger, Chief, Pain and Palliative Care at the NIH.

DR. BERGER: Thank you. I want to also thank Radion and James Witter. In looking at what I could offer here, it is similar to Dan in that I can offer the clinical perspective of pain and palliative care.

Prior to coming here, I had run both the Pain and Palliative Care Service at Yale and at Cooper Hospital, which is part of the University of Medicine and Dentistry of New Jersey, so I have had a lot of experience with palliative care patients,

as well as chronic benign pain patients.

In looking at the total pain picture, I brought a handout and I am sorry I didn't make a slide, I didn't know we could show slides, the total pain picture is really made up of the physical pain, which at least clinically, from my experience, is usually not just neuropathic pain, it's not just visceral pain, it's not must somatic pain, it is usually a combination pain.

So, it is going to be pretty difficult to say you are going to do a study just on neuropathic pain because unless you are talking about something like brachial plexopathy or diabetic neuropathy, because many of the pains are mixed pains.

We see this all the time with patients, but then besides the total pain picture of being all those physical different mechanisms, we have a whole element of suffering, and I think that is where we really miss the boat in medicine.

The suffering components is not only depression, it is not only the psychological states, but it is social issues, it's loss issues. When somebody came up and spoke about pain in the elderly, that's a huge problem and partly it's a huge problem because the loss issues are so huge.

These are people who have lost their pets, their furniture, their families, their friends, and that is something we never take into account. Suffering also involves spiritual concerns, and for anybody in pain, whether they are religious or not, it is always a spiritual issue because anyone who is sick or anyone is in pain, it's why is this happening to me, purpose-meaning type issues, as well as social family functioning, physical disability, and for palliative care syndromes, it is fear of death.

Now, the only difference in my mind clinically, when I look at a patient, is, is this a palliative care patient or is this a chronic benign pain patient, and the way I define that is palliative care are patients that can ultimately die from their disease, so they have a life-threatening disease, something like cancer, something like HIV disease. Clearly, there are lists of those, you know, because many diseases we don't cure, so COPD, CHF, you know, many diseases.

Chronic benign pain are patients like with low back pain, fibromyalgia, endometriosis, chronic pancreatitis, and these people are not going to die from their disease, but the treatments really need

to be very similar to the cancer pain population.

My background and how I got into this, I was initially an oncologist and I consider myself a reformed oncologist, and actually started the Palliative Care Service at Yale, and at the time started ending up seeing a lot of chronic benign patients.

How did that happen? It happened that an oncologist was doing that because the principles were the same principles. So, you know, it is not unusual to get lower back pain, reflex sympathetic dystrophy, fibromyalgia, and I was a little concerned with looking at the guidelines to say, well, you are going to just divide it up into little departments of all these different pains, when it is really a much broader issue, and these chronic pain patients are very similar in many, many ways.

What has struck me so many times, you know, initially, when I got into more of the chronic benign pain part, but just all the time, is that the suffering issues of these patients are at least as much, if not more, than the palliative care, cancer pain, HIV population, overwhelming.

So, I say that this is a component that we

have missed in medicine, we have missed the boat because we always think that there is a medication for that, and there is no medication for suffering.

I would like to share an example of a patient that I took care of for a while in New Jersey, a man who had back pain after being disabled on his job as truckdriver, and he ended up going for all kinds of epidural injections, facet blocks, and continued to have pain, then had surgery, and continued to have pain.

I mean we all know the story, we have all seen it many times, and he actually became more depressed, was seeing psychiatry, was put on four or five different antidepressant type medication anti-anxiety medicines, was in a stupor, but was still having pain, and ultimately ended up going to a neurosurgeon to have a dorsal com stimulator placed, which failed. Not a big surprise that this failed.

At this point, they said all right, send him to Ann, she seems to know how to fix these people. He came to my office crying, crying, crying with his wife, and so we started--the assessment I do is the same like I would on a palliative care patient. I am like what is going

on here, what is going on.

He was a truckdriver, had lost his job, again, all these losses, had lost his job, lost his finances. This was his whole self-esteem to be a truckdriver. Six months later his daughter actually died of a brain aneurysm and left him with a six-month old baby. Two years after that, his father died of Alzheimer's, and a year after that, his sister died of bone cancer.

This is not an unusual story. This is a story that comes into my office every day, whether the patient has low back pain or RSD or fibromyalgia, the stories are usually very similar. The losses are very similar.

In terms of the suffering component, the only thing that helps that is all the nonpharmacologic things, counseling. There is no Prozac, there is no Zoloft, there is no medicine. It is counseling, it's art therapy, it's music therapy, it's pet therapy, it's acupuncture, it's Reiki, it's spiritual, it's all these other components.

In terms of, in my mind, when I look clinically at a palliative care patient versus chronic benign pain, really, the most important

difference in terms of how I treat them medically, with the medications, is clearly, if they are palliative care, quality of life has to come first, and you are absolutely correct, function may not increase.

You know, sometimes just being awake and breathing is increased function. Whereas, in chronic benign pain, yes, we expect function to increase, and that is the big difference. I don't care what numbers the patients are using. This guy I was talking about before was on heavy doses of oxycontin, up to actually 2,400 milligrams, and still remains at that dose.

It didn't matter because he started working, he was functioning after this, and that is the important thing, are you functual again if you have chronic benign pain.

The things that I think we don't have enough data on, we clearly don't have enough data on cancer drugs, on neuropathic pain, and also on things like post-treatment pain syndromes. It is very interesting that we don't look at post-treatment pain syndromes.

Again, in the elderly, people who have multiple, multiple operations, it is not unusual

that they are going to have pain after their operations, and this is not something that we think about. It is not only postmastectomy pain, postnephrectomy pain, but it is anytime a surgeon lifts the knife, you could ultimately end up with chronic pain, so a lot of people with abdominal surgery, it is from endometriosis, from pancreatitis, from whatever.

DR. FIRESTEIN: Thank you very much.

The next speaker is Dr. Thomas Schnitzer from Northwestern.

DR. SCHNITZER: I appreciate the opportunity to be here to speak today. I am here, although I do interact with the pharmaceutical industry significantly, I am really here representing myself as a rheumatologist, a Professor of Medicine, and Assistant Dean for Clinical Research at Northwestern University, Feinberg School of Medicine.

[Slide.

I actually wanted to talk about three specific things. I had three topics that I thought I would want to discuss, but, first, I would really like to commend the FDA, both of the divisions that are here, and Dr. Witter and Dr. Simon for their

ability to bring together this discussion, which I think is clearly, after the discussions we have heard today, much need.

There were three topics I really wanted to talk about, but given the fact that I had limited time, which manages to focus you intensely, decided to really cut down to really just speaking about two of these, the nosology of chronic pain, which I think we have heard a lot about, I will not speak to further.

But I would like to talk about the methodology of the efficacy trials, particularly in musculoskeletal pain, really in an attempt to demonstrate I think some of the limitations and some of the opportunities and that exist in terms of methodology.

As I am talking to my clinical pharmacology colleagues, I think what is clear, as they say, is that a really good investigator can design a trial that will give the results that he or she wants. So, study design is actually critical, and what I would like to do is focus on the traditional study design we have used to demonstrate some of the limitations of this design, and then to talk about opportunities.

[Slide.

In the area that certainly I have had 15 or 20 years experience, a flare design, whether it is osteoarthritis, rheumatoid arthritis, or other types of musculoskeletal disease, is typically what is done.

This is what we use for these conditions to be able to demonstrate efficacy. What we haven't really I think given enough thought about is the issue of defining an analgesia-dependent population that we are studying, that we are dealing with high levels of pain, so at the time of randomization, when we actually start to treat patients, their mean pain score is often greater than 70 mm on a 100-mm visual analog scale, so this is not minor league, minor pain, this is I think high intensity pain.

I would submit that we are really not looking at a chronic pain model, but we are looking at a subacute pain model, and I was glad to see Dr. Simon in his definition of acute pain actually include subacute pain, which I actually think the models we use would fit very well.

Finally, I think we are selecting for drugs that work in acute pain rather than looking

for drugs that work in a chronic pain mode.

[Slide.

To be able to perhaps explain that better, I will just take a slide here, which really represents no specific trial, but is similar to what we see in many of these OA trials, looking at pain on walking.

The first point represents the patient population that we are screening, so when they come in on their medication. What I would want to indicate is the fact that these patients, in many of these trials, are required to be on full doses, prescription doses of analgesic medication, so they need to be on this medication.

To qualify to be in the trial, they need to have an increase in their pain. So, they are analgesia-dependent patients.

Now, this population is hardly representative. As an active investigator and as an investigator who believes in collecting metrics at our research center, I can tell you that when we advertise for patients with knee pain, that for every 20 telephone calls we get, we may have one patient enter a trial.

So, that is 5 percent of those people who

were willing to pick up the telephone, call us, and say they have a problem and they would like to be in a trial. Of the patients who actually come in and we can talk to, and we put in the trials, about 20 percent qualify in this type of trial.

So, the idea that this is giving us a representative sample of patients with osteoarthritis or rheumatoid arthritis is clearly not the case. This is a subset, this is not a general population.

The second point to be made is clearly these patients have to flare, so they have now a chronic pain background, but we are requiring that they have the onset of acute pain over the course of usually five half-lives of a drug. Their pain gets up in the range of 70 to 80 mm on a 100-mm visual analog scale, and I will submit this is not looking at chronic pain, this is looking at a flare of acute pain that has been induced by the study design.

This is hardly what we, as clinicians, typically see. We don't start patients in our clinic on another drug after they have stopped their previous drug for three or four days. So, this is an artificial situation.

As I said, I would submit that we are looking at a subacute pain model, not a chronic pain model. When you think about it, what type of drug are we going to select? We need a drug which is going to work quickly. Patients are going to drop out if this drug doesn't work fast. This is going to sound very much like the acute pain argument.

So, we need a drug that works quickly, and we need a drug, in addition, not only working quickly, but a drug that is effective for high levels of pain, not mild or moderate levels of pain, but high levels of pain.

So, we are selecting for drugs that have already proven that they work in the acute pain setting. We have just gone through a dental pain model for acute pain, which looks at issues not dissimilar to this, and actually has pain levels that are very similar to what we are seeing here.

So, I would submit that we are probably not using the right model even though it has been clearly validated and does develop, we will approve drugs, but probably for acute for subacute uses.

[Slide.

Now, is there another way? Well, it is

hard to believe, but I actually did not speak to Dr. Laska before this meeting, but I would like to talk about withdrawal trials, as well, and actually, having such an accomplished statistician present this information before I am means that I don't have to deal with the statistical aspect of this at all, which I don't feel qualified to do.

But I think there are significant advantages to looking at a withdrawal design. Now, this is not unusual, it has been used in pediatric studies repeatedly for ethical reasons. It is actually included in the RA guidance document, so this is not something which does not have a history.

The advantages, in addition to the statistical strengths that Dr. Laska submitted, is that all subjects receive active medication, so this is a real advantage. Everybody gets treatment. For many patients, if you get them for trials, this is important.

There is no necessity for disease flare although you can put one in if you want, but there is absolutely no necessity to have a disease flare, so you can actually look at baseline pain levels on treatment, and there is no artificial definition of

responders.

What I mean by that is we are going to have a long discussion, I am sure, both today and tomorrow, about how many millimeters if a clinically meaningful response.

Well, in this model, the patient decides that. I mean we don't have to have physicians sitting back trying to make the decision about how much is appropriate. What you really have is the patient says I have had enough, I want out of the trial. That will be different for each patient, but it doesn't matter, because you will actually have a response.

[Slide.

So, this is what a trial might look like, and there is run-in phase here, which I shouldn't leave out the importance of, because this run-in phase on active medication, so patients are first on active medication for a number of days, allows you to learn a lot about the use of that drug in an open-label fashion. I think that is also an important aspect.

Patients are then randomized at some point. The other point about this is they can be randomized at anytime, so the investigator nor the

patient has to know when that occurs. Then, you see patients dropping out for lack of efficacy or whatever you want to use as your objective endpoint, and a differential dropout rate between patients on active therapy, which would be indicated here, and on placebo or another less active therapy on the bottom line.

The intent is really not to say the withdrawal trials are the way to go. It is just to say that I think we need to consider a number of other approaches in terms of methodology, and this may be one of them.

[Slide.

The last thing I want to talk about is long-term safety. It is really something that has not been talked about today, but I think is absolutely critical.

We know from discussions here at the Agency and I think eloquent discussions, that the datasets at the time of NDA are really inadequate to be able to detect uncommon events. We know that some sort of postmarketing surveillance program is required if we want to be able to determine these uncommon events. So, I would say it is required or let's say needed rather than making it a

requirement.

These studies need to be well defined, they need to be carefully planned, and I think, most importantly, they need to be done in a timely manner, so these programs are going to be of any value if we have them shortly after a drug is approved, and long after it is history.

I think the way we go about this is to provide appropriate incentives to pharma to do these studies. What I mean by that is I think we should take a page out of the book that exists, we ought to look at what has been done in the pediatric world, and saying that we should give incentives to industry, and say if you do an appropriate postmarketing surveillance study, that you have the potential--and this will be something clearly the Agency cannot do alone, but will take Congress--the potential to have perhaps six months of additional patent protection if these long-term surveillance programs are put into place.

I think it is a shame that this country, that spends so much money on health care, can't spend money in determining safety of these drugs we use. The point about this is that if we have a drug that is used, these uncommon events, even with

the datasets that are as large as we see for NSAIDs, 10- 12,000 patients, we can't rule out an uncommon event that occurs 1 in 4,000 patients, let's say, we will take rule of 3.

If we are treating millions of patients with these drugs, which we will, very successful drugs, we have the potential for having thousands of people have an adverse event that may be life-threatening, that could not be detected in the NDA dataset.

So, I think we need to develop these surveillance programs, and I think the only way to do it is really to provide the incentives appropriately.

[Slide.

So, in summary, I would like to say I think we need to stimulate new approaches, and I am glad to see this conference is really focusing on that, different and appropriate methodologies, and I think we need more in the way of safety and outcomes data.

I really believe that the way to do that is really through an effective partnership among government, industry, academia, and the public, who are all demanding this.

Thank you very much.

DR. FIRESTEIN: Thank you.

The final presentation will be by Dr. Michael Hufford, Vice President, Scientific Affairs, The Science of Patient Experience.

While he is getting set up, I would just let the panel know that there is, in addition, a letter from Dr. Shainhouse that will be entered into the record, but will not be read today.

Letter from Z. Shainhouse, M.D.,
Dimethaid Health Care, Ltd.

"As Dimethaid Health Care, Inc. has an interest in topical NSAIDs for symptom relief of rheumatic diseases, we would appreciate the panel taking into consideration the application of any proposed trial models and designs to a topical NSAID.

"In trial design for topicals in OA symptom relief, one can use as a model the usual designs for oral NSAIDs. The efficacy variables of pain and physical function, which are used to assess the study joint, are readily studied with topicals. The role of the Patient Global Assessment is less clear.

"Questions on Patient Global Assessment

are often used to inquire about the non-signal joints which are treated simultaneously by oral NSAIDs that provide full, systematic distribution of a therapeutic concentration of drug.

"The site-specific nature of topical treatment is unlikely to deliver fully-therapeutic systemic drug levels to provide 'global' benefit to other, non-study joints. Even if one restricts enrollment through trial design, non-study joints may flare during the trial. A Patient Global Assessment for a topical cannot mean the same thing as for an oral.

"There are other aspects unique to the study of topicals. Approvability trials, for reasons of practicality and design standards, always study the hip or knee. Topicals are not appropriate for treatment of hips. There is very little literature for oral NSAIDs, let alone topicals, in the treatment of other joints. Do we have sufficient studies on the natural history and spontaneous remission of symptoms in other joints to determine the appropriate duration of study? For that matter, is the now-standard 3-month trial design for OA of the knee or hip based on any such evidence on the natural history of the disease?

"Clinical experience suggests that where disease is less than bone on bone, symptoms do, indeed, tend to resolve with time - which is perhaps the basis for the usual recommendations to stop oral NSAIDs when symptoms resolve. Is this not further proven by the failure of so many patients to 'flare' during the screening, washout-out stage for drug studies?

"The literature describes a significant placebo effect for topicals, thereby complicating study of the onset of pain relief.

"In Europe, topical NSAIDs are usually approved and prescribed for the treatment of soft tissue injuries. We are aware of no guidelines for trial design for such studies. Duration would of necessity be shorter because of the self-limited nature of the disorder.

"We will appreciate comments from the panel members on the applicability of any guidelines they may propose to the field of topical NSAIDs."

"Sincerely, Z. Shainhouse, M.D."

[End of letter]

DR. HUFFORD: You can see I have tried to rise to the challenge to do a very quick swapout.

[Slide.

Let me begin by saying the company that I work for, In Vivo Data, provides electronic diaries to sponsors in clinical trials, and as such, a number of compounds either are or will be under review by the Agency.

[Slide.

What I would like to speak to you about is something I have been working on myself for 10 years, and my colleagues, for an additional five, using diaries to help patients succeed in providing real-time, real-world data in clinical trials.

Of course, diaries are used widely in arthritis trials to capture patients' experiences in a variety of real world settings, and has been mentioned throughout the day today, as well as at the NIH-FDA Conference on Analgesic Drug Development a while back, the collection of pain data in particular, either using the VAS or Rick Graceley's modified VAS scale, is one common implementation, as well as collecting data on functional attributes, stiffness, physical functioning, and nighttime awakenings, and there is good psychometric reasons for this.

A number of studies have shown that diary

data can be more sensitive to medication effects than recall-based reports at the site. One key concern, though, about paper diaries, in addition to the generally poor data quality in terms of legibility, is really noncompliance, because when you use paper diaries, compliance with timely completion if left completely up to the patient to enter the time and date, and you go by that record.

Of course, that is very vulnerable to hoarding and falsification, as I am sure many people in this room, including myself when I was a professor, can testify, it is not uncommon to catch patients filling out a week's worth of diary cards immediately before a site visit. Indeed, this happens so often that John Urquhart [ph] has termed it "parking lots compliance."

Noncompliance importantly, not only violates the protocol, but it undoes the expected advantage of the diary method because the reason that you implement diaries is to avoid the systematic inaccuracy and bias inherent in recall. It is not pain patient's fault, but simply the way they encode and retrieve information.

So, one of the best known biases is patients in a great deal of pain will

systematically exaggerate their mean pain over the course of the week. Again, it is not fault, but you can't extract yourself from current pain to provide an accurate estimate or recall-based pain, so diaries are used as a way to avoid their recall biases.

[Slide.

I would like briefly to present a study that my colleagues and I recently published in the March 18th issue of the British Medical Journal. Dr. Arthur Stone, who is the Vice Chair of Psychiatry at SUNY-Stonybrook, what we did is we had two objectives. We wanted to quantify subjects' compliance with paper diaries in a way that was objective really for the first time, and to compare that paper diary compliance to an electronic diary benchmark, something that a number of us, including myself, have been working on in an academic context for over a decade.

The endpoints was reported compliance, what patients said they did in terms of telling us about their real-world pain, actual compliance, which we will get to in just a moment, as well as hoarding, that parking lot compliance that I mentioned.

This was a randomized, parallel, two-arm study with 80 heterogeneous chronic pain patients being assigned to one of two groups, either a paper diary or an electronic diary. What patients didn't realize--and this is actually a sample one--is the paper diary was covertly instrumented, such that photo cells, that we built into the binder, would detect the change in light and write the time and date stamp to an onboard wafer-thin computer chip that we had built into the binder.

This was unique insofar as for the first time, you could have an objective documentation. So, the patient said it's Monday at 10:00 a.m. and I am telling you about my pain, well, you could look at the objective electronic record and say, well, is it possible, was the diary even open on Monday for them to complete that report.

Again, half of the patients were then assigned to a compliance-enhanced electronic diary with a variety of features that helped them be more compliant with the protocol.

It was a three-week pain study with patients completing three reports of their pain, both in the morning, afternoon, and evening, and we asked them to do them at specific times of the day.

What we found is when you simply look at the paper diary cards, it looks like they were 90 percent compliant, that is, 90 percent of the time you had paper diary cards at the date and time that you asked the patient to give the report, so you would be thrilled.

Of course, we, for the first time, had an objective records team and could look at actual compliance.

[Slide.

To our surprise, we thought it would be bad, we didn't think it would be this bad, we had 11 percent compliance. So, 79 percent of the time, the patients were not completing the diary card as they told us that they were.

[Slide.

When we compared that to the patients randomly assigned to use the electronic diary, because one could argue that it was an artifact, chronic pain patients can't possibly be expected to fill out diaries, although we asked them to all the time, what we found is with the variety of compliance enhancing features, we were able to get very high rates of compliance documented over the course of the study, time and date stamp verified

as required by the protocol.

[Slide.

So, we looked at the completion of those paper diary cards in batches, trying to understand what happened to those other 79 percent of diary cards. It turns out 1 out of every 3 days, the diary was never even opened. On those days, reported compliance was 96 percent. So, it on the very days that patients forget to do anything with the diary that they are most likely to go back and back-fill a day's or at times even a week's worth of diary cards, so we found a great deal of back-filling really more disturbing to all of us, including myself. Having written the statistical analytic plan, I can tell you that we did not even originally take this into account.

We also found forward-filling, that is, there were instances where the patient, say, on a Wednesday evening, would open the diary for about 30 minutes. This was a very short pain assessment, only took about 2 minutes to complete. If you open it for 30 minutes and then closed, closed all day Thursday, closed all day Friday, they come in for a site visit on Saturday, and lo and behold, they had Thursday's and Friday's diary cards, so there was

clear evidence of forward-filling, as well.

[Slide.

To give you a sense of whether or not the high rates of compliance achieved in the electronic diary group were a fluke, this is a sample of my colleagues and I's peer-reviewed publications, not all of them, but stretching back nearly a decade now.

This was the paper compliance at 11 percent, the electronic diary compliance at a verified 94 percent compliance, and this is just a sample of some of the work we have done across therapeutic categories showing that patients can succeed in providing real-time, real-world data, but they do need help to do it.

[Slide.

So, in sum, diary data are critically important to a variety of trials including arthritis trials to avoid retrospective bias that Ike and Rademeyer and Com, and Bradburn, in his famous 1987 Science paper, have outlined so cogently.

Paper diaries, though, are vulnerable. In fact, we were able to show objectively both poor and faked compliance using paper diaries. On the

other hand, electronic diaries with science-based compliance principles can be used to provide documented high, real-time compliance rates. They can also enable more sophisticated diary designs. I don't have time to get into this, but there is an entire field of study called ecological momentary assessment who aim is to densely sample patients' waking experience including dynamic sampling to capture things like time of onset, time to relief in trials.

Then, lastly, of course, the validity and integrity in diary data is essential obviously to the evaluation of medication. So, reprints of the British Medical Journal study, I believe have been distributed.

Thank you very much for your time.

DR. KATZ: May I ask a question, Dr. Firestein?

DR. FIRESTEIN: Sure.

DR. KATZ: Let me just first congratulate you on a wonderful little study.

DR. HUFFORD: Thank you very much.

DR. KATZ: I think it is a good example of how methodological issues can be subjected to rational analysis and empirical investigation. We

so often talk about these important methodological issues, and it is so unusual that we see somebody that actually tries to test a hypothesis in practice.

It also matches perfectly with our experience including our published experience in comparing paper and electronic diaries.

My question is, were the pain ratings different?

DR. HUFFORD: That is one thing we are actually currently pursuing. That has actually taken a tremendous amount of time ironically, to clean and lock the paper diary data. So, that is something that we are working on currently, to look at the psychometric differences.

One of the challenges is with the forward-filling in particular, and how to deal with that, but that is something that we are following up on right now.

DR. KATZ: Right. We are still cleaning a database that was locked in 1996 from an electronic diary study, it's no small task.

DR. FIRESTEIN: Thank you very much for a very provocative discussion.

At this point, we are going to take

another break. At five minutes to 3:00, we are going to start.

[Break.]

DR. FIRESTEIN: We are going to begin this session with an introduction from Jim Witter.

Introduction

James Witter, M.D., Ph.D.

DR. WITTER: Good afternoon.

[Slide.

What we thought this afternoon, what we will try and do, and it's going to be an imperfect division, was to make sure that we don't lose the focus on safety, but there is going to be a little bit of a schizophrenia in the sense that we will be talking about some efficacy also this afternoon, and then we will open it up for more general discussion.

[Slide.

If we were to, for example, take, as I have done here, a line, and on one side of it, write "pain," and the other side "pleasure, we could probably spend these two days just talking about the meanings behind that.

What we are interested in really are these concepts of safety, tolerance, and tolerability,

and as you look, for example, at NSAIDs and opioids as general medicines, they would fall somewhere on this particular line.

[Slide.

The real question then would be what is the perfect drug and it should be totally safe, but how safe is safe and who should be deciding that, and it should be totally effective, and as we all know, there is no such drug, be it analgesic or otherwise.

[Slide.

What we thought we should do is take some time to discuss safety and really what we do as an assessment of drug safety, during the development, during the IND phases, before NDA approval--and realize we don't want to confuse on some of these acronyms, but I think we want to use these, so that everybody gets familiar with them if you are not--and then what happens at approval and then after that. We don't want to lose focus on any of these.

So, before the NDA is approved, we have preclinical, or I guess we should be referring to this now as non-clinical studies to help guide us, to get some idea of what the profile of the

compound looks like.

Then, we have, as well, various phases, Phases I through III, which enroll larger and larger numbers of patients, and by the time these are completed, if everything has gone well, this information is submitted to us, we look it over, we review it and make an assessment as to whether it's efficacious, really trying to judge effectiveness, and then whether it is also safe enough.

If that is approved, then, we have a compound that has a label, and yet that is not the end of the drug's life cycle. There are things that happen post-approval and as Dr. Schnitzer noted before--and maybe we had talked about this beforehand, but we didn't--there really is an incomplete safety assessment when a compound is released, no matter how hard we try, it is just not possible.

[Slide.

So, we need to be looking at adverse events. As I described, we look at adverse events both before and after approval, and these are from the patients and they are also from the investigators.

Now, there has been a discussion, and

maybe we should have that continue today, that the patient global is also something that should really be intended to catch that something is not quite right experience with an analgesic. Maybe that is what this is best geared for in these particular trials.

[Slide.

But I think it is safe to say that drug safety is really synonymous with drug information. The more information we have, the better.

[Slide.

Now, once something is approved, there are various tools--and this important because again we don't catch everything pre-approval--we have this AERS database, adverse events reporting system, which is a passive surveillance system, which has various problems in and of itself, Weber effects, when something is on people's minds, they report it, when it is not, they forget it, but we have other mechanisms, as well.

We have abilities to look for drug utilization in certain databases. We can look at external databases for other issues, whatever may be of interest to us. We can look at background incident rates of various adverse events, for

example, and then we can actually also undergo active surveillance real-time and prospective types of programs, and they have all been employed to some extent.

[Slide.

So, what these are termed really is risk management tools, and some these then, postmarketing, there are some routine things that we do. For example, we can change the product labeling, we can add adverse events, we can add contraindications, precautions and warnings, and, in fact, the dreaded black box warning.

We can make recommendations on monitoring, in fact, we can make this directive - you shouldn't give this until that, for example, follow a lab result, and we can also change indications to make them second line.

[Slide.

Other things that we can do, which are less commonly done, are to provide patients with information, medication guides as an example here. We can provide clinicians with Dear Doctor letters. We can make public announcements through other forums, such as today.

[Slide.

We can also have patient registries either on a voluntary or a mandatory basis, and there was some discussion about that earlier, too. Then, we can also, and I think this is the thing that everybody tries to avoid, is the product can be withdrawn.

[Slide.

What are some of the lessons we have learned postmarketing? With regards to labeling changes, there is a feeling that in many ways, these are largely ineffective for widely used drugs because they send out just too complex messages, and that there have, in fact, been failures due to persistent adverse events or studies--some of those active surveillance that I had mentioned before--studies showing that contraindications have been ignored, have led to market withdrawal. Tomorrow, we will be hearing discussion about Durak as an example.

[Slide.

Patient registries are useful for estimating the denominator, so to speak, in long-term safety. They don't manage risk per se, but certainly overseas I think it is safe to say that they are heavily utilized for gathering safety

information.

So, without further delay, I would like to introduce then Dr. Katz, who will be discussing some of the issues of safety and tolerance with opioids, and then Dr. Lu later will follow with some discussion on some efficacy issues.

Tolerance and Toxicity

Nathaniel P. Katz, M.D.

DR. KATZ: Good afternoon. Let me begin by thanking the Division, Dr. Simon, Dr. Firestein, Dr. Witter, and everybody else for giving me the chance to come and share some thoughts with you about side effects of opioids, also to Drs. McCormack and Rappaport from the other division who have given me an opportunity to gain some experience in the regulatory world on that side.

I will be talking about side effects of opioids and what I think are the potential down sides of opioid therapy that are of concern to patients and to physicians, and that need to be understood in order to inform our risk-benefit assessment.

I will also be trying to address what we know to date about those potential side effects from the clinical trials that are available.

[Slide.

Let me just begin by saying that when you give a talk just on the down sides of a medication or a class of medications, it may come across as being very unbalanced and that you don't get a chance to emphasize the up side, so let me just get my balance statement out of the way upfront.

It has been universally acknowledged now I think, at least in Western medical professional societies, that opioids have an essential, an unreplaceable role at this point in time in the treatment of both acute and chronic pain, and that, in general, they are safe medications.

Now, having said that, let me try to expand a bit on the potential down sides of that class of medications.

[Slide.

Here is what people want to know about - do people get addicted, tolerance, well, I guess that is not really a toxicity, is it, but it is a phenomenon that may result in loss of efficacy over time, potentially side effects, and so it is important to talk about.

People are concerned about neuropsychological effects of these medications,

can people drive, do they lose their ability to function, has their psychomotor reaction time changed, all those sorts of things, can they write their will, can they engage in business, et cetera.

Then, there is the plain old garden variety symptoms - nausea, vomiting, constipation, dizziness, sweating, itching, et cetera, et cetera. There are a bunch more. You can pick up any package insert and see what they are.

These are the things that are of concern to people, maybe others, and let's see what we know about them in terms of opioid therapy, and I will be focusing mainly on chronic pain.

[Slide.

Just first to get a couple of definitions out of the way. I am sure that folks in this room know these things, but just to make sure that we are using the same language because language has been a terrible problem in the study of these phenomena.

Addiction, which is also known as dependence, psychological dependence, abuse, all related terms, it implies that patients on opioids lose their control over their use of the drug. This is the loss of control model, sort of the

modern model of what addiction is, compulsive drug use, continued used despite harm.

These are things that it is sort of like art or pornography. Everyone knows what it is when they see it, but when you actually try to define it, it is very difficult to come to any consensus. But what we are talking about here is loss of control over the medication.

Physical dependence just means that when you stop the drug, you have a withdrawal syndrome, or you suddenly reduce your dose, or you get an antagonist or something like that, and this is something that is expected of people on opioid therapy.

It is not an adverse effect per se, it is not connected with addiction in any particular way, and it is just when the terminology was changed from addiction to dependence, it created this confusion between addiction and physical dependence.

So, get that out of your mind right now, I will not talk any further today about physical dependence because it is not, as far as I can see, a toxicity we need to worry about if we counsel our patients appropriately.

Tolerance means less bang for your buck over time in a word, less effective medication after prolonged use, or if you want to look at it the other way, you need to increase your dose in order to maintain the same effect. So, these are the phenomenon that I am going to be talking about.

What I would like to add just parenthetically in a moment is that there may be other negative behavioral syndromes of opioid therapy that we don't have good words for, that the syndromologists have not really defined yet.

For example, there is something that we all have seen that Steve Passaic is calling "the chemical coper syndrome," where we have all I think seen these patients, where you have a patient on high-dose opioid therapy, they are telling you that they need it and that it is helping them. Their pain score is still a 9 out of 10.

If you ask them, well, you know, how is it helping you if it is a 9 out of 10, and they will say it would be a 20 out of 10 without my pain medication. They can't get off of it, they may have subtle side effects.

They would give you a positive global satisfaction rating, by the way, to you fans of

global satisfaction ratings, although their pain relief is not there. These are the patients who may do well after opioid detoxification. Their pain scores may be no different, if not better, and they may feel more alert, et cetera. There is a literature on this.

Again, this is not a syndrome that has been well defined, but it is something that we all see, and we can keep it in the back of our minds. I won't talk about it any further.

[Slide.

So, what do we know about these things? First of all, there is nothing new under the sun. In my worst moments sometimes I think I am the first person to think about these things.

Diagoras of Melos, Third Century B.C., a Greek physician, "It is better to suffer pain than to become dependent upon opium." Again, they are talking about the use of opiates for chronic nonmalignant pain. This is what was being discussed in the medical literature of the third century B.C. 2,400 years ago.

Again, Erasistratus, if you ever want to look him up, his name is spelled a number of different ways, a Greek physician who actually was

one of the heads of the Alexandrian School of Medicine in ancient Egypt. Mainly, he got his name through anatomical studies, but he also said opium should be completely avoided, period, and he was referring there to the risk of dependence.

At the same time, there were other physicians who were promoting the use of opioids as a cure-all for all sorts of illnesses, again, just showing you this does not give a balanced historical approach, but it does suggest that people have been concerned about these things for a long time.

Of course, in the modern era, with the advent of the randomized, controlled trial that has been available to us for more than 50 years now, doubtless we have high quality evidence concerning the incidence of these side effects, and you will soon see the quality of the evidence that we have.

[Slide.

Now, we do know that opioids are abused, that is no secret to anybody. This is DAWN data and shows the prescription analgesics. This is ER Mentions [ph], for what that is worth, it is gives you some sort of a signal, and it is really of the same order of magnitude as cocaine, a bit less than

alcohol, far greater than marijuana, et cetera.

So, are these patients abusing them, are they addicts who are non-patients? Again, we don't know. We suspect that they are mostly non-patients, but again you will see the quality of the information that we have, clearly, it is an issue.

[Slide.

In the 70's and 80's, during the era, as was pointed out earlier by Dr. Sunshine, where treating pain with opioids was basically a no-no, a few radical and provocative studies were published.

There was one by Medina and Diamond that looked at drug dependency and people treated primarily with intermittent opioids for chronic headaches, pointing out that of their 2,000 some-odd patients, few, if any, became addicted.

Porter and Jick, this is probably the most famous study which has been quoted millions of times, addiction rare in patients treated with narcotics. This study, published in 1980, again, 11,000 some-odd patients treated for acute pain in Boston area hospitals over a period of time, and only something like 4 out of this 11,000 were later on felt to have become addicted to their opioids.

Then, Perry and Heidrich, another one, similar study, management of pain during burn debridement, use of opioids in many thousands of patients, only rarely was addiction noted.

These studies created a new vocabulary for the discussion of addiction with opioid therapy. Now, for the first time in a long time, or at least we thought, we could actually discuss the possibility that maybe opioids are okay for the treatment of pain.

Then, at the same time, you had the cancer pain literature that was coming out demonstrating the safety and efficacy of opioids in treating cancer pain. There were a number of retrospective survey studies in non-cancer pain, suggesting that addiction was rare.

From this, there created a climate, at least among pain specialists, that you wouldn't get your patients addicted if you gave them opioids for pain, although none of these studies actually addressed the issue at hand.

These three studies, the most famous one, the Porter and Jick one, is actually a one-paragraph Letter to the Editor in the New England Journal of Medicine. None of these studies

actually defined addiction in any way. None of them actually implemented any particular plan for how they were going to detect addiction.

They were all retrospective based on the judgment of the physician, and none of them were related to the use of opioids for the treatment of chronic pain. So, again, whether or not opioids are addictive in the management of chronic pain, maybe they aren't, maybe they are, maybe there is a number, but we certainly don't know anything about it from these particular studies.

[Slide.

It is fair to summarize this at this point and say that no published study of opioids for chronic pain has prospectively evaluated the incidence of addiction by any definition. That is the state of the literature at this point in time.

[Slide.

There are some methodological issues buried in how one would assess this if one wanted to anyway. There are lot of very thorny methodological issues. The first issue is which population.

The studies that I showed you earlier, in general, dealt with a patient population with no

history of addiction, no psychiatric comorbidity as are most of the randomized, controlled trials that are done today.

So, we became interested in what happened if you gave opioid therapy long term for patients with a history of substance abuse, which is probably not an insignificant proportion of the patients that we see in pain management centers. If fact, those prevalence numbers vary between around 3 and 20 percent.

This is a retrospective study of all of our patients that we could find who had a history of substance abuse documented in their chart. There were only 20 patients. The bottom line is about half of them did fine and half of them self-destructed. We tried to outline some risk factors for who would be in the good outcome group and who would be in the bad outcome group.

The only point I am trying to make here is not that there is a great study either, but that the choice of population determines the results that you see.

[Slide.

Another very thorny issue is what instrument would you use to measure the rate of

addiction in patients on opioids for chronic pain. I think the most widely subscribed-to assessment tool for opioid addiction, in the first place, is the DSM-IV or various measurements, the DIS, et cetera, that are based on the DSM-IV, and these are the criteria. You need to have 3 of the following 9 symptoms. This is all based on self-report and a doctor-patient interaction, and the self-report is an issue that we will talk about momentarily.

But the bottom line is that this doesn't really make sense in people on opioids for chronic pain, and without spending a lot of time going through the details, diminished effect with same dose, does that mean you are addicted? I don't think so.

Dose escalation or prolonged use is a sign of addiction. Does that mean you are addicted? In our population, I don't think so. Desire to cut down, excessive time spend obtaining, using, or recovering from use of the substance, well, you can ask most of your patients on chronic pain whether they ever had to spend excessive time obtaining their medication, they have, et cetera, et cetera.

So, this it the most well-established criteria, and they are really not relevant to the

patients that we are looking at, and there actually is no instrument right now that has been validated for detecting addiction in this population although I am happy to say that there is some work being done on that.

[Slide.

The measures that have been used in the addiction world are based primarily on self-report. Certainly, all the prevalence information that I gave you based on these few quasi-studies are all based on either self-report or impressions of the physician, again based on patients behaviors and patient reporting.

What do we know about self-report measures in patients on opioids for chronic pain? There have been four studies, to my knowledge, that look at that. One is the study by Brian Ready, which showed that patients with chronic pain don't report accurately their use of the medications that have been prescribed to them. This was based on inpatient charting by nurses of what the patients were actually given.

Another study by David Fishbain comparing self-reported drug use to urine toxicology screens and other measures showing that validity is not

reliable.

We did a study comparing behavioral monitoring of patients to urine toxicology again. I will show you that in a second. There was another study that basically did what we did in a way and confirmed our findings.

Again, in our study, I won't spend a lot of time on this, but just very, very briefly. In 122 patients from two centers, we instituted urine toxicology monitoring on all patients over a three-year period of time that were on opioids.

The bottom line is that 29 percent of our patients had a positive urine toxicology screen. These are patients who had an opioid contract in effect. It said we are not supposed to be doing other things. Twenty-nine percent had a positive urine toxicology screen meaning either illicit substances, cocaine, marihuana, et cetera, or things in their urine that they were not supposed to have.

We have them on methadone, they have got hydromorphone. We have them on codeine, they have fentenyl, et cetera. About one-third positive, and if you looked at the monitoring behavioral issues suggestive of inappropriate medication use, about

22 percent of our patients had inappropriate behaviors of one kind or another, 43 percent either had a positive urine toxicology screen or a suggested behavior.

The interesting thing to me is that there is this dogma prevalent in the pain management community that an astute physician, if you monitor your patients carefully and you are attuned to their behaviors, you know what is going on with your patients, you don't need anything fancy, and you can unmask the diverters and drug sellers and criminals and drug addicts simply by your own astute presence and by monitoring self-report.

This data suggests that if you only monitored patient behaviors, you miss about half the patients who have a positive urine toxicology screen. I think it is this sort of data, which is also confirmed by this other study I won't tell you about in detail, that confirms, I think in my mind anyway, that self-report measures alone, if you are trying to monitor for noncompliance anyway, are inadequate.

I should issue a very quick caveat just so that I don't give the wrong impression. We were not measuring addiction in this study. I don't

have any idea of the extent to which these signs correlate with addiction. As far as I know, none of these patients were addicted, but certainly if somebody on opioids has cocaine in their urine or they have opioids that they are getting from another source, that is something that I think I want to know about.

[Slide.

Another potential source of external information outside of patient self-report that has not really been talked about as a patient monitoring tool on a formal basis, is the whole idea of using prescription monitoring program data.

Many of you know that right now I think it is 19 states in the United States have prescription monitoring programs that track some or all of the scheduled medications that these patients are on. In Massachusetts, we have a prescription monitoring program that tracks only Schedule II data, and not any other scheduled medications.

So, the idea of using this as a way of getting verification of patient self-report of compliance has really not been pursued, and there is a lot of interesting data buried in these prescription monitoring programs that could be

used.

For example, we found--we are just starting to validate this database--in Massachusetts, in the year 2000, there were over a million Schedule II opioid prescriptions that were given. There is only 6 million people in the State of Massachusetts, which is interesting, and it looks like there were about half a million unique individuals in Massachusetts that got a prescription for opioids.

Now, this database happens to exclude the VA, which is probably not a small issue, and there are a few other exclusions, as well. So, about 9 or 10 percent of the Massachusetts population got Schedule II opioids. If you include the other schedules, that probably would double, triple, or quadruple this number.

Before I started looking at this, there is really no notion of the epidemiology of opioid therapy, and we do have information on this database on what proportion of people have five or more prescribers, what proportion of people use five or more pharmacies, what proportion of people run out of their day's supply early every month.

We can get this data, and we are hoping to

actually report these numbers as our work goes on. I think one could consider even using this in a clinical trial or postmarketing or risk management program to look at noncompliance.

I am going to leave the issue of addiction there with the unfortunate conclusion that we don't know a lot about the incidence of addiction in patients given opioids for chronic pain.

[Slide.

Tolerance is another issue and also it seems so easy when you first look at it, and then it gets very complicated when you try to figure out exactly what you mean by tolerance and how you are going to measure it.

This is just a concept slide to give you a sense for how one might think about tolerance and begin to approach the idea of how to measure it. Look at these green lines here for a minute. These are little graphs looking at--and this is all invented out of my mind, this is not clinical trial data, this is all conceptual--this is the dose required to produce analgesia over time.

In an ideal world, a medication that did not produce tolerance would have a flat line. Here is a different way it might go. You might have a

bit of a dose escalation at the beginning and then you might be stable over time, in fact, there is a school of thought that suggests that this is what happens to most people on chronic opioid therapy, or it might escalate over time, or it might escalate faster over time.

So, this is fine. Looking at dose escalation is a perfectly good place to start I think if you allowed patients to free titrate to the dose that gives them adequate analgesia.

The complexities start to emerge, though, and one of the complexities is side effects. Because the usefulness of the drug, or if you want to call it the therapeutic index of the drug, really depends upon having a dosage range for an individual patient where they can get adequate analgesia without intolerable side effects, that is what we are talking about.

If that difference between the dose they need for analgesia and side effects remains in a useful range, that is more useful sign of a medication that is not associated with problematic tolerance. Of course, if both of them escalate equally, then, that is fine, too.

Tolerance might even be a good thing. For

example, we know from clinical experience that people often become tolerant to nausea and dizziness and neuropsychological side effects, and other bad things, so you may find that, in fact, tolerance can work in your favor. Your therapeutic index may broaden over time.

On the other hand, it is conceivable that your does that you need for analgesia increases, but you don't become as tolerant to the side effects, in which case you crash and burn on your drug. They maybe is someone who drops out of your clinical trial.

Unless these things are assessed, unless you are assessing adequacy of pain relief, unless you are assessing overall tolerability of your drug, which is never done to my knowledge, and you are modeling how those go over time, then, you can't really say anything about tolerance or you can't make a sophisticated statement about tolerance, to my view.

[Slide.

So, what do we know from clinical trials? This, sorry to say, I know nobody can read this, but it is just there to give you a visual impression, anyway, these are all the randomized,

controlled trials that have been published using non-opioid comparators, placebo or a non-opioid, for chronic, non-cancer pain where we are watching the patients for at least one month. I think that is a reasonable benchmark if you are having a discussion about tolerance.

These are all the ones in the published literature. For those of you with good eyes, if I have forgotten one or two, then, you can come up and yell at me after we talk, but this will give you a good visual.

I put the asterisks next to the trials where you can learn something about tolerance from the trial, usually because there is a prolonged, so-called open label extension period where patients are watched open label on their drug for some period of time.

I will just briefly highlight what it is that we know. Again, here is one trial where pain relief was stable at 19 weeks, don't have dose information, and again, in all these trials, a blurb doesn't really do justice, and you can learn a lot more from getting to the trials themselves. There are people in the room who have been involved with these trials who could probably educate us

further about them, but just to give a visual.

Here, this is the trial that we did. We found that actually in our patients, only 36 dose and pain relief were stable after an initial period of escalation. This is the Watson and Babul, Najib Babul addressed this earlier today, their very nice study of oxycontin for postherpetic neuralgia.

Again, in their open label extension, there was a small subgroup of patients--Najib, you will have to remind me--I think it was about 11 or so out of the 50 patients were still there at the end of follow-up, still enjoying analgesia, and you can go on down the line.

The bottom line is that as you follow patients out, here is an example, about 18 months, only 15 of 106 patients still in the trial, still getting good analgesia, still at a stable dose.

I think what these sorts of studies tell us is that although none of these studies have actually, to my knowledge, said we define tolerance in this way, this is how we are going to measure it, this is our result. That has never been done, to my knowledge. Somebody can challenge me if they think I am wrong about that, but all we can get is an indistinct window about what happens long term.

It looks like only a minority of patients are still on drug over time. Now, should we expect that everyone should be on drug a year later? Obviously not. If you look at trials of NSAIDs for osteoarthritis, you are also not going to have everybody on trial at the end of a year because that's not how it works.

People get better people get worse and drop out, people move to Florida, people die of a heart attack, all sorts of things happen to people, but it still suggested to me that--it doesn't really reassure me that tolerance is not a problem in clinical practice--and it suggests to me that we need a methodology for evaluating this prospectively with some rigor.

Interestingly, this study, which I put in italics, is a study of tramadol. I excluded tramadol except for this one study for patients with painful diabetic neuropathy, 117 patients. Tramadol is a drug that is an opioid and a non-opioid in the same drug, and clinically speaking, we don't think tramadol is associated with tolerance or at least not much.

Interestingly, only 4 out of 117 patients at six months dropped out due to lack of efficacy,

which is interesting because that is dramatically different than what we see in the trials of the pure new agonist, and it makes me wonder whether the fact that only a small number of patients are in these new agonist trials is indeed indicative of tolerance developing because we didn't see that to the same extent in the tramadol study.

[Slide.

Now, this is all speculation, nuance. I think really the only robust conclusion is that we need to start measuring tolerance. Again, just to give you a quick visual of that, what we often see in the way these studies are reported--and again this is whitewash data of not any particular drug, is that as the months wear on, the patients' dose or their pain score, if you want to look at pain scores, remains stable, but the trick is that only a small fraction of the patients are present here that started here, and we no doubt have informative censoring, and can't say too much about long-term efficacy from this type of report.

[Slide.

In my view, it is fair to say that the phenomenon of tolerance to opioids in the treatment of chronic pain has not been systematically

investigated in the published medical literature.

[Slide.

Neuropsychological function, I outlined the concerns earlier. I am not going to really speak about that because again, there is actually no published prospective controlled trial on opioids for non-cancer pain that has evaluated neuropsychological function.

There is a published uncontrolled trial where patients on a hodgepodge of opioids were put on controlled release opioids. That is Jennifer Hathorne Waites [ph] trial that actually suggested in that setting, neuropsychological function improved.

There is a study that, Mitchell, you alluded to earlier that you did with Raja and those folks that is still unpublished, that I have heard rumors about, that I have heard rumors is going to reassure us all about neuropsychological function measured in a prospective way.

I, myself, have been involved in yet another unpublished trial that I hope will come to light soon, that also will find reassuring, so I think that this is going to probably work out okay, but at this point in time, this remains the fact of

the matter.

[Slide.

One final note on another sort of occult toxicity that has been getting a little more press lately, but hasn't really been addressed formally, is the whole issue of opioids in endocrine function. I think this is actually a very big deal.

It is known that in animals, every animal endocrinologist knows this. When I go up an animal endocrinologist and I say, you know, I am a little concerned about opioids and testosterone, they say, da, what are you talking about, we have known about that for 100 years already, about opioids and testosterone.

It is known that opioids lower testosterone and actually have other endocrine effects, as well, in animals. There is one study on heroin addicts showing low testosterone levels, one study on methadone maintenance patients showing low testosterone levels, and two studies now of patients on intrathecal opioids showing profoundly lower testosterone levels in men who develop a central or hypogonadotrophic hypogonadism on intrathecal opioids.

In the intrathecal studies, those were the only ones that tried to address symptoms, and it does turn out that loss of libido and impotence are associated with low testosterone seen in those trials.

In one of the two trials, it was actually a pre-post study where they measured endocrine function before going on intrathecal opioids and then after, showing the declines, so very interesting information. We have known about that anecdotally for a while. In women, we see amenorrhea and infertility, and other things.

What are the symptoms of low testosterone? Fatigue, loss of muscle mass, you don't want to get up and go, mood disturbances, osteoporosis and compression fractures, so a potential public health hooked to this.

So, has anyone seeing patients with chronic pain ever seen any of these symptoms in anybody? I think that these symptoms are basically universal. So, you would think that somebody would have asked the question of what proportion of patients on opioid therapy for chronic pain have low testosterone levels. You would think that that question would have been asked.

[Slide.

This is preliminary data from our group, our data, trying to address this question. Again, I am always a little bit nervous about presenting unpublished and non-peer-reviewed data, but I think this is big enough to at least flag your interest in this area.

All of my patients on opioid therapy for nonmalignant pain had to undergo an endocrine battery of blood tests at least once a year, and this has been going on for about four years now. There were complete enough data available on 25 males. I haven't tried to understand the female data because it is just too confusing.

We found that free testosterone, which I think is the more sensitive of the two, was below the reference range in 63 percent of our patients age 25 to 49. This is how the normal testosterone levels come packaged at least at our institution, 25 to 49, and 50 to 75.

Free testosterone levels were below the reference range in 88 percent of patients age 50 to 75, the older group, and our mean LH and FSH levels, compared to normal controls, were below normal, suggesting that the majority of our

patients had central hypogonadism, were on opioids for chronic pain.

We looked at mean levels compared to healthy controls, et cetera, and also found that they were low.

Again, I think this is very provocative and needs to be followed up further by a properly controlled trial, and suggests to me anyway that endocrine dysfunction may actually be the major organ toxicity of opioid therapy.

[Slide.

Let's not forget about the little symptoms, the garden variety symptoms I spoke about earlier - nausea, vomiting, blah-blah-blah. In clinical trials, we all know how these side effects are captured. They are captured by the passive capture methods. The patient has to raise their hand and speak up and say I am dizzy or I am nauseous.

Then, the study coordinator has to write it down. Then, it has to be coded by somebody and put in the database. We know from a variety of sources of information that passive side effects captured like that are inadequate in the sense they don't nearly tell you what you would find if you

asked patients how they are feeling.

We know that dropouts due to symptomatic side effects are substantial in both acute and chronic pain trials of opioids, and the chronic pain trials that I see, that range from 10 to even 50 percent, so it has got to be that these inform the risk-benefit analysis of opioids for chronic pain.

We also know that if you look at--I am not going to take the time to present data--but if you do symptom distress assessments prospectively by giving patients a checklist on how they are according to a variety of symptoms, and how severe they are, you can find out a lot more, and you can actually get data that predicts dropouts more accurately than just passive side effects captured, and there are some very nice studies by Richard Anderson and Marsha Testa and other people showing that these are very sensitive measures of how patients are doing.

You would think that somebody would have asked the question about how patients with opioids do if you give them a prospective symptom checklist to inventory. We did that in at least a preliminary way in our study that came out in 1998

of patients and back pain.

We gave them a checklist like this, it had 20 items. It had them rate none, mild, moderate to severe, and got a lot of interesting information, which I won't take the time to give you, but one of the interesting things was that we were able to discriminate side effects intensity scores between a high dose and a low dose opioid regimen and also from a nonsteroidal anti-inflammatory drug regimen.

So, this checklist analysis did discriminate between regimens. We also found interestingly--I don't really know how to understand this--people on low-dose opioids had fewer side effects, but were more bothered by them, people on high-dose opioids were less bothered by their side effects, strangely.

So, it seemed like maybe opioids influences how much you are bothered by whatever it is that ails you. Maybe you understand that better than I do. Anyway, do this, that is what I am trying to say.

[Slide.

I will end with just a quick comment on the use of opioid sparing as an outcome measure since that was mentioned as a question in the

background materials, so everybody knows what this means. You have a drug X compared to placebo or some comparator, and you look at how much opioid the patients in both groups use in outcome measure,what does that mean, is that good, is that bad.

First of all, just conceptually, if a patient in one treatment group has decreased opioid requirements, there is a few things that could be due to. The first, which is the one that we are all interested in, is that your study drug is an analgesic. That is good, and the obvious examples there are NSAIDs compared to placebo in postoperative pain, where patient controlled analgesia or other things are very nice discriminative analgesic effect.

The other possibility is that your drug is not an analgesic by itself, but together with opioids, enhances opioid analgesia, and some people think that are some NMDA receptor antagonists that might do that. It is hard to discriminate between an analgesic and an opioid enhancer in that sort of model.

The other possibility I will just mention, although you maybe you won't like hearing it, is that the study drug, all it does is enhance opioid

side effects, so that patients can't use as much, and that certainly is a conceptual possibility although one should be able to tease that out by looking at pain scores and by looking at side effects, if you look at side effects in an appropriate way, which is often not done.

So, you have to be able to provide supportive data to classify what is going on in terms of these possibilities, should you have opioid sparing.

[Slide.

Lastly, is opioid sparing meaningful in your clinical trial. I am remind of the expression, "A difference is only a difference if it makes a difference," and so if you do reduce your opioid dose, does that mean anything.

Well, I think it does mean something if the scientific question is whether the drug has analgesic activity in the model that you chose, so for a proof of concept trial, for example, if you are just trying to show does your drug have analgesic effects or not, given the caveats I mentioned earlier, you know, I think that answers your question, but if you are trying to show does the treatment help the patient, which I think

ultimately is what we need to have an evidentiary body of information about, the answer is no, by itself, if you are on 10 milligrams of morphine or 20 milligrams of morphine, that doesn't mean you are better or not better.

You need to show I think, in my opinion, if you are interested in whether the patient is benefiting, some benefit, which could be decreased pain, it could be decreased side effects, which again you are not going to get unless you address in an aggressive way.

By decreased pain, we have to be a little bit careful there. The example that comes to mind for me is that we know that in the postoperative setting, opioids work pretty well for rest pain, but not as well for movement-associated pain, whereas, NSAIDs tend to work well for movement-associated pain, maybe even better than opioids in some circumstances.

In the postoperative world, movement-associated pain is where the rubber meets the road, because patients get up and rehab themselves and ship themselves out of the hospital these days.

So, one could conceive of showing benefit

of NSAIDs by focusing specifically on movement-associated pain compared to an opioid-only regimen as opposed to just global pain. As people were saying earlier, just looking at global pain, you may miss the boat on something important.

So, I think that opioid sparing, by itself, needs to be looked at very carefully, and you have to really address the scientific question of the study by looking at clinical benefit.

[Slide.

In conclusion, opioid toxicity, just to recapitulate, opioids are generally safe medications. We don't have 17,000 patients a year dying of GI bleeding in the United States from opioids.

So, looking at the big picture, opioids are generally safe medications. I think it is fair to say that the treatment response does appear to be durable in a subgroup. How large is that subgroup, I don't know, and again, tolerance has really not been systematically looked at in any published studies.

In my view, symptom distress scales or toxicity scales, especially trying to look at why people drop out, so that you don't have informative

censoring going on, must be used to assess the overall treatment effect.

Addiction, the major concern in chronic treatment I think has not been investigated, in my view, using any legitimate methods, and endocrinopathies may, in fact, wind up if this preliminary data pans out to be actually the major organ toxicity of opioids as we go forward.

Thank you for your attention.

DR. FIRESTEIN: Thank you very much, and we will have an opportunity to discuss some of this in a few minutes during our open discussion after the next talk, which is Statistical Issues for Measurements by Dr. Lu.

Statistical Issues for Measurements

Laura Lu, Ph.D.

DR. LU: Good afternoon. I am going to discuss issues in time-specific measurements and time-weighted average for pain in chronic and acute analgesia trials.

This discussion is to set a stage for tomorrow's further discussion of endpoints.

[Slide.

First, I am going to introduce time-specific measurements and time-weighted

average. Then, I will discuss issues in chronic analgesia trials for those measurements in terms of interpretation of drug benefit and data imputation methods, and the parallel issues in acute analgesia trials. At the end, I will provide summary.

[Slide.

I will use an individual patient's pain curve to illustrate those measurements I will talk about. Suppose a patient's pain was evaluated at time 2, 4, 8, and 12, and these vertical segments represent change from baseline in pain scores at each specific time 2, 4, 8, and 12. So, these are what I call time-specific measurements.

I will refer to the area under this pain curve as AUC later.

[Slide.

I denote those time-specific measurements for change from baseline in pain as d1, d2, d3, and d4, and the time intervals between each neighborhood measurements as t1, t2, t3, and t4.

[Slide.

The time-weighted average can be defined as AUC divided by the patient's treatment period. In another form, it can be also described as a weighted average of time-specific measurements, and

the weights are decided by the neighborhood intervals of disorder and the treatment period. That is why we call this normalized AUC measurements as time-weighted average, and one-time weighted average is used as an endpoint we quite often refer to it as AUC approach.

[Slide.

Now, the issues in chronic analgesia trials. First, the interpretation of drug benefit by those measurements.

[Slide.

End-of-the-trial measurement is a time-specific measurement. It is commonly used in chronic analgesia trials. It measures drug effect at the end of the trial. Time-weighted average is another endpoint being used. It measures average effect through the trial.

The two measurements actually describe different aspects of drug effect, and no matter which measurement is used at the endpoint, the consistency of drug benefit over time is always an important review issue.

[Slide.

As shown in this graph, when two treatments switch advantage over time, then, there