FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

ARTHRITIS ADVISORY COMMITTEE

8:05 a.m

Monday, June 23, 2003

Versailles Ballroom
Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

ATTENDEES

COMMITTEE MEMBERS:

GARY S. FIRESTEIN, M.D., Chair
Chief, Division of Rheumatology,
Allergy and Immunology
Department of Medicine
University of California at San Diego
9500 Gilman Drive
Basic Science Building, Room 5098
La Jolla, California 92093

JOHANNA M. CLIFFORD, M.S., R.N., B.S.N.
Advisors and Consultants Staff (HFD-21)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Building 5630, Room 1093
Rockville, Maryland 20857

JENNIFER J. ANDERSON, PH.D.
Research Professor of Public Health
Department of Epidemiology and Biostatistics
Boston University School of Medicine
A-203
715 Albany Street
Boston, Massachusetts 02118

JOHN J. CUSH, M.D.
Chief of Rheumatology and Clinical Immunology
Presbyterian Hospital
8200 Walnut Hill Lane
Dallas, Texas 75231-4496

WENDY McBRAIR, R.N., M.S., C.H.E.S.
Consumer Representative
Director
Southern New Jersey Regional Arthritis Center
Virtua Health
1 Carnie Boulevard
Voorhees, New Jersey 08043

HOWARD J. WILLIAMS, JR., M.D.
Department of Internal Medicine
Division of Rheumatology
University of Utah School of Medicine
50 North Medical Drive
Salt Lake City, Utah 84132

ATTENDEES (Continued)

CONSULTANTS: (Voting)

STEVEN ABRAMSON, M.D.
Chairman of Rheumatology and Immunology
Hospital for Joint Diseases
301 East 17th Street
New York, New York 10003

LAURENCE BRADLEY, PH.D.
Professor of Medicine
University of Alabama at Birmingham
467 Boshell Diabetes Building
Birmingham, Alabama 35294

ALLAN GIBOFSKY, M.D., J.D.
Hospital for Special Surgery
Weill Medical College
Cornell University
425 East 79th Street
New York, New York 10021

MICHAEL FINLEY, D.O.
Western University
College of Osteopathic Medicine
309 East Second Street
College Plaza
Pamona, California 91766-1854

GARY HOFFMAN, M.D., M.S.
Chairman, Department of Rheumatic and
Immunologic Diseases
The Cleveland Clinic Foundation A/50
9500 Euclid Avenue
Cleveland, Ohio 44195

NATHANIEL KATZ, M.D.
Assistant Professor of Anesthesiology
Harvard Medical School
Pain Trials Center
75 Francis Street
Boston, Massachusetts 02115

ATTENDEES (Continued)

CONSULTANTS: (Voting)

ROLAND STAUD, M.D.
Associate Professor of Medicine
University of Florida
Division of Rheumatology and
Clinical Immunology
1600 SW Archer Road
Gainesville, Florida 32610-0221

DENNIS TURK, PH.D.
Professor
Department of Anesthesiology
University of Washington
School of Medicine
1959 NE Pacific Street
Room BB1425, HSB
Seattle, Washington 91895-2958

CONSULTANTS: (Non-voting)

DANIEL CLAUW, M.D.
(Center for Devices and Radiologic Health)
Professor
University of Michigan
Chronic Pain & Fatigue Research Program
24 Frank Lloyd Wright Drive
Ann Arbor, Michigan 48106

ACTING INDUSTRY REPRESENTATIVE: (Non-voting)

FRED LASKY, PH.D.
Director, Regulatory Affairs
Genzyme Diagnostics
1 Kendall Square
Cambridge, Massachusetts 02139-1562

ATTENDEES (Continued)

GUEST SPEAKERS: (Non-voting)

LESLIE CROFFORD, M.D.
Associate Professor of Internal Medicine
University of Michigan
Division of Rheumatology
5510 MSRB-1
Ann Arbor, Michigan 48109

GEORGE WELLS, M.S.C., PH.D.
Chair and Professor
Department of Epidemiology and
Community Medicine
University of Ottawa
Ontario, Canada K1H 8M5

PATIENT REPRESENTATIVE: (Voting)

Lynne Kennedy Matallana, M.S., B.A.
National Fibromyalgia Association
Orange, California

FOOD AND DRUG ADMINISTRATION STAFF:

MARIA LOURDES-VILLALBA, M.D.
LEE SIMON, M.D.
JAMES WITTER, M.D., PH.D.

ALSO PRESENT:

VIBEKE STRAND, M.D., FACP

C O N T E N T S

AGENDA ITEM	PAGE
CONFLICT OF INTEREST STATEMENT by Ms. Johanna Clifford	9
OPENING REMARKS by Dr. James Witter	11
HISTORICAL BACKGROUND OF FIBROMYALGIA Pre-ACR Diagnostic Criteria by Dr. Laurence Bradley	31
Basic Mechanisms by Dr. Leslie Crofford	58
Post-ACR Diagnostic Criteria by Dr. Daniel Clauw	86
A Patient's Perspective by Ms. Lynne Matallana	129
Outcomes: Multi-System Impact by Dr. George Wells	138
OPEN PUBLIC HEARING	159
CHARGE TO THE COMMITTEE by Dr. Lee Simon	159
COMMITTEE DISCUSSION AND RESPONSE TO FDA QUESTIONS	177

P R O C E E D I N G S

(8:05 a.m.)

DR. FIRESTEIN: Thank you very much, and welcome to everybody, to this meeting of the Arthritis Advisory Committee.

I'm Gary Firestein, currently the Chair, and we have a number of new people sitting at the table. So I think the first thing that we ought to do is go around the table and introduce everybody. Why don't we start with our august leader?

DR. SIMON: Hi. Good morning. I'm Lee Simon. I'm the Division Director of Analgesic, Anti-inflammatory and Ophthalmologic Drug Products, and a rheumatologist.

DR. WITTER: Good morning. Jim Witter, waking up here, clinical team leader in 550.

DR. ABRAMSON: Steve Abramson, rheumatologist, NYU and Hospital for Joint Diseases.

DR. GIBOFSKY: Allan Gibofsky, rheumatologist, Hospital for Special Surgery, Cornell.

DR. WILLIAMS: Jim Williams, rheumatologist, University of Utah.

MS. McBRAIR: Wendy McBrair, Director of Arthritis Services, Virtua Health, in New Jersey, consumer rep.

DR. HOFFMAN: Gary Hoffman, rheumatologist,

Cleveland Clinic.

DR. BRADLEY: Larry Bradley, psychologist, Division of Rheumatology, University of Alabama at Birmingham.

MS. CLIFFORD: Johanna Clifford, Food and Drug Administration, Executive Secretary to this meeting.

DR. KATZ: Nathaniel Katz, a neurologist in Boston, Massachusetts.

MS. MATALLANA: Lynne Matallana, patient representative, Founder and President of the National Fibromyalgia Association.

DR. FINLEY: Michael Finley, rheumatologist, Western University.

DR. ANDERSON: Jennifer Anderson, statistician, Boston University.

DR. CUSH: Jack Cush, rheumatologist, Presbyterian Hospital, Dallas.

DR. STAUD: Roland Staud, rheumatologist, University of Florida.

DR. TURK: Dennis Turk, psychologist, University of Washington.

DR. LASKY: Fred Lasky, Director of Regulatory Affairs, Genzyme, industry representative.

DR. FIRESTEIN: Thank you very much.

And before we get started, one minor change in

the schedule. Because there were no requests for presenting at the open public hearing, that is going to be canceled, and Dr. Simon's charge to committee will replace that at 11:30.

So why don't we go ahead and get started with the "Conflict of Interest Statement" from Ms. Clifford.

MS. CLIFFORD: The following announcement addresses conflict of interest issues with respect to this meeting and is made a part of the record to preclude even the appearance of impropriety at this meeting.

The topics to be discussed today will not focus on any particular product or company but rather may affect those companies developing and studying products for treatment of fibromyalgia. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their own or their employer's financial interests. All participants have been screened for interests in the products and companies that could be affected by today's discussions.

In accordance with 18 United States Code, section 208(b)(3), the Food and Drug Administration has granted waivers for the following individuals, because the agency has determined that the need for their services outweighs the potential for conflict of interest. They include Gary Firestein, Dr. Gary Hoffman, Dr. Steven

Abramson, Dr. Allan Gibofsky, Dr. Dennis Turk, Dr. Nathaniel Katz, and Dr. Laurence Bradley.

In addition, Dr. Daniel Clauw has been granted a limited waiver that permits him to give his presentation on "Post-ACR Diagnostic Criteria" and to answer questions directly related to his presentation. Dr. Clauw is excluded from participating in the remainder of the committee's discussion.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Act Office, room 12A-30 in the Parklawn Building.

With respect to FDA's invited guests, there are reported interests that we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Leslie Crofford has been involved in studies of Pfizer's pregabalin and Eli Lilly's duloxetine. She consults for Pfizer and Wyeth and previously consulted with Cypress. Dr. Crofford also receives speaker fees and is a scientific advisory for Pfizer.

Dr. Fred Lasky is participating as a non-voting industry representative, acting on behalf of regulated industry. Dr. Lasky is a full-time employee of Genzyme and has a sales relationship with Wyeth. He would like to

disclose that he owns a nominal amount of stock in Johnson & Johnson.

In the event the discussions involve products or firms not on the agenda for which a FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. FIRESTEIN: Thank you very much.

The first item on the agenda is from Dr. Witter, who's going to make some opening remarks.

DR. WITTER: Good morning.

We arranged for some sun for you today. We haven't had that around here a lot, so please enjoy it in here.

We have an interesting day, I think, set up. This has a potential to be an historic day. We're going to be discussing something today that we have not at this point really discussed in any great detail at an advisory committee meeting, and we have a task today, which is essentially to go about and have a discussion about creating a claim for fibromyalgia. So I'm sure we'll find

it interesting, and some folks would hope that at the next meeting, we are actually talking about approving something for fibromyalgia. Time will tell.

So we have several goals for the meeting. I'd like to just review those for today. One of those is essentially to gather input then regarding the development and approval for drugs that treat fibromyalgia. This discussion will help us and will enrich the analgesic guidance process in rewriting the document. I think most of you know that we are in the process of revising the 1992 guidance documents. So this will be an informative meeting in that regard as well.

We hope to address what we've come to understand is an important public health issue. Estimates are, depending on where you read, it affects anywhere from 4 to 10 million people in the United States alone, and we hope that this discussion will also help us to better understand how fibromyalgia represents a "model" of chronic pain. I'll be discussing a bit later what we mean by the term "model".

So we talk about claims and labels. Let's make sure that we are on the same page. It's stated quite often that although label claims have legal and regulatory uses, their central purpose is to inform health care providers and patients about the documented, and I stress documented,

benefits and risks associated with a product. So claims, therefore, describe clinical benefits and that's really what we're going to be trying to address today. What are those clinical benefits? The better that a product is labeled, the more effective it is then to allow for a useful risk management program which is something that we're all very much concerned about these days.

So fibromyalgia. What is it? Well, if you look at the Arthritis Foundation's web page, you'll find some of the following. They describe it as an arthritis-related condition, characterized by generalized muscular pain and fatigue. I'd like to stress the word "and". It's described as a condition, referred to really as a syndrome, because it is a set of signs and symptoms that occur together. It's confusing. It's often misunderstood and a lot of people, including health care providers, maybe don't even believe that it exists. Part of the problem is that it has very common symptoms with no specific laboratory criteria.

How does the American College of Rheumatology classify fibromyalgia? I know that that'll be a big part of our discussion today. Well, there are really two criteria that need to be satisfied. One is that you have a history of chronic, in this case defined as 3 months, widespread pain. The pain needs to be on the left side and

the right side. It needs to be both above and below the waist. It needs to involve the axial skeleton, and then you have to have pain when you digitally palpate in 11 of 18 tender spots. This palpation has to be with the force of 4 kilograms and this has to be described as pain, not tenderness. So what we'll be discussing today, I'm sure, is whether or not this is a viable and workable inclusion criteria for some of the clinical trials that will be coming.

Well, how do we treat fibromyalgia? Again turning to the Arthritis Foundation's web page, there are a variety of strategies. One important one is education, so that patients can understand and hopefully better manage what this condition is or isn't. Relaxation techniques, which are intended to ease tension and anxiety. Various forms of exercise to increase one's flexibility and cardiovascular fitness, and then certain drugs, which are intended to decrease pain and improve sleep, and again I stress the word "and".

There are some interesting drugs here, anti-depressants, such as tricyclics and select serotonin receptor inhibitors, and benzodiazepines. What is not on this list that's interesting are things like NSAIDs and Cox-2s and opioids. It may be telling us something about this disease in particular.

So I'd like to just take a few minutes and kind of get us all on the same page, so to speak, as to how it is that we came to be having this particular meeting today, and I think that there were two meetings that occurred last year that were particularly informative. One of those was the NIH-FDA workshop that occurred in March of 2002. I'll be describing this, in a bit, more. But one of the important features of this meeting was that we came to an agreement at this meeting that chronic pain is in fact an important unmet medical need and needs to be addressed, and during that discussion, we had a breakout session with Dr. Clauw looking at fibromyalgia as an example of chronic pain.

A few months later, we had an Arthritis Advisory Committee meeting -- and I believe it was in this room -- that really was focusing on pain. We talked about a variety of claims for marketing for analgesics. I will describe that in a bit, and I'd just like to point out that all of this information is available from our committee meetings on our website. There's just a tremendous amount of information available on the websites in general at FDA.

Speaking of pages, I'd like to point out about eight of those. This is a recent publication that just came out. It's entitled "NIH-FDA Analgesic Drug Development Workshop: Translating Scientific Advances into

Improved Pain Relief." This is a fairly complete summary of that meeting back in 2002. So if you haven't had a chance to look at it yet, please do so. It's worth the time.

At that meeting then, we, as I indicated, discussed about chronic pain, and we had a discussion about looking for new models, and again I'll describe models, what I mean by that term, in just a second, but we thought it was important at this meeting to get better models so that we could understand some of the important clinical aspects of chronic pain, certainly part of what we'll be discussing today, and if we could also then better understand the chronic pain mechanisms which may serve as treatment targets down the road, this would hopefully allow the design of better clinical trials and, in the long run, hopefully ultimately improve the treatment of chronic pain which is the goal.

Now, as I've alluded to twice already, we talked about models of chronic pain at this meeting, and what we mean by a model is really a setting that's adapted to a clinical trial to understand one of the conditions listed here, for example. It's not necessarily the same kind of thing that you have in clinical practice. In fact, it may be quite different, but it allows us to make certain kinds of decisions from a regulatory perspective. So we

looked at osteoarthritis, chronic mechanical lower back pain, diabetic neuropathy, cancer pain, fibromyalgia, AIDS, and temporomandibular disease as potential models of chronic pain.

We also discussed at that meeting what should be some of the clinical outcomes that should be studied in any particular chronic pain situation. Pain, of course, was first on the list, not surprisingly. We also talked about the use of the patient global, health-related quality of life. Those that are specific to the disease itself were considered to be better, as well as we talked about physical function, again anything that is specific for the disease was felt to be better than if it was just a general questionnaire. We talked about the use of rescue medications, interesting economic considerations which we don't usually get into at FDA, and also how to position adverse events as an outcome measure.

Now, a few months later then at the July Arthritis Advisory Committee, we talked about pain and we had an interesting two-day discussion about various types of claims that we might be granting for pain in general, and we broke this up into really two categories. First, clinical claims. So we talked about a claim for acute pain and those of you that were there will recall our discussion of the ABCs of acute pain which we won't describe today,

but they are at the website. We also talked about chronic pain which will be, again, the focus for today, and the potential for mechanistic claims, that this might be a way to facilitate bridging studies and also a way to push the field forward in the sense of understanding what mechanisms may be. So, for example, for fibromyalgia, one might envision, just as a for instance, a claim to prevent autonomic dysfunction as an example, and that's the discussion that we had at that point in time.

We wrestled with the idea, as we often do, about what is a minimally clinically-important difference in pain relief. We talked about a responder approach in analgesia, which we'll be describing again today, and we talked about the need to revise the analgesic guidance document.

So at the meeting, we specifically talked about claim structures. We talked about a variety of ways to approach this. One of the first things we talked about was to continue to grant, which we've been doing to a certain extent, a claim for general pain, and this affectionately became known as the "six pack" for those of you that were there, and what it really described was a situation where any particular analgesic should really treat a variety of pain conditions from a variety of mechanistic situations. So, for example, anything that would be given and granted

this general claim would treat something, for example, like osteoarthritis, fibromyalgia, and cancer pain, trying to get at a broad swath of mechanisms and etiologies for chronic pain. This was thought to be too high of a hurdle as the discussion went on.

We then had a limited discussion about the possibility for a more limited claim, for example, something that might treat all musculoskeletal pain. So, for example, this would be a combination of something that treats osteoarthritis, fibromyalgia, and chronic lower back pain. But as the discussion continued at that point in time, it seemed the best as we thought through what we had heard that we should continue to push forward with what we've been doing, which is really granting claims for specific diseases. You know about osteoarthritis, today's discussion being fibromyalgia and chronic lower back pain. So that's the current tactic and again that's another reason for today's meeting.

So this is all history. Today, we need to push forward, and so the charge and the challenge for today is in how do we structure a claim. We now know what a claim is. It's a clinical benefit. So how should we approach it? There are fundamentally two different ways. One would be to approach fibromyalgia as a symptom or cluster of symptoms, as is indicated on the Arthritis Foundation web

page, for example. Another way, which may be more useful, is to consider fibromyalgia as a complex disease state with varying clinical presentations, and I'll be describing both of those briefly.

So taking a symptoms approach, we could then look at a pain outcome. Again, this is an obvious and necessary outcome, but I think we need to think it through in more of a deeper fashion. For example, we don't want to get into the situation of overpowering clinical trials to drive meaningless endpoints, clinical endpoints that may be statistically important but have no clinical relevance.

We also should be considering the use of the patient global outcome. As we've been thinking this through in the division, what we are after for this particular outcome is something that is not another look at efficacy. It's not really another look at safety. It's that something in between, that gray zone in between.

And we maybe then should be discussing the inclusion of a physical function or a health-related quality of life outcome. This seems to make sense because these are quite often adversely impacted by pain, particularly chronic pain, and analgesics should improve this or at least they certainly should not worsen it.

I think it's safe to say that it's the feeling of the division that a combination of these really allows

us, we feel, to get a better and improved assessment of the patient's experience with the analgesic which is a key feature of what we're after and will be the discussion today.

Well, what about if we take a disease approach to fibromyalgia? There has been a lot of discussion that fibromyalgia represents, and in fact it was at the NIH-FDA meeting, a chronic pain state. It's a centrally-mediated process. So if we look at fibromyalgia as a chronic pain state, like we do chronic diseases, in chronic diseases, we're comfortable in thinking through treating the disease, curing the disease, even potentially preventing the disease. So should we be taking that same kind of mentality here with fibromyalgia, and would that be useful?

So as we then have positioned, as is on this cartoon, pain as the central player, is it more useful then to think this through, that pain causes, for example, sleep disturbances and pain can cause fatigue, can diminish your quality of life, can lead to cognitive difficulties, and can lead to dysfunction, either autonomic or some kind of loss of functional ability and that may then be all a result of the pain? So, really, we need to address the pain, but it's not sufficient.

So as we take a step back then from the hypothetical and deal with the challenge today then, in

either fibromyalgia or chronic pain, what really is important to the patient? I think we need to keep that as a focus for our discussion today. There's a large effort underway at FDA, as well as outside, for something that has become to be known as the PRO, or patient reported outcomes, and in fact, there's a draft guidance that should be coming out before the end of the year from us.

So what are PROs? They are essentially a patient report of a health condition or treatment. They are scientific, patient-centered measures that can evaluate change in health outcomes. They are handled much like other outcomes for both drug approval and promotion, which I think is a very interesting aspect to think through today, and their selection, their development, and their validation have issues very similar to any other clinical measure, and in particular for pain-related outcomes, we need to then think through psychosocial and all the various other aspects that can be impacted.

Well, what are some of the ideal characteristics for a metric in, for example, pain? It should, of course, be understandable to patients and clinicians. We all know that pain is the fifth vital sign nowadays, and so it seems to make sense that as we transition from the information that we gather in a clinical trial and try and write that into a product label,

we should be doing as much as we can to make that a seamless transition, so that one understands what was studied in the clinical trial when you look through the label.

It should also be applicable across various studies to allow across-trial comparisons. One of the reasons a lot of people feel that pain, particularly chronic pain, hasn't moved forward in a more rapid fashion is because you can't do rigorous and robust meta-analyses because the outcomes just don't allow it, and so we should be thinking forward in that regard to prevent that situation in the future. It should, as I've been describing, detect a clinically-meaningful result. The metric should be responsive to differences in analgesia, and, of course, it should be valid.

So I'd just like to take a second and talk about a highly-valid index that we utilize in the division for WOMAC, in particular the WOMAC pain index subscale, and WOMAC stands, for those of you that may not remember, the Western Ontario and McMaster Universities. I still don't know how they get MAC out of that. But what it really is is a combination of five questions, and as you read through the questions, these are not simple questions about pain. They have in them, as you can see, a functional component, at least some of the questions. So, for example, walking

on a flat surface, pain going up or down stairs, pain at night while in bed, sitting or lying or standing upright.

These questions are really intended to get at the overall pain experienced in OA. As those of us that take care of patients know, the pain of OA has many different faces, and so I think these questions really do a fairly good job of looking at all of these various situations as we study them in osteoarthritis.

And as is on this slide then, we do grant for osteoarthritis, for the treatment of signs and symptoms claim, something that has to be based upon -- we've become comfortable with utilizing three co-primary endpoints of pain, function, and global in a trial that is 3 months in length. So the WOMAC pain subscale, for example, is quite often utilized for the pain component.

So then as we think through fibromyalgia and consider some of what needs to be thought through, whatever the outcome may be, some of the important points are as follows. For example, as we just discussed with the pain, should this be a single question or is it better to come through with a composite question to get a more robust assessment of the outcome? Of course, it has to be both statistically and clinically meaningful.

We have to think through who is included and excluded from the trials because it has an impact on the

labeling and the generalizability once this is released.

We need to think through whether a landmark analysis, meaning at the end of the trial as compared to the beginning, is the better way to go, or should we be thinking through a time-weighted approach, trying to get more of a feel for what happens during the entire trial, not just at the end?

We need to think through about the issue of daily, in this case I've written here, pain, whether it should be on a daily basis or on a weekly basis. There are pluses and minuses for both. There's a lot of effort nowadays in looking at diaries, particularly electronic diaries, as that may be better to capture the moment pain. That appears to be important for fibromyalgia.

We need to discuss the length of the clinical trials. Is 3 months enough? Is 6 months better? And then, we're going to be wrestling, I'm sure today, with the issue of superiority to placebo, and do we need to continue to follow that paradigm?

So another way to look through and consider how we might fashion a label and get at a response in fibromyalgia would be to look at the responder approach. As I said, we've discussed this at other venues. It has some potential advantages to it. One of those is that it can allow the outcomes of interest to really be explored

and studied in the same patient which can be highly useful. It may lessen or eliminate data imputation which is always a problem, as we're all aware. It allows a certain flexibility in design to capture different aspects of the condition, and it's something that is widely utilized in rheumatoid arthritis. We've become very comfortable with it.

So I thought I'd just take a moment to refresh our memories as to what the ACR 20 responder index is. ACR again stands for the American College of Rheumatology. The 20 stands for 20 percent improvement. So it comes also as a 50 and 70 percent variety.

There are two components to this index. One is a required component where you have to have in this case a 20 percent improvement in swollen and tender joints. In addition, you have to have a 20 percent improvement in three of the five following: patient and physician global, patient pain score, a modified health assessment questionnaire, and acute phase reactant. In this case, I've written here C-reactive protein or sedimentation rate.

So is this useful, this particular responder approach, in terms of fibromyalgia, and if it is, how could we fashion a particular responder endpoint? I've put in this slide a "for instance." This is not at all intended to say that this is what we would like to do. This is just

a for instance.

So we could envision that pain would be the required outcome, again makes sense.

And then we have other important outcomes that I think we need to be considering, as we've been discussing: qualify of life outcome, either a general or a specific; a function or, in this case I've written, a dysfunction outcome; looking at sleep disturbance, fatigue, cognitive impairment as outcomes; and then patient global.

Would it be then, for example, that we would say that someone is a responder if they have achieved four of the important outcomes, plus pain, and then should we be also thinking through that we want to have this in a tiered structure like we do with the ACR 20/50/70? Would that be useful for this condition?

I'd like to just take a minute and close out here by bringing everybody up to speed on a process that is ongoing. It's called the IMMPACT process. The acronym stands for Initiative in Metrics and Measurements in Analgesic Clinical Trials. This is an international organization which has really been devoting itself recently to looking at chronic pain, and in fact, there is a publication which has been submitted entitled Selecting Core Outcome Domains in Chronic Pain Clinical Trials.

It's interesting to look at the six

recommendations from this group, being as I've listed here, pain, physical functioning, emotional functioning, patient global, negative health states, and patient disposition, as being representative and overlapping, in fact, what we've been discussing at other meetings.

So when all is said and done and when we're finally writing a label, we need to remember that the label is, as I've been trying to stress here, the end product of all these efforts. It's the end result of all the randomized, controlled trials and everything that's gone into their thinking.

So what should the label mean? To the health care provider, for example, the label needs to be describing for this person who can take it, and what type of risk management should be involved in thinking through any particular issues, and importantly, what should it mean to the patient. What can they expect in terms of relief of pain? What can they expect in terms of relief of associated symptoms? And what is the duration of this relief and the degree of this relief? All important issues we need to think through today.

This is from the latest issue of a magazine entitled Fibromyalgia Aware. It's reminding us that fibromyalgia does not just involve women, but let's hope that today's discussion will lead to a future where more

patients look like this gentleman than less that have fibromyalgia.

And I'd like to close with something that was also the close of the second meeting of the IMMPACT process, which I think is an important reminder for us as well today and that I think I've been stressing throughout here, is that it's important really to think about the patient, to assess the patient, and not just the pain.

So thank you very much.

(Applause.)

DR. FIRESTEIN: We have a minute or two for questions from the committee.

Yes, Dr. Cush?

DR. CUSH: Jim, that was a good overview.

Do you think, though, that we can as an advisory body make recommendations on outcome measures or composite outcome measures when clearly there are none that have been tested or validated and whatnot? So we could throw it out there, but how useful is that to the agency without any sort of testing or confirmation of its value?

DR. WITTER: I think you've hit on really the core of the problem, that we need to bring that discussion forward, and then I think all of us wrestle whether or not we can actually do this. If things are not validated in the other areas, can we be pushing forward without those

kind of indices like we've had, for example, with rheumatoid arthritis, with osteoarthritis? What do we do? So I think you've hit on the head. That really is what we need to be discussing today.

DR. FIRESTEIN: One of the advantages that we had in those other indications is that there were effective agents that could be then used to validate the endpoints, and do you have some notion in terms of how one is going to be able to validate an endpoint when there are no truly effective agents?

DR. WITTER: Well, yes, but I'd prefer to hear your discussion later.

DR. FIRESTEIN: Okay.

Lee?

DR. SIMON: Well, isn't this always the dilemma, Jack? The reality is, is that, what came first, the chicken or the egg, and without a discussion that's public and with the experts to determine what may be useful things to look at and what is this real process, based on whatever science exists, then the ability to validate the outcomes in the context of applying potential therapies becomes very difficult until we have that discussion, the fundamental beginning step-off to understand what we as some experienced clinicians believe might be a useful way to approach the particular conundrum. So that's really the

reason. Although we don't have good validation of the outcomes, we don't have great therapies to date, we do have to make that leap to be able to begin to target what we believe, based on the science, will be useful, and then hopefully people will respond by coming in with potential therapeutics that will actually then allow us to test and validate the outcomes.

DR. FIRESTEIN: Thanks very much.

The next presentation on Pre-ACR Diagnostic Criteria will be given by Dr. Bradley.

DR. BRADLEY: Thank you very much.

I'm going to fumble here, the requisite fumbling at the podium, while I get my presentation up.

I want to thank you very much for inviting me here today, and I am going to try today to provide something of a historical perspective on the way we think about fibromyalgia, but really the primary points that I'm going to try to make today are that, one, the abnormal processing of sensory information in fibromyalgia is something that is identifiable, it's been reliably observed among different investigators and different clinicians, and this abnormal processing or abnormal sensitivity to pain is something that's not, at least from the data we have so far, highly affected by psychosocial factors. However, what people say about their pain, how they report their

pain, how they behave in response to pain or their pain behavior is highly modifiable by psychosocial factors.

Then, I'll also try to conclude by some speculations regarding what types of changes might we expect from compounds that are in development or about to be tested for chronic pain conditions, such as fibromyalgia.

First of all, as you've already seen from Dr. Witter, fibromyalgia is characterized by several symptoms and the primary characteristics of fibromyalgia include widespread generalized pain and abnormal pain sensitivity evoked by low-intensity stimuli that really vary in nature. These include pressure stimulation, heat stimulation, cold stimulation and so on. And all the criteria that have been developed over the years have really focused on those two primary characteristics.

In addition, just as Dr. Witter mentioned, there's a variety of other symptoms that occur with fibromyalgia, such as headache, fatigue, sleep disturbance, and a number of other symptoms, too.

Now, there are also alterations in behavior, so that fibromyalgia symptoms are associated with behavioral disturbances and activity levels, social interaction, functional ability, avoidance of events that evoke pain, affective distress and relatively high usage of the health

care system.

Historically, these abnormalities and pain sensitivity, difficulties in function and affect, in the absence of reliable biological markers, have led investigators to take different types of research and clinical pathways. For many years, I think there was sort of a dichotomy between those investigators who were searching for a single source of symptoms versus people who tended to attribute fibromyalgia to psychiatric illness or other psychosocial factors.

When we see the different types of labels that have been applied to people who show abnormal pain sensitivity and widespread pain -- and these are labels ranging from DaCosta syndrome and shell shock, all the way to fibrositis and affective spectrum disorder -- you see that most of these diagnostic labels have either focused on sort of biological factors, such as concussive effects on the brain, nerve dysfunction, viral illnesses, or they have focused primarily on psychological and psychosocial factors.

I think in thinking about fibromyalgia now, I think this is truly a disorder where there's abnormal pain sensitivity that's mediated by abnormal processing of sensory input at the spinal and the super-spinal levels, but certainly the way people act with fibromyalgia, what

they say about their pain, is influenced by a number of factors.

The three factors that I think have really helped us better study and understand fibromyalgia are, one, the development of gate control theory back in 1965, work that was done in the 1980s that at least in my mind was really begun by Doug Drossman and the group studying irritable bowel syndrome regarding psychosocial factors that influence health care-seeking behavior, and current work in fibromyalgia specifically beginning in the early 1990s by people like Rob Bennett and Jon Russell who began to try to identify various biological factors that might be associated with pain and pain sensitivity in people with fibromyalgia.

With regard to gate control theory, very quickly, the basic tenets are that multiple biological and psychosocial factors influence pain perception as well as pain behavior, and therefore, all pain perception and pain behavior is determined by this combination of biological and psychosocial factors. So it's really no longer appropriate to identify pain and related symptoms as either organic in nature or functional in nature.

This slide actually shows Ron Melzack's current version of the gate control theory which he refers to as the neuromatrix construct, and essentially what this refers

to is that the neuromatrix is a construct which is really comprised of a complex set of pathways involving the spinal cord, also various regions of the brain, limbic system, somatosensory cortex, thalamus and so on. And the function of this neuromatrix is in part genetically influenced, but there's a variety of biological and psychosocial and cognitive factors that can influence the functioning of the neuromatrix which then produces pain perception and pain behavior.

Now, I'll just show you a few slides showing you sort of the robustness of the sensory processing phenomena that are observed in fibromyalgia. This is a slide from our group in which we compared mechanical pressure pain thresholds at a subset of the ACR tender points in a group of about 20 fibromyalgia patients who did not meet current criteria for major depressive disorder, a group of 10 patients who met criteria for major depressive disorder but did not suffer from generalized pain, and a group of healthy controls without pain, without major depressive disorder. What you see is that the pain threshold levels to pressure stimulation in these fibromyalgia patients is about one-half the level of what you see in healthy controls, and at least in our laboratory and I think in most other laboratories, that's a very common finding, that the pain thresholds are about one-half

the level in these patients with fibromyalgia. What you see here in these depressed patients, their pain threshold levels are really no different from what you see in the healthy controls, and to us, that suggests that depression alone doesn't account for the abnormal pain sensitivity in fibromyalgia. I'll show you some more data on this in a bit.

This is some other data from our laboratory looking at thermal pain thresholds, thermal stimulation applied to the skin, and you see a reliable, significant difference in pain threshold levels where the fibromyalgia patients' threshold level is about 5 degrees Centigrade lower than what you see in healthy controls.

These are some data actually from Mike Geisser and the group at Michigan showing differences between patients with fibromyalgia which you see in this line and healthy controls in magnitude estimates of pain intensity in response to a variety of thermal stimuli, ranging from 40 degrees Centigrade to 51 degrees Centigrade, and you see very reliable differences in pain intensity ratings between these two groups.

Some additional data from Roland Staud who's here. This is a slide from one of Roland's recent studies showing greater temporal summation effects in patients with fibromyalgia compared to healthy controls, and regardless

of whether the stimuli or the repetitive stimuli are applied with a 3-second or 5-second interstimulus interval, you see much greater evidence of temporal summation in the patients compared to healthy controls.

So what this shows is that in a variety of laboratories using different techniques, different stimulation, you see very robust and reliable differences in responses to relatively low-intensity stimuli between fibromyalgia patients and healthy controls.

Well, let's turn to the question of what we know about psychosocial factors and how that affects pain behavior, including health care-seeking behavior. It's been established in a variety of chronic illnesses that psychological distress or psychiatric illness is associated with greater health care-seeking behavior at tertiary care facilities. In the case of fibromyalgia, there is some evidence that psychological factors are not really necessary or sufficient to produce fibromyalgia symptoms.

And the person that really, I think, got me at least thinking about this and certainly has influenced other investigators, too, is Fred Wolfe who originally came up with this funnel slide which shows that in research studies, we primarily focus on people at tertiary care centers, but these people may well be very different from the general population of individuals with fibromyalgia or

any other sort of chronic pain disorder.

We did a study in our laboratory where we examined a group of about -- actually now about 70 patients with fibromyalgia and 40 individuals that we recruited from the community who met criteria for fibromyalgia but had not gone to see a doctor for their pain within the past 10 years. We compared these two groups of individuals with regard to a group of healthy controls recruited from the community.

This particular slide shows the number of lifetime psychiatric diagnoses among these three groups that were determined by the subjects' responses to the diagnostic interview schedule. What you see on this slide is that the fibromyalgia patients are actually characterized by a fairly high level of psychiatric morbidity. The patients are characterized by a mean number of 2.5 psychiatric diagnoses over the lifetime compared to our healthy controls who have a mean number of diagnoses of 1, and in the case of the healthy controls, these are primarily social phobias and really very minor disturbances. Among our non-patients, actually they show a significantly lower number of lifetime psychiatric diagnoses than the patients but they don't differ from the healthy controls in terms of psychiatric morbidity, and as you'll see in a moment, the pain sensitivity to pressure

stimulation of the non-patients and the patients, is approximately the same.

However, when we followed the non-patients over a two-and-a-half-year period, we wanted to see to what extent the non-patients in a sense would convert to patients, how many of those people would become patients over time. What we found, and actually much to our surprise and much to the surprise of our reviewers, is that only 10 of the 40 non-patients actually became patients, sought medical care during that first 2-and-a-half years.

But the factor that best distinguished those who became patients from those who remained non-patients was the number of lifetime psychiatric diagnoses at baseline, and essentially among our non-patients, those who had one or fewer or zero lifetime psychiatric diagnoses had about a 95 percent chance of remaining a non-patient. Those with two lifetime psychiatric diagnoses or greater actually only had about a 50-percent chance of remaining a non-patient. So it was the number of psychiatric diagnoses or psychiatric morbidity that was a very great determinant of who became a patient within that 2-and-a-half year period.

Now, returning back to the baseline data, this slide shows in a separate study where we examined another group of fibromyalgia patients, another group of

fibromyalgia non-patients, healthy controls, and we compared these groups on pain threshold levels. What we found is that regardless of whether we were stimulating with pressure stimulation the ACR tender points or a set of control points which were primarily points, such as the mid-tibia and the forearm that would involve stimulation of sort of bony skeletal tissue, and regardless of whether the patients reported an insidious or a gradual onset to their pain versus a traumatic onset to their pain, we saw approximately the same pain threshold levels in the aggregate among all three groups of individuals with fibromyalgia compared to the healthy controls. And we saw that again both at the tender points, as well as at our set of control points.

So what this suggests is again that regardless of psychiatric morbidity, regardless of the nature of the onset of the pain or the factors that people identify as the onset of their pain, you see very similar pressure pain thresholds.

In our particular study, we also drew cerebral spinal fluid to look at levels of substance P and again you see the same relationship, very similar to what Jon Russell had found in his series of studies. We found that among our three groups of people with fibromyalgia, regardless of whether they were patients or non-patients, we found

elevated levels of substance P compared to our healthy controls.

Well, let's turn now and talk about what we know about psychosocial factors and how they affect what people report about their pain. The example that I'm going to use in this next series of slides is reports of stressors, and I think it's pretty well known that patients with fibromyalgia frequently report that their symptoms are intensified by emotional distress or emotional stress or also physical stress.

Actually there was a study that came out of a couple of years ago from Alex Zautra and the group at Arizona State in which they examined a group of fibromyalgia patients, a group of patients with knee osteoarthritis and healthy controls, and asked each participants to describe a stressful experience in their life over a 30-minute period. What they found was that the fibromyalgia patients at the end of that 30-minute period reported a much greater increase in their clinical symptoms compared to the reports of the patients with knee osteoarthritis and also the healthy controls.

We began a study with Roger Fillingim of the University of Florida, which is still ongoing, where we've been looking at the effects of really very brief stressors in the laboratory on patients' and controls' responses to

thermal stimulation of the skin, and in our particular paradigm, we asked participants to very vividly imagine either a very stressful event from their own life or a relatively neutral or relatively sometimes pleasant event from their own life right before we applied the stimulation.

And in this particular slide, what I'm going to show you are mean increases in pain unpleasantness ratings among the fibromyalgia patients and the healthy controls at four different levels of thermal stimulation. What this slide shows is actually these bars represent differences in pain unpleasantness ratings in the period following the stressful imagery versus the period following the relatively neutral imagery. What you see is that at 45 degrees, 47 degrees, 49 degrees Centigrade, you see substantially greater increases in pain unpleasantness among the fibromyalgia patients, very little effect of the imagery on pain unpleasantness ratings among the healthy controls. And at 51 degrees -- this is actually a total of about 15 people here -- so again you see no effect among the healthy controls, and due primarily to 1 person, you see actually a very large decrease in ratings among fibromyalgia patients. But the primary finding is that at these lower levels of stimulus intensity, just thinking about a stressful event over a 4-minute period has a very

strong effect on pain unpleasantness ratings.

Now, when we asked people to give us their ratings of pain intensity, the intensity ratings by both groups are not really strongly affected by thinking about stressful events, but ratings of pain unpleasantness are affected.

Also, we've been drawing blood and drawing saliva and what we find is, actually with both measures, that our patients with fibromyalgia, about 20 minutes after the stressful imagery, show a relative decrease in cortisol levels compared to the neutral imagery, and we don't see that kind of effect in our healthy controls. So there's not enough people yet to look at association between changes in cortisol and changes in pain unpleasantness, but the point is that you do see some evidence of HPA axis dysfunction as a result of the stressful imagery in the fibromyalgia patients compared to the healthy controls.

Well, what do we know about biological factors that are associated with pain and distress in people with fibromyalgia? I think there's very interesting work that's going on now regarding both genetic influences on pain and analgesia and also some very good work that's being done using neuroimaging techniques that have documented altered central processing of sensory input in people with fibromyalgia.

These are data. Actually, these data come from Dan Buskila's group in Israel. Martin Offenbaecher in Munich was the first person to really identify this finding, but both groups, using very different populations, have shown that individuals with fibromyalgia -- in Offenbaecher's group, it was primarily women, in Buskila's group, it was all women -- actually a greater proportion of the patients with fibromyalgia compared to controls show a functional polymorphism in the 5-HTT gene promoter region or in the regulatory region of the 5-HTT serotonin transporter gene. And what you see is that there's a greater proportion of patients with fibromyalgia who show this short/short allele compared to healthy controls and again that's been found in two separate groups now.

There's also some work being done on sex-related genetic influences on analgesia which may eventually have some impact on fibromyalgia research. This is a slide from a paper that Jeff Mogil and Roland Staud, Roger Fillingim, and a large group of investigators recently published showing an interaction between sex and a polymorphism in the melanocortin 1 receptor gene. And what this slide shows is that regardless of whether one is using thermal stimulation or ischemic stimulation, that among females having a particular polymorphism, characterized by two variant alleles in this MC1R gene, is associated with

greater analgesic responses to pentazocine. Among the males, you don't see this sex effect, and I think this is a very interesting line of research, particularly given the fact that fibromyalgia is a disorder which affects primarily women.

What about altered central processing of sensory input? These are some slides from Rick Gracely and Dan Clauw's group at Michigan, and what this shows is that when fibromyalgia patients and healthy controls are exposed to pressure stimulation that varies in intensity but which produces approximately the same report of pain intensity -- and in this case, there was a pain report of about 11 on a 20-point scale -- you see a number of brain regions in which both patients with fibromyalgia and healthy controls show significant activation on fMRI imaging. So by equivalent levels of pain intensity or perceived pain intensity, you see the same brain regions being activated in patients and controls.

However, when you take the healthy controls and you expose them to the same level of stimulation which produced pain in the fibromyalgia patients but which are relatively innocuous to the healthy controls, you primarily see significant levels of activation in a variety of regions in the patients with fibromyalgia. You see very little significant activation in the healthy controls

So the point that these two slides show is that fibromyalgia patients are characterized by augmentation of sensory input which can be identified through neuroimaging of activity in the cerebral hemispheres

Well, let me conclude the data and sort of summarize the data from this talk. First of all, I think what we've shown is that pain sensitivity, pain-related symptoms, and behavioral disturbances in fibromyalgia are reliably observed by a variety of investigators and can be done so by clinicians and this can be done using a variety of measurement techniques.

Pain sensitivity and related symptoms are influenced by biological factors. There's evidence that there may be a genetic predisposition for development of fibromyalgia. That particular serotonin transporter gene or that particular functional polymorphism in that gene is also associated with chronic headaches and also some anxiety disorders. So this particular gene might be related to the development of a number of disorders that are part of the fibromyalgia symptom complex.

Also, we've seen that abnormal pain sensitivity is associated in our laboratory and in a number of other laboratories with elevated cerebral spinal fluid levels of substance P, and also what we will very soon see in the future, I think, is that there's a number of investigators

using neuroimaging techniques and I think we'll see a number of studies coming along soon which show that abnormal pain sensitivity is associated with augmented sensory neural input.

Now, what we've also seen is that, at least in our laboratory, pressure pain sensitivity and CSF levels of substance P really don't vary very greatly as a function of affective illness or lifetime psychiatric morbidity. However, what we do see is that changes in plasma cortisol levels, reports of pain unpleasantness in response to thermal stimulation, and other sorts of pain-related behaviors, such as health care-seeking behavior, are associated with variations in psychosocial factors and affective disturbance.

Well, what does this mean for clinical trials? I think a number of pharmacologic interventions that are used currently, also the interventions that are being developed for use in fibromyalgia are all compounds that alter activity at the superspinal level. They alter activity in the brain that can influence pain inhibition or to a certain extent alter central processing of neural input. And I think that what we should be able to observe in clinical trials is that these compounds should be able to influence ratings of pain intensity, and I think some of the newer compounds that are in preclinical trials, for

example, some of the new glutamate receptor inhibitors that are in development, may actually also alter abnormal pain sensitivity.

These interventions, both the current interventions and the interventions that are in development, may also modify pain behaviors through alterations in pain intensity, but also secondary alterations on pain affect, affective disturbance, and other psychosocial factors.

And while this wasn't really part of what we're talking about today, I do want to mention that I think that the development of effective compounds that may alter pain in people with fibromyalgia may also be helpful to clinicians who use psychosocial interventions with fibromyalgia patients. When I look at the literature on cognitive-behavioral therapy, other sorts of psychosocial interventions, when you look at the studies that really use adequate attention placebo controls, at least my reading of those studies is that most of them don't produce effects that are much greater than what you see with a good placebo control, and I think one thing that psychosocial investigators have yet to really think much about is why do we see these relatively modest effects with psychosocial interventions compared to what we see in patients who are treated by psychosocial interventions, patients who have

rheumatoid arthritis, osteoarthritis, irritable bowel syndrome and so on. And I think that one of the factors is that for these other kinds of diseases and disorders, there are relatively effective pharmacologic compounds that influence pain, and I think that so far, we really don't have very good compounds that reliably influence pain in fibromyalgia. But I think that once these compounds are developed and tested, and if they are shown to be effective, I think that they will have a secondary effect in the sense that they will enhance the effectiveness of psychosocial interventions for pain and pain behavior in fibromyalgia.

So I'll conclude there and thank you very much, and I'll be glad to take any questions you might have.

(Applause.)

DR. FIRESTEIN: Thank you.

Dr. Katz?

DR. KATZ: Yes. Hi. Thanks. Two quick questions.

Number one, the distinction that you made between the two subgroups of people with fibromyalgia, the patients versus the non-patients, was the clinical expression of the syndrome any different between those two groups?

DR. BRADLEY: Yes, that's a very good question,

and even though the pain sensitivity was very similar in the two groups, the non-patients reported significantly lower levels of pain on the McGill Pain Questionnaire compared to the patients. And they also again -- and this is in accord with their difference in psychiatric status -- reported lower levels of depression and anxiety on standardized questionnaires. So the expression of the disorder was different, although the pain sensitivity was the same.

DR. KATZ: And the second question is, I was interested in your very helpful summary of the studies looking at hyperalgesia to various forms of stimuli and neuroimaging, which are obviously used to suggest that this disease therefore is independent from psychiatric influences.

But my question is about the control groups used in those studies. Have any of those studies used patients with somatoform pain disorders as the control? That would seem to be the relevant control group here.

DR. BRADLEY: Yes. To my knowledge, no, and we've not tried to look at that. I don't know of other investigators looking at that right now. I don't know if your group is looking at that at present.

(Off microphone speaker.)

DR. FIRESTEIN: I have one quick question. I

think the data that you presented on patients versus non-patients was fascinating. One of the questions is, if patients don't or if individuals that meet the criteria, in terms of the number of tender points, don't seek medical attention and don't view this necessarily as a medical illness, do we want an indication for treating such individuals, and is it a disease only when the psychiatric manifestations come?

The corollary of that is whether or not the real full expression of the disease is really related to psychiatric manifestations, and is the perception of pain a self-selecting group of individuals that represent a bell-shaped curve? In other words, do those individuals that meet the criteria because there's a broad spectrum of individuals that are tender at 4 kilograms per X number of square centimeters but that's within normal human experience?

DR. BRADLEY: I'm going to try to respond to those two different dimensions of your question and please tell me if I'm really responding to the issues.

I think with regard to the bell-shaped curve, yes, there is a bell-shaped curve in terms of pain sensitivity. I think what's important is that both the patients and non-patients were really on the far side of that bell-shaped curve. I mean, they were way up in that

upper 2.5 percent. So those two groups were really equivalent in terms of pain sensitivity and that was really not associated with psychological, psychosocial, psychiatric factors. And we've done that study twice now. So at least in our laboratory, that's a very reliable finding.

I think in my mind, the issue is how people perceive their pain and whether they seek health care for their pain. I think that is very much influenced by the variety of factors, and it's not just psychological or psychiatric factors. I think there's a wide array of socioeconomic, cultural, family learning/history variables that influence that type of behavior. So I think the question that you're asking is, is the identification of fibromyalgia sort of a psychosocial phenomenon, and I would say that the perception that one has musculoskeletal pain and that one is -- well, and this is the way we really did recruit people for the study, is we put out advertisements in the newspaper and through the television media looking for people with persistent, longer-than-6-month history of widespread musculoskeletal pain. And when people responded to those advertisements, we then went through sort of a three-step process of screening them.

We would screen them very briefly over the telephone using Fred Wolfe's questionnaire from 1992, I

think one of his papers in '92. If they passed that screen, we would then ask them to send us copies of their recent medical records. In these two studies, we wanted to exclude people who had other kinds of illnesses, diseases, that could cause widespread pain, such as people with neuropathies, people with a variety of other problems, back surgeries, neck surgeries, and so on, that could produce the symptoms. So these were really people without other medical causes that we could identify for their pain.

Then if they passed that screen, then they came into our GCRC and one of my rheumatology colleagues, Graciela Alarcon, would examine and interview each person, and we would, to the best that we could, really try to screen out people who had other sorts of medical problems that might account for their pain.

So most of the non-patients really didn't have a label for what they were experiencing, except that they hurt all over, and the non-patients also -- I guess I should mention this, too. If you looked at sort of measures of self-efficacy and coping strategy usage, these people were very, very good copers and really most of them had an experience at some point longer than 10 years ago when they went to see a doctor for their pain. And these studies were done in the early 1990s. So they would have an experience, the doctor would say, well, I don't know

what's causing your pain, and these people would go home and just stop there and take care of themselves.

So the perception of pain and the pain sensitivity was not influenced by psychological factors. How people responded to the pain certainly was influenced by psychological factors, and actually, again, the non-patients were such a robust group in terms of coping, that after 2-and-a-half years, again only 10 of them had become patients. So I think the pain problem was not a construct of their psychological situation, but their behavior certainly was influenced by it.

DR. FIRESTEIN: Dr. Strand? Oh, I'm sorry. Never mind.

DR. STAUD: I was wondering if you would like to comment on the striking sex difference in fibromyalgia with the ratio discussed in 8 to 1 or 8 to 2 or 9 to 1 in males versus females and what particularly the psychosocial aspects are that explain most of this, because in the general population, males generally have, on psychophysical testing, lower sensitivities to painful stimuli.

DR. BRADLEY: That's a phenomenon that's really not well understood. I mean, we all are aware that in rheumatic diseases, that there's a tendency for women to be more susceptible to rheumatic diseases than men, but the ratio that we see in fibromyalgia is even more striking

than what we see in the inflammatory rheumatic diseases.

I can really only speculate and I think that there must be, for example, factors, and to some extent, we already know that, for example, fluctuations in hormonal status, sex hormone status, among women influences their perceptions of pain.

So I think that certainly there's probably a combination of genetic and also hormonal factors and perhaps other biological and to some extent perhaps even non-biological factors that account for that sex difference, but it's really striking and it's more striking than what you see in really any other disease or disorder.

DR. FIRESTEIN: Two more quick questions. Dr. Cush and Dr. Turk.

DR. CUSH: Last year at our pain workshop, we had talked about setting up outcome measures or trying to go towards outcome measures that were not only based on symptomatic control but also mechanisms. So do you think that we're at a point or as we try to formulate some guidelines for trials and outcomes where we can talk beyond symptoms and talk about sort of mechanistic control of pain?

DR. BRADLEY: Well, yes. I think that probably the state of the art is right now -- the problem is not the state of the art of measurement, but I think the problem is

sort of the state of the art of where we are in developing compounds for persistent pain. I think right now, we don't have compounds that can be really used safely in human beings. For example, the NMDA receptor antagonists really are very problematic for use with humans because they induce sort of hallucinations and all kinds of other problems.

I think eventually there will be compounds that will influence events more at the dorsal horn level of the spinal cord, and I think at that point, I think it's reasonable to then try to use measures of sensitivity, whether they're biological measures or sort of behavioral measures of sensitivity, as an outcome measure.

I think for right now, I think it's really interesting to use those measures as sort of secondary outcome measures but without any great expectation that the compounds that we have currently will have a great effect on pain sensitivity, regardless of whether you're looking at that from a behavioral level or from a more neuroimaging or other type of biological level.

DR. TURK: Thank you for that overview, Larry.

As you presented your data, other than the insidious onset, traumatic onset, you really tended to look at averages across large groups of patients, and I'm wondering if there's any thoughts you might have on whether

there may be subgroups of patients with fibromyalgia based on either physiological factors, on symptom presentations, on sensory sensitivity, psychological factors, because there are several groups that have tried to look at whether there may be differences among those groups. I was interested in your insidious onset, traumatic onset, because there's at least two or three studies that have shown pretty large differences in people with different reports of onset of symptoms. So I wonder if you have any comments about that.

DR. BRADLEY: Well, I think in regard to the first part of your question, with regard to subgroups, yes, I think that you're right, and I'm glad you brought this point up. Within the patient population, there is really a variation, particularly in terms of psychological functioning, actual displays of functional abilities, and I think that it is important to note that patients do vary. There are patients who have relatively low levels of psychological distress, even though on the average you tend to see very, very high levels of distress.

I think that it's worthwhile looking at those subgroups and regardless of whether one uses techniques like the MPI, for example, which is a very good technique, or other types of techniques, it is worthwhile to look at potential interactions between variations in distress or

function and response to pharmacologic treatments and responses to behavioral treatments, too.

I think I've lost the second part of your question. What was the last point you raised?

DR. TURK: I think you covered it. It was just on the traumatic versus insidious onset.

DR. BRADLEY: It may have something to do with the fact that -- again, we were very careful to screen people, to eliminate people, for example, who had other problems that potentially could produce chronic pain. So, for example, we did not take anybody into our studies who had a back surgery or a neck surgery. So there probably was a certain group of people with a certain type of trauma that resulted in surgical intervention who were not part of our studies. So factors such as that may account for the relative sort of group or the average level of homogeneity between those groups which I think we're probably much more stringent than other groups have been in the past in looking at that issue.

DR. FIRESTEIN: Thank you very much for a very interesting presentation.

Next, Dr. Crofford's going to talk about basic mechanisms.

DR. CROFFORD: Thanks, Gary, and I'd like to thank the FDA. I actually would like to congratulate you

on taking on this problem. This is a problem that we've been struggling with in rheumatology for many years, and I think that the FDA really ought to receive the credit that they deserve for really taking this on. So I'm pleased to be here.

In framing my comments this morning, what I'd like to do is start with some thoughts about actually developing effective treatments for fibromyalgia syndrome, and I think from a very incredibly pragmatic standpoint, which is, I think, where we need to start with this condition, the first question is whether or not fibromyalgia syndrome can be clinically recognized and diagnosed using the current ACR criteria because that's where we are.

I would submit that even though the ACR criteria aren't perfect -- and we can certainly talk about them at great detail and you'll probably get a lot of different opinions -- that they actually do identify patients with a predictable symptom profile which is what we want. We want to be able to use the criteria to identify a group of patients that are predictable and have the opportunity to respond to certain types of interventions.

Now, that's not to say that fibromyalgia syndrome patients identified by the ACR criteria don't

contain subsets. I think they certainly do contain subsets of patients, but when you apply these ACR criteria correctly, you do get a group of patients that are a good subject pool for clinical trials.

The second point is we need to understand what are the critical symptom domains in these patients that must improve for an intervention to be an effective treatment for fibromyalgia syndrome, and one could jump off the excellent presentation of Dr. Witter and think about all kinds of different ways that you could develop criteria that may be important to patients with fibromyalgia syndrome. This is certainly what we're about today, and I think certainly there are some thoughts that I'll present later on.

Thirdly, what mechanisms underlie fibromyalgia syndrome that may allow us to predict the types of treatments that may be effective in fibromyalgia syndrome? I think we ought to think about that or at least the pharmaceutical companies ought to think about that as they move forward in attempting to predict what types of compounds may be useful in this syndrome, and then, lastly, which I won't address at all but I think Dan Clauw will address quite thoroughly and Jim has already talked about it and Dr. Wells as well, how best can we measure improvement in response to treatment?

So I brought this slide just because I think it's important that we recognize that fibromyalgia syndrome is debilitating, that the patients have an impact on their lives for the most part by the presence of these symptoms, whether they seek treatment or not. They answer advertisements. So they notice that there's something wrong with them.

In thinking about the fibromyalgia symptom domains, I think the first thing that we all recognize is that patients have pain. It's required that this pain be widespread and involve the musculoskeletal system. That having been said, patients with fibromyalgia also have other types of pain, including regional musculoskeletal pain syndromes, including temporomandibular disorder, and visceral pain syndromes, and I won't spend any time specifically talking about these things, but pain is one of those things that has to be a given when we think about fibromyalgia syndrome and when we think about its management.

But fibromyalgia patients also have non-pain symptoms, and we've already heard about some of them, and I'll spend the majority of my time talking about the non-pain symptoms which include fatigue, sleep disturbance, cognitive dysfunction, depressive and anxiety symptoms which I should be careful to distinguish between diagnosis

of major depressive disorder. These are not required but they're almost universally present in patients with fibromyalgia syndrome.

As we heard from Larry, the pain is widespread clinical pain, and no mechanism is implied in this definition of widespread clinical pain. However, the ACR tender points have to be present and the tender points measure a domain that incorporates probably both this concept that Dr. Bradley brought up, that there's either hyperalgesia or allodynia in these individuals, but they probably also incorporate non-pain domains or something that we call distress. What I'd like to just bring your attention to, when Larry brings up data that demonstrate that patients with fibromyalgia have an increased noxious threshold for thermal sensitivity, for example, that measures this domain of whatever we want to call allodynia or hyperalgesia, but that the tender points probably measure something in addition to this noxious stimulus, and these are data that were very nicely demonstrated by Dan Clauw looking at different paradigms and the comparison between what tender points measure and what the kind of more sensitive measures of allodynia actually measure.

Now, I actually don't think this is a bad thing because I think maybe by happenstance that's what has happened when we developed the tender points, is that for

some reason -- and maybe this was just prescience on the part of the committee that developed the tender points -- these ACR tender points actually do measure some kind of a combination domain.

Then the question of whether the pain of fibromyalgia syndrome is real always comes up when you talk to rheumatologists because many rheumatologists don't believe that the pain is real, but I think that you've just seen a demonstration from Dr. Bradley that with respect to psychophysical testing, you can demonstrate measurable differences. He didn't present data that evoked potentials which Jurgen Lorenz has used to demonstrate actual differences in central representation of pain inputs, and then he showed data from Dan Clauw and Rick Gracely's group demonstrating that the central representation of pain by fMRI actually demonstrates the veracity of the patient's complaint to increased pain.

So stimulus detection of patients with fibromyalgia is normal. There is an ultranoxious threshold that is multimodality, so that that is something that we can point to as a mechanism of pain. As I previously said, the central representation of pain confirms the veracity of the subjective pain complaints. And pain cannot be explained by tissue damage. That having been said, pain generators are very common in fibromyalgia and oftentimes

you can improve the overall clinical experience of pain by addressing these pain generators, for example, in patients with rheumatoid arthritis, osteoarthritis, or other types of mechanical problems. Taken together, all of these implicate central factors in fibromyalgia syndrome pain.

Now, Larry presented all the clinical data, and I'd just like to make some comments about how one might get there. Certainly the data that Roland Staud and Don Price and their group have presented as well as data from our own group and Dan Clauw's group suggest that central sensitization, otherwise known as activity-dependent plasticity, may be present in these patients. Certainly it's difficult to prove but that's something that's been suggested. Neuronal plasticity in the spinal cord modifies the performance of the nociceptive pathways, so that one develops an exaggerated or prolonged response to noxious input, called hyperalgesia, and enables normally innocuous inputs to activate nociceptive pathways, called allodynia.

These mechanisms are transcription independent and dependent and the mediators of this spinal central sensitization would include such things as the excitatory amino acids and their receptors, the NMDA receptors, substance P and other neuropeptides, that are acting through their G protein-coupled receptors. And certainly it's known that in models of pain, that there's increased

activity of kinases, such as protein kinase C and many others, that phosphorylate ion channels and receptors and result in neuronal hyperexcitability. So that, at least from animal models, the mechanisms by which this activity-dependent plasticity is modulated are known and some of the types of drugs that may work in this type of process could be predicted from these data.

It's also important to note that there's descending modulation of pain. It's bidirectional, including inhibitory and facilitatory descending control. These pathways that actually modulate the inputs at the dorsal horn are mediated by serotonin and noradrenaline and again this may give us some clues as to why certain drugs may be effective in central pain syndromes and why non-steroidals, for example, are typically not very effective in these syndromes.

Now, it's clear that injury-induced hyperalgesia is dampened by descending pathways, but it's also clear that cortical and subcortical structures can stimulate these facilitatory pathways. Most of the input is integrated at the level of the peri-aqueductal gray and rostral ventral medulla, but the types of inputs that come into these systems would include things like vagal afferents, would include things like inputs from the stress axes, that Dr. Bradley nicely described the influence of

stress on pain perception, certainly their cortical structures, including the anterior singulate gyrus and many others, whose input is integrated at these levels. And it also should be noted that the dynamic plasticity at the level of the rostral ventral medulla is also mediated by NMDA receptors.

Just in pictorial representation, the cerebral cortex influences this descending bidirectional modulatory control through many different mechanisms. Goal-directed behaviors can certainly change the experience of pain. Attention and distraction can change the experience of pain; expectancy, interaction with the limbic system. Subcortical systems would include stress-induced analgesia but also hyperalgesia, and mid-brain and brain stem systems integrate signals from the brain and spinal cord. They're the site of opiate action. They're the principal relays of these chemical signals to the spinal cord which again include norepinephrine and serotonin.

So what are the treatment implications for the concept of central pain? The implications would include such things as the treatments that usually are used for normal musculoskeletal pain do not actually work very well for most patients with fibromyalgia, and that the treatments must address the problem of this altered pain processing in the spinal cord and potentially alter

descending inhibition of pain signals.

Now, I'd like to move on from pain and talk about the non-pain symptoms and the question of whether or not you can attribute these non-pain symptoms to specific mechanisms.

Non-pain symptoms form something that epidemiologists refer to as a distress cluster which is often associated with multifocal chronic pain. Fatigue itself is actually exceptionally difficult to attribute to a specific mechanism, and I think all of us who are rheumatologists, when we think about any of our connective tissue disease patients, recognize this.

The sleep disturbance. I'll talk further about this, but no specific alteration has been described. Certainly the disturbances overlap with other conditions that share this distress cluster of symptoms with fibromyalgia syndrome.

Cognitive dysfunction is present in these patients. There's evidence that cognitive complaints correlate with fMRI differences. I brought this for you, Dr. Turk, to show some data that there are actually differences in the way that patients' brains function under a cognitive load.

Depression and anxiety are certainly present, and I think Larry nicely pointed out that there's a marked

increase in the lifetime prevalence, and it is associated with health care-seeking.

So in terms of fatigue, what does it mean? In general, it means decreased energy, need to rest, sleepiness or unrefreshing sleep, struggle to overcome inactivity. From a physical standpoint, it can mean weakness, limb heaviness or post-exertional malaise which is exceptionally common in these patients. On an emotional side, it could be decreased motivation or interest. From a mental or cognitive side, diminished concentration or memory. Functional, difficulty completing daily tasks.

And you can see by the diversity of what patients actually mean when they say that they're fatigued, that attribution to a specific mechanism really is something beyond what most of us can do. Nevertheless, when one thinks about a reduction in fatigue, you can see how a reduction in the perception of fatigue may actually imply improvement across multiple different biological mechanisms.

Certainly the possible causes of fatigue in fibromyalgia are legion, including the sleep disturbance, depression, anxiety, pain, medications, deconditioning, neurally-mediated hypotension, which may form a subset of some patients, and central mechanisms.

The one thing that I will say is that fatigue

is correlated with many of the other symptoms, and if you actually look at a correlation matrix of fatigue, you can see that the symptom of fatigue is significantly correlated with pain and sleep and actually less so with depression and anxiety, but one can think of it as perhaps a marker for many of these other non-pain symptoms.

In terms of the sleep disturbances in fibromyalgia syndrome, this is probably understudied and hopefully that's something that will be corrected. The alpha-delta sleep disturbance was first reported by Harvey Moldofsky in 1975 and was actually the first biological finding in patients with fibromyalgia. Unfortunately, this alpha-delta sleep abnormality is non-specific. It's certainly not universal and certainly occurs in many other types of illnesses and even in normal patients but not nearly to the extent as seen in fibromyalgia and patients with other syndromes.

It's also been reported that patients with fibromyalgia have reduced slow-wave sleep, that's stage 3-4, or delta sleep. It's also not specific, not universal, and unfortunately no spectral analyses have actually been reported to examine delta power or even alpha power in patients with fibromyalgia syndrome. Sleep medicine has certainly advanced significantly with new techniques towards spectral analysis and hopefully those will be done

in the near future.

The insomnia of fibromyalgia has also been described as psychophysiological insomnia and that's altered sensitivity to extrinsic stimuli. And these are the kinds of things that can actually be measured in a sleep laboratory these days and hopefully will come in the near future.

Now, changing gears to cognitive, I'd like to show this slide, which is always alarming to the audience. Most of us fall about halfway down this cognitive slide, but you can see that in most patients, their peak of cognitive prowess occurs at about 20 and we slip and slide from there down to where we mostly currently are. This occurs across all domains of cognition actually, with the exception of semantic memory, here measured by vocabulary, but that is preserved and perhaps even enhanced and most of us like to think of it as wisdom that makes up for a loss of actual cognitive activity.

This is a study that we did with Denise Park and Jennifer Glass looking at information processing speed, and one can see that the cognitive problems in patients with fibromyalgia are actually not universal but actually selective in that patients with fibromyalgia syndrome, looking at age-matched controls, have their information processing speed preserved, whereas one can see the

predicted reduction in processing speed that one sees in older controls, and in fact, in older controls, it's thought that speed of processing actually explains many of the other elements of cognitive decline.

But when one looks at fibromyalgia patients with demanding tasks, such as working memory tasks, patients with fibromyalgia do not perform similar to age-matched controls and, in fact, perform similar to older controls that are 20 to 30 years older than the fibromyalgia patients and exceptionally carefully matched with respect to education.

Additionally, in other types of memory performance, like long-term memory or free recall, fibromyalgia patients perform like older adults.

Now, when one looks by functional imaging at older versus younger adults, you can see that one of the things that older adults do is that in comparison to younger adults that use primarily one hemisphere of their brain, and I'll just point you to the middle slide because this is somewhat complicated, certainly on the left side, you can see a little bit more utilization in the older adults. You can see this bilaterality in the older adults, suggesting that they're recruiting more areas of their cortex to actually perform certain cognitive tasks, and you can see very clearly the bilaterality in the older adults

compared with the younger adults.

We did a study recently -- this is actually an unpublished study -- looking at patients with fibromyalgia compared with age- and education-matched controls in a working memory task where the subjects were asked to look at a series of consonants for 1 second. And then in this interval, they were asked to put these in alphabetical order; that is, to perform a complex reorganization task, while the screen was blank, and then they were given a prompt and asked to determine whether or not this S was in the proper position with respect to its alphabetical organization. And in this trial, the patients would respond yes because the letter S is in the correct alphabetical position.

This was subtracted from a condition which we called a maintenance condition where we would demonstrate or show the patients letters that were actually already in alphabetical condition and they were just asked to hold those in their memory as a maintenance condition rather than alphabetizing, so that they weren't asked to do a manipulation.

Then what we did was we looked at the difference between the alphabetizing condition and the maintenance condition in the fibromyalgia patients versus the controls, and you can see a couple of interesting

things. I should say that patients with fibromyalgia actually performed equally well on this task. So it wasn't that the task was so hard and that they couldn't do it or that they weren't trying. They performed equally well as the control subjects.

What you can see is that fibromyalgia patients showed this bilaterality, bilateral activation in the middle frontal gyrus while alphabetizing, increased activation in the right superior parietal lobe which is an area that's specialized for processing of spatial location of objects, meaning and storage of items during working memory tasks. They had a midline medial frontal gyrus activation which was associated with eye fields, and they overall showed more activation when alphabetizing than when they were in the maintenance condition. Additionally, there was a region bordering the right inferior frontal gyrus and precentral gyrus in fibromyalgia patients and also the right BA 44 which was homologous to Broca's area in the left hemisphere and an activation of Broca's area 9 thought to be involved in reasoning.

The control subjects actually did not find this task to be more difficult and the normal controls did not show more activation in any part of the brain in the alphabetizing minus maintenance condition. Only a small non-significant region was identified, so that the control

subjects really did not have to work harder to alphabetize compared to the maintenance control, which again identifies the veracity of the patient's complaints, that they're actually feeling that their cognitive abilities have declined compared with what's age-appropriate.

Now, in thinking about depression and anxiety in fibromyalgia, these psychiatric conditions are neither necessary nor sufficient for the diagnosis of fibromyalgia syndrome. As I mentioned a number of times, there's a higher point prevalence than in the general population, and certainly the lifetime prevalence in the tertiary care population is quite high, with a study by Epstein and colleagues noting depression at 68 percent and anxiety disorders at 35 percent. And Larry previously showed his data on health care-seeking associated with psychiatric co-morbidity.

In thinking about how these non-pain symptoms might be linked in a mechanistic way, many of us have focused on the stress response systems, and I'd like to spend a couple of minutes demonstrating some of the mechanisms that may be operative. I certainly don't have time to talk about all the potential mechanisms but I'll just mention a couple.

The quote that "stress is life and life is stress" is something that I think we all recognize and

can't escape, but from a strictly biological sense, stressors are thought of as forces that disturb homeostasis and can include any number of stressors. Now, these are counterbalanced by adaptive forces and these adaptive forces are collectively called the stress response systems and they mediate not only central adaptation because under stress, your brain certainly has to adapt, and peripheral adaptation as well because your body has to respond to these forces.

The stress response systems, I wouldn't think of them as unitary because different stressors activate different responses, as might be expected, but in general, the major players are the hypothalamic-pituitary-adrenal axis and the autonomic nervous system, and these are critical components of the coordinated physiologic response to stress.

Now, the response to stress because of the central and peripheral factors includes physical but also behavioral and psychological symptoms and these domains have been linked to HPA axis and autonomic system abnormalities.

So what is a healthy HPA axis? I'll focus on the HPA axis, because that's what I do, and show you some data on the HPA axis, but I don't want to suggest that this is the only potential mechanism that could be involved in

fibromyalgia syndrome and certainly autonomic nervous system pathways have been implicated as well.

So what's healthy? Healthy is that there's a wide dynamic range and what that means is that there's a circadian variation with a high cortisol in the morning and low cortisol in the evening, a very wide dynamic range. It should be responsive to physiologic and stressful stimuli. We don't like to see putzy responses to stress. We like to see people whose cortisol levels go up in response to stress and that's healthy. It's also sensitive to feedback suppression and one measures that by using dexamethasone, but you can also measure it in the laboratory and we like the HPA axis to be able to shut off after it's been activated. And so what's really a healthy stress response is that it ought to be responsive and it ought to be resilient.

So what happens in patients with fibromyalgia syndrome? I'll just show you a study that we've recently completed and again is unpublished looking at a number of different ways to stress the HPA axis, first using a low-dose physiologic injection of corticotropin-releasing hormone and then coming back with graded doses of dexamethasone. I think we could have taken people and done public speaking three days in a row or all kinds of other things, but we used this as a potential marker for elevated

cortisol and what happens in response to this facsimile of a stressed HPA axis.

First, I'll show you that the resiliency of the HPA axis in fibromyalgia patients isn't quite normal. It doesn't tend to quite get back to what happens in a normal individual.

More interesting is what happens if you keep doing this, if you have these repeated stressors, and what I'd like you to focus on is this green line first which is a healthy control population. This is the morning after. These are salivary cortisol measurements the morning after the CRH stimulation test. They have a fairly normal high cortisol, not quite as high as we'd like it to be, so it's still a little bit suppressed, but you can see a very nice drop in the cortisol in the evening and then on a baseline day when we don't do anything to them, they have this very nice wide dynamic range. If you give them dexamethasone, they're suppressed in the morning but again give you this very low cortisol in the afternoon, and then when you don't do anything to them, they go back up with this very nice wide dynamic range. Again even with .5 micrograms of dexamethasone, they suppress in the morning but again they still have this low evening level.

And I'd ask you to contrast that with the patients with fibromyalgia. They certainly do suppress in

response to the oCRH, but in contradistinction to the patients that are normal, they actually fail to go back to a normal low evening cortisol. And as we get going with the paradigm, you can see that they do give you a little bit of a wide dynamic range on the second day. You hit them with dexamethasone, they suppress, but then they actually reverse their circadian rhythm. And then you start to see an impact on the dynamic range of the HPA axis over time, so that the difference between morning and evening becomes obliterated. And when you hit patients with a half a milligram of dexamethasone, you start to see this rebound or reversal of circadian rhythm.

What this demonstrates is that with repeated facsimiles of stressors, that patients with fibromyalgia syndrome actually don't have the responsiveness and resiliency that one might see in a normal individual and graphically, you can see that on these non-stressed days, that means that the difference between the morning and the evening cortisol becomes blunted and that one can actually see even a reversal of that circadian variation in patients with fibromyalgia syndrome.

Now, I don't have time to talk about similar studies with the autonomic nervous system, but I think that it's been shown by a number of studies that their altered sympathetic and sympathoadrenal dynamic variability,

including a reduced heart rate variability -- so again, there's this lack of this dynamic range that one would expect in a normal individual -- altered stimulus-induced blood flow and altered stimulus-induced release of noradrenaline and even adrenaline in some studies.

So that, there is evidence in fibromyalgia syndrome patients, not only by groups in this country but groups all over the world, that there's an altered dynamic function of the stress response systems. The problem is, is that, it's not always the same in every patient, and I think that you ought to now keep in mind, with respect to biological subsets, that these endocrine systems are much like other endocrine systems that we're more familiar with; that is, for example, thyroid disease. If you have hypothyroidism, you can present with fatigue, but if you have hyperthyroidism, you can present with fatigue and musculoskeletal aches, and in hypothyroidism, you can also present with musculoskeletal aches.

So I think what we need to keep in mind is, as with this neuroendocrine system as well as other neuroendocrine systems, that there's a concept of an allostat and what that means is that there's an optimal operating range and that you can go too low or you can go too high and it's no longer optimal, and that some of the symptoms of patients with alterations in these stress

response systems may actually overlap. And some of the times, for example, a potential dichotomy between chronic fatigue syndrome and fibromyalgia, even though the same system may be involved, the symptom complex may be a little bit different.

There's also the concept that the function of these stress response axes because of their nature can differ under different physical and psychosocial stress. So that, whenever you have an allostat or some kind of a guide that ought to stay centered, the stress on that system changes, depending on the load that's applied to it, and there can be minor load and there can be heavy load, and the function of the allostat may perform as well or not quite as well, depending on the load that's applied to it.

I'd also like to note that there's a very strong drive to maintain the overall hormone levels. So if anybody thinks you can measure a 24-hour urine cortisol and get significant findings, you can't because there's a very strong drive, as you saw in my studies that I presented. If you go really low in the morning, you go higher in the afternoon, so that there's a very strong drive to maintain those levels.

And I should note that current therapies influence the expression of key components of the system. Tricyclic antidepressants and SSRIs, for example, influence

the expression of mineralocorticoid and glucocorticoid receptors in the central nervous system perhaps better than any other treatments that are available, and I should also note that exercise which is an effective therapy in this condition is known to modulate the set point of the allostat.

So what are the implications of all of these comments for drug therapy? Well, I would say that fibromyalgia syndrome, whether it's clinically diagnosed or laboratorially diagnosed, is certainly recognizable. As I said before, this does not exclude the likelihood of subsets of patients with different underlying mechanisms, but when a patient with fibromyalgia syndrome walks into the office in my clinic, I can make the diagnosis reliably, and I think most clinicians can do so or most thoughtful clinicians can do so.

Clinically important improvements in pain are likely to occur in response to treatments that address central mechanisms and reduced pain is likely to improve the health-related quality of life in patients with fibromyalgia. Non-pain symptoms are also important to the health-related quality of life in these patients and influence health care-seeking and utilization.

I should point out that these non-pain symptoms often cluster with central pain and neurobiological

mechanisms actually may be shared as a cause for pain and non-pain symptoms or at least they may co-occur. And clinically-significant improvements in non-pain symptoms are also likely to result in global improvement in patients with fibromyalgia.

I'll conclude there and thank you for your attention. I'm happy to take any questions.

(Applause.)

DR. FIRESTEIN: Thank you very much.

Are there any questions?

DR. GIBOFSKY: Leslie, I was intrigued by your slide earlier showing the mechanisms involved in spinal central sensitization or I think you referred to it as activity-dependent plasticity. I'm wondering, would it follow from that that a sine qua non for any pharmacologic agent to treat fibromyalgia or any of the manifestations of fibromyalgia would have to be some effect on the central nervous system, therefore by extension physiologically an agent being able to cross the blood-brain barrier.

DR. CROFFORD: That's a good question. Certainly many of the agents that we know impact central sensitization, impact some of the modulatory inputs. So we talked about NMDA, for example, and the NK1 receptor antagonist, for example, that might potentially influence things like the effects of excitatory amino acids or

substance P, for example. I would think that those kind of mechanisms or those kinds of agents might have to cross the blood-brain barrier, but I'd certainly want to see data in that regard.

With respect to the other types of agents that we know influence what goes on at the spinal cord, agents that influence the availability of norepinephrine and serotonin certainly do exist and are among those that are the most effective for this condition, which obviously you can't totally draw conclusions from that, but certainly it suggests the possibility that influencing those central factors may be important.

Other types of agents, like non-steroidals, for example, and I think it's been mentioned a number of times that they don't seem to be quite as effective. However, as you know and I know, there's certainly central prostaglandin expression and I don't think it's out of the realm of possibility that certain agents that might affect peripheral mechanisms may have a positive impact, but I doubt that they will be as effective as agents that address some of these particular central mechanisms.

DR. FIRESTEIN: Dr. Abramson?

DR. ABRAMSON: Leslie, the tender points are obviously important for the diagnosis. Is there any data that's been able to validate tender points with regard to

fMRI or other kinds of pain thresholds that distinguishes these areas from other areas?

DR. CROFFORD: My response to that is that there's nothing special about the tender points. I think you saw in Larry's slide that patients with fibromyalgia are tender to control point palpation as well and that the selection of the tender points -- I was not present. I think Larry probably was present in the formulation of these tender points. The thing about them is, is that, they're widespread, so that you have to exhibit hyperalgesia, allodynia in a lot of different body areas to cross the threshold of 11 of 18. A lot of people have strong feelings about whether the tender points are useful or not.

So I think from a historical standpoint, you could probably pick fewer tender points that are above and below the waist and get a similar feeling that this was a patient that exhibited widespread rather than regional allodynia and hyperalgesia, and there's really nothing special about them.

Most of the imaging studies have been done using alternate mechanisms, but obviously it's difficult with an fMRI to get in there and exert pressure. I think Larry has done that with SPECT using tender points, but you get the same thing no matter what you do. Dan Clauw has

done it with pressure on the thumbnail. The Gracely studies were done with a thumbnail smasher, and I've done similar studies with Ken Casey using a thermal probe that give you similar results.

So the answer is they're a very useful tool for identifying patients in the clinic. They're simple. They're reliable. They're validated. There's nothing special about them.

DR. FIRESTEIN: One last question.

DR. STAUD: Leslie, you showed us a lot of data about the abnormalities in the HPA axis in fibromyalgia patients compared to normal controls. Now, this is group data, and I was wondering if you could tell us something about the relationship to individuals, particularly in terms of predicting abnormalities of the HPA axis.

DR. CROFFORD: We've looked at that a lot, Roland, and tried to figure out how we could use clinical data to predict who was going to have the HPA axis abnormalities and we've just failed. We've certainly tried to do cluster analyses and I'm going to ask Dan to help me with some of these data that we have, some older data, to try to look at a clinical symptom profile that would help us to predict which patients are going to exhibit the most severe responses, but we haven't been able to do that.

What you point out is correct, and I'd like to

certainly make that clear to the audience, that there's a spectrum of responsiveness, just like there's a spectrum of every other biological measure that we vary, and when you look at group means, there are going to be some that are going to look more normal and some that are going to look more abnormal, and I certainly would agree with that.

You may be able to use some paradigms that we're working on to actually subset the patients. As Dennis pointed out, there probably are biological subsets and we're continuing to try to develop simple measurement techniques, so that we can actually do subsetting.

DR. FIRESTEIN: Thank you very much, Leslie.

The last talk of this session will be Dr. Clauw talking about Post-ACR Diagnostic Criteria, and then we'll take a short break.

DR. CLAUW: Let me also begin by thanking/acknowledging the people on the FDA. Jim Witter first asked me to come and talk to the agency over three years ago about fibromyalgia because the agency was interested in fibromyalgia and viewed that this is where it should be. More recently, Lee has been a very strong advocate of the whole fibromyalgia construct. This is a secret that most people won't know till August or so, but he and I actually co-edited an issue of Bailliere's, an entire issue, having to do with fibromyalgia. So look at

how far Lee has come.

(Laughter.)

DR. CLAUW: I'm certainly not going to be presumptuous enough to tell this audience how we should in the future define chronic pain conditions, but for purposes of my talk, I just want to make a couple distinctions. These are distinctions that have already been made by both Larry and Leslie about what is different about fibromyalgia than some of the diseases that we as rheumatologists or members of the panel might be more used to seeing. But I think that it's really important to distinguish between peripheral or nociceptive pain syndromes which are primarily due to inflammation or damage in peripheral tissues which are classically quite responsive to both NSAIDs and opioids and where behavioral factors are relatively minor contributors to symptom expression and central or non-nociceptive pain syndromes of which fibromyalgia would perhaps be the poster child.

Again, you've heard a lot about this, but I think that as rheumatologists, the only non-nociceptive pain syndrome that we see is fibromyalgia which is perhaps why we find it so different and so hard to reconcile some of what we think vis-a-vis pain and what should make it better and how these people should act with all the other diseases that we, in fact, take care of and we take care of

quite well.

But fibromyalgia is not the only central pain syndrome. Irritable bowel syndrome, vulvodynia, interstitial cystitis, tension and migraine headaches. There's a whole host of illnesses where the pain is not coming or occurring because of some damage or inflammation in peripheral tissues; it's instead occurring because of some central nervous system process or some process that's leading to disturbances in pain processing.

Of course, with any attempt to make a clean demarcation, there are going to be illnesses or diseases that don't fit nicely into one category or another. An example of this would perhaps be neuropathic pain. Another example would be low back pain where certainly subsets of individuals with low back pain have peripheral causes for their pain and subsets have more central causes for their pain.

But, again, the main reason to point this out is that what I'm going to do when I talk about some of the different outcomes that have been studied in fibromyalgia is in particular point out the outcomes that are different in fibromyalgia, especially with respect to how they relate to other symptoms than they are in peripheral pain syndromes.

One of the advantages I have in giving this

talk is there have been a couple nice meta-analyses that have been done looking at effect sizes of various types of treatments for fibromyalgia. I'll show a couple slides from this study that was done by Rossy and published in Annals of Behavioral Medicine in 1999 that looked at pharmacologic therapy, exercise, and cognitive behavioral therapy and looked at the different domains that theoretically could be improved: symptoms, psychological status and, in italics here, functional status.

What you see here is that for pharmacologic therapies, there are moderate effect sizes for improvements in symptoms and improvements in psychological status, but really poor effect sizes with respect to pharmacologic therapies being able to change functional status in fibromyalgia.

Exercise does about the same with respect to symptoms and psychological status, and even though exercise theoretically is something where we're teaching people how to improve physical function, you reproducibly see again modest effect sizes in functional status when exercise is used as a treatment for fibromyalgia.

Then finally, cognitive-behavioral therapy. Again, moderate effect sizes here for symptoms and psychological status and sort of a low effect size with respect to functional status.

If you look at specific classes of medications, you see here that, by and large, the antidepressants are the most effective class and that they again have moderate effect sizes with respect to symptoms and lesser effects with respect to both psychological status and functional status.

Muscle relaxants. This is a little bit of an aberration because Flexeril, which is really a tricyclic drug, is included in muscle relaxants. So the overwhelming majority of these compounds that are studied under the category of muscle relaxants are in fact cyclobenzaprine which is a tricyclic compound. This is probably why you see that they perform very similarly to what is largely tricyclic compounds in the antidepressant category.

And then finally nonsteroidal anti-inflammatory drugs. Don't be misled by this n of 1 study where one single study did, in fact, lead to a moderate effect size in psychological status. None of us really think NSAIDs make psychological status better and again here you see that NSAIDs don't lead to any improvement, in fact, in this single study led to a worsening, in functional status.

Leslie Arnold did a nice meta-analysis looking only at tricyclic compounds in fibromyalgia and again looking at pooled effect sizes and found that the domain that tricyclics affected most predictably was sleep.

Physician global, pain, fatigue and patient global all were affected in the sort of range that we classically think of as moderate effect sizes.

Here, you see that tenderness was the most difficult domain to improve and this is something that we see over and over again, that tenderness, especially as measured by tender points, is not something that generally gets better in clinical trials of fibromyalgia. There are exceptions to this, but it's not something that is as responsive to therapy as we might hope or think that it should be.

So what I'm going to do is go through and talk about potential outcome measures in fibromyalgia. I'm going to spend the most time focusing on pain and on functional status because those are the domains I think that are perhaps most controversial vis-a-vis the discussion that's going to transpire after the talks today. So I'm going to present a fair amount of data with respect to whether these domains move or not in the setting of fibromyalgia.

When we're talking about pain, there's a whole bunch of different issues. Again, all of you are quite familiar with pain and how it's classically been studied. One of the things that I think has been interesting about this recent movement in those of us who study fibromyalgia

in doing clinical trials in this spectrum is that if I was studying RA or OA, I really wouldn't have much of a choice as to what outcome measure that I chose. If I was studying osteoarthritis, I would be using the WOMAC. If I was studying rheumatoid arthritis, I would be using one of the ACR 20, 50, or 70, but when you study fibromyalgia, basically you have a blank slate. You can do anything that you want to do and then try to justify why it is that you did that.

So I'll talk about some of the things that I think in fact have been fairly innovative in some of the clinical trials that have been done in fibromyalgia just because of the fact that we, if you will, are allowed to innovate because there's basically no one saying that this is how we should or need to study fibromyalgia.

The next couple slides are slides that I stole from Dave Williams in our group, from a talk that he gave about a year or so ago, talking specifically about pain. But I'm just going to show a couple slides showing how different artists have tried to depict the complex symptom that it is that we call pain. Now, I wish I knew the actual artists here, but since I was putting this together on the fly, I didn't actually have a chance to talk to Dave about who the artists are but perhaps some of you know.

This is a picture that most of us in

rheumatology have seen at one time or another looking at the pain associated with gout and showing how sort of the gnawing, grabbing, aching pain that's associated with gout.

Then finally, this is another depiction by an artist of the pain that she was describing in herself. She, in retrospect, is thought to actually have fibromyalgia.

And then contrast this with our visual analog scale. Basically, we ask people in clinical trials to put an X on the line and say that they have pain somewhere between no pain and as bad as it could possibly be.

Now, some of the problems with visual analog scales and with current measures of pain measurement. With respect to the VAS in particular, it isn't a very good measure with respect to the dynamics of measurement in that when someone moves from 3 centimeters to 1 centimeter on a visual analog scale, that isn't the same as someone moving from 10 centimeters to 8 centimeters. So there's a number of issues with respect to the different areas of a visual analog scale are used differently by different people. So there are scaling problems with visual analog scales.

Another problem with the VAS is that it only captures a single dimension of the pain experience, and multidimensional measures, like the McGill, are certainly richer with respect to looking qualitatively at the

differences both in different types of pain as well as the differences in how different types of treatments might lead to a differential qualitative response with respect to pain.

I'm not going to talk a great deal about these two issues. I am going to allude, though, to this issue of the problems with retrospective report of a symptom because some of the data that happens to have been collected in the setting of fibromyalgia with respect to pain measurement is, in fact, relevant to anyone that's studying pain vis-a-vis problems with paper and pencil diaries and perhaps improvements that could be made by looking at electronic assessments of diaries.

And then finally some of the other problems with the current measurements of pain is that they miss other important domains that might be at least as important as the actual intensity of the pain.

This is a scale that although it certainly has not been well enough validated to be used in a trial for registration of a drug, it's an instrument that Rick Gracely took about 15 or 20 years to develop that has verbal anchors where basically individuals, both patient groups and control groups, were given these verbs in a mixed-up version and told to rate these verbs with respect to the intensity. And this, with all the work that's been

done on it, now turns out to be actually a fairly linear scale in contrast to a VAS and such that a movement in 4 points from 20 to 16 is the same as a movement in 4 points from 4 to 0. Again, this is of interest, I think, and something that we all perhaps could aspire to and begin using in pain trials but isn't nearly well enough validated to be used in trials that the FDA may be looking at.

Another issue that was particularly brought home by an article published by Arthur Stone and his group last year in the British Medical Journal was the poor compliance that typically occurs with paper and pencil diaries. I think most of you are probably aware of this study, but for those of you who aren't, you should be. This is a study where Stone and his colleagues took a group of chronic pain patients over 21 days. Unbeknownst to these individuals, there was a microchip embedded in their paper diaries, such that the investigators could tell when these diaries were opened and closed. They asked people to recount their pain in a classic sort of paper and pencil diary way that we all are familiar with, and when they looked backwards at compliance rates, even though individuals said that they were compliant, 89 percent of their entries, even when you gave people a 30-minute window vis-a-vis compliance, the actual compliance rate was only 11 percent. That is, only 11 percent of the entries could

have occurred within 30 minutes of when the patients said they occurred because the only time they could occur is if someone had their diary open.

The scary thing about this study was -- all of us who do randomized clinical trials know about backward filling. We all see people that come into our office and are sitting in the exam room and filling in the last week of their diary while they're in the exam room, and although that has some problems, at least they theoretically are recalling their pain and trying to retrospectively sort of integrate their pain and that's what they're recording.

One of the things, though, about this study was that a surprising number of people forward filled their diaries. A surprising number of people filled their diaries in, they closed the diary Tuesday, it wasn't opened until the investigators opened it on Friday, and yet they had recordings in for Wednesday, Thursday, and Friday. So the forward filling, as well as a number of other issues, really raise serious questions with respect to the validity of paper and pencil diaries and to the validity of the data that are captured with paper and pencil diaries.

Because of this, our group has been interested in looking at what Stone and his colleagues have termed ecological momentary assessments. Again, there's a number of people that have been doing work in this field for an

awful long time. This is just sort of the last iteration of this work. This is one such device. There are a number of different devices on the market and a number of different companies in fact that are marketing devices looking at the real-time collection of systems. This happens to be a palm-based device that randomly prompts individuals as many times a day as you figure that you can bother people to enter whatever symptom it is that you want them to enter. In this case, we were looking at pain randomly prompted five times a day over the course of first a non-interventional trial and then more recently an interventional study.

This was alluded to earlier vis-a-vis some work that Alex Zautra did showing that the levels of stress in fibromyalgia subjects lead to differences in their pain report. Every-day stress leads to differences in their pain report. This might be what we're seeing here. You can't see these yellow lines very well, and I apologize for that, but you see the tremendous variability in this one day, for example, someone who went from a 0 to a 9 over the course of a single day with respect to a VAS rating of their pain score. This variability in fact was very common in the fibromyalgia subjects, this tremendous variability from hour to hour that occurred when we prompted people five times a day to record their pain.

One of the other things that was interesting and now this -- these are data from Cypress' phase II study of milnacipran. I'm not going to present the results of the data. All I'm going to present are the data looking at the differences between different measures of pain, whether you're looking at a diary that's filled out or a visual analog scale that's filled out in a clinic versus an electronic diary versus a paper and pencil diary.

There were a couple things that we saw both in this study as well as in a smaller non-interventional study that we had done at Georgetown using the same palm-based recordings of pain, and that is, that the random prompt recordings of pain were much lower than the clinical reportings of pain that occurred at the exact same time. So you see here that as you move from random prompt where we averaged 50 random prompts to get this average of 11.9 to daily ratings of pain where there were 14 that were given over a 2-week period to weekly ratings to weekly paper ratings, you see here a large difference in the baseline ratings of pain of individuals when that pain is recorded in an EMA type of momentary way versus in a clinical sample here, again the way that we typically record pain.

Now, if that was consistent throughout the clinical trial, that wouldn't cause any problems. So if

there was always this 4-point difference between the random prompts and the weekly paper recordings of pain, then that theoretically wouldn't cause a problem. All the measures would just be elevated in the weekly paper ratings.

But that isn't in fact what was found in the Cypress study. What was found is that the difference at the baseline was the 4-unit difference that I showed you, whereas the difference at the end of the trial was 2 units. So what happened is there seems to be something different about psychologically or perhaps there's demand characteristics on the subjects when they're entering a clinical trial, but there's a larger offset here between the random prompts and the clinic visit here rating of pain of 4 units -- now, this is on a 0 to 20 scale, not a 0 to 10 scale, just so you all are oriented -- than there is at the end of the study where this difference between the random prompts and the clinic samples average was 2 units.

Now, that 2-unit difference between the beginning and the end of the trial would normally be considered to be something that we would wrap under the umbrella of a placebo response, but it's not a placebo response. It's a measurement artifact. It's an artifact of the fact that we classically have measured pain using these paper and pencil instruments that at least theoretically have a lot of inherent biases with respect to

recall, with respect to demand characteristics, with respect to other things that influence how people report pain. And this is just showing you here how this difference occurred over the course of the trial.

So to summarize here, the random prompt pain is extremely variable in fibromyalgia. We haven't yet done studies to show that it's more variable in fibromyalgia or other central pain syndromes than it is in a peripheral nociceptive pain syndrome, but I think that that would be the most logical hypothesis, that if someone has nociceptive pain that is occurring because of activation of a nociceptor, that that pain might be more constant and more consistent from hour to hour and day to day and week to week than central pain because there's so many things that influence central pain, i.e., day-to-day stress or hour-to-hour stress that people are experiencing.

Interestingly enough -- and again, I'm not going to present all this data -- despite this difference that I've shown you which is quite interesting and intriguing, it didn't really make a huge difference in the Cypress trial. All of the measures in fact tended to be equally responsive to change, although there are issues, I think, with the validity of paper and pencil diaries vis-a-vis the Stone work and some of the other work that's been published. It didn't seem to make a big difference with

respect to responsiveness to change whether we were collecting these outcomes electronically in random prompts or whether we were collecting them with paper and pencil and looking at people's recall of information.

Now, with respect to functional status, I'm going to make a distinction between what people are reporting vis-a-vis functional status in fibromyalgia and what really is going on vis-a-vis functional status in fibromyalgia because what I hope to convince you of is, again, this is an area that is inherently different in fibromyalgia than it is in nociceptive pain syndromes, where there is more than just a decrease in activity and the sort of classic dysfunction that we think of, for example, in OA of the knee, going on in the average person that has fibromyalgia.

So the first thing I'll talk about is something that was alluded to by both Leslie and Larry, and this is something that Larry is largely responsible for. He was giving Doug Drossman a lot of credit for doing this in IBS, but his group was the one and it still is the one that's really been the leader in doing this in fibromyalgia, showing that people who we recruit in tertiary care samples are different than people who are in primary care samples who are different than people who are in the general population. And that is, the tertiary care samples have

higher levels of distress, higher levels of cognitive factors, higher levels of psychiatric co-morbidities, and higher levels of other sort of psychological factors.

Now, the problem with all the stuff on the right side of the screen here is that this leads to dysfunction and this, in particular, leads to self-report of dysfunction. Yet these things are not very amenable to pharmacologic therapies. These are the things that cognitive-behavioral therapy really tries to target and tries to impact on because when someone gets to the point that they have one or more of these psychological, behavioral, cognitive factors that are driving symptom expression, that are driving self-report of symptoms, just giving them a drug isn't necessarily going to make that better.

And so another way of depicting this -- this is another slide that I borrowed from Leslie in this case of this poor little mouse here in an inner tube -- is that some combination of stress plus bad genes plus environment leads to symptom expression in fibromyalgia.

Those of us who were trained as internists and rheumatologists have a tendency to focus on symptoms and there's nothing wrong in particular with focusing on symptoms, but over the last 8 or 10 years, as I've worked closely with psychologists and psychiatrists, psychologists

and psychiatrists in fact focus on different things than we focus on. They focus on psychological and behavioral consequences of symptoms, things like decreased activity, like poor sleep, like increased distress and maladaptive illness behaviors, and the reason they focus on that is they know these all make symptoms worse.

The reason I show this slide is again to look at the interaction between symptoms and function in fibromyalgia and realize that there isn't a direct relationship here between symptoms and decreased function. I draw the arrows, but there's not a direct relationship. You could imagine a scenario where someone with fibromyalgia who's had it for 10 years, is on disability for fibromyalgia, if and when we ever develop the magical drug that makes symptoms better in fibromyalgia, they could take that drug and nothing would change vis-a-vis these types of factors because fibromyalgia has essentially become a way of a life. What's happened to this person with fibromyalgia is their pain, their fatigue, has led to isolation, has led to limitations in their day-to-day activity, and just because they take a drug that makes them feel better doesn't mean that they're dramatically then going to have an improvement in functional status.

Now, if you look at functional status in fibromyalgia, there's a couple outcome measures that you

can theoretically use and that would be primarily the Fibromyalgia Impact Questionnaire. The Fibromyalgia Impact Questionnaire has a unique distinction of being the best outcome measure of functional status in fibromyalgia and the worst outcome measure of fibromyalgia functional status because it's the only disease-specific outcome measure in fibromyalgia.

Some of the reasons that many of us are not enamored with the Fibromyalgia Impact Questionnaire are that some of the questions that it asks are fairly gender-specific, and I might get in trouble by saying that because many women don't even do these things any more like wash dishes by hand. So these are perhaps things that might have been relevant 20 years ago when this outcome measure was developed, but they're perhaps not very germane right now. In fact everyone that's used the FIQ has noted the problem with missing items in the FIQ. People just won't fill out some of these items, like wash dishes by hand, prepare meals, or vacuum a rug, because they don't happen to apply to that particular individual.

Another problem with the FIQ is it was meant as a multidimensional measure, not a pure functional status measure. So when it measures function, it in fact looks at domains like anxiety and depression as symptoms of dysfunction. So it's a measure that is somewhat

contaminated. It's not a pure functional status measure. It's a measure that's contaminated by, if you will, psychological factors, like anxiety and depression, which arguably should be measured independently by a scale that purely is measuring depression and anxiety rather than by an aggregate scale that includes in fact all of those different measures.

Having said that, the FIQ is fairly responsive to change in many studies that have been done in fibromyalgia, but one particular problem with the FIQ is this floor effect. These are data from the Cypress study just to illustrate real data rather than just tell you something, and this is at the end of the Cypress study. The number of individuals here in the bar graphs, the frequency of scores on the FIQ, and you see that at the end of this study, there were 16 individuals who had 0's on the Fibromyalgia Impact Questionnaire and a substantial number of individuals who had very low scores on the Fibromyalgia Impact Questionnaire.

Again, the problem with the Fibromyalgia Impact Questionnaire is that it was developed by Rob Bennett for use in tertiary care of fibromyalgia which is what he was seeing. It doesn't actually perform nearly as well when you start to do a randomized clinical trial and you aim for looking at primary care patients with fibromyalgia because

a number of individuals will have either pre-treatment measures or, in particular, post-treatment measures that are at the end of this continuum. They're basically unmeasurable because of the floor effect.

This shows the physical component summary score of the SF-36. I indicate here just so you don't get confused that the higher number is higher function in the SF-36, whereas lower number is higher function in the FIQ. You see here that there isn't really a floor effect with the SF-36. The problem, though, with the SF-36 and the PCS score is that it's a generic health status measure and thus it's not nearly as responsive to change as the FIQ is.

The other measures of functional status that could theoretically be used in a study of fibromyalgia would include the Health Assessment Questionnaire or the Modified Health Assessment Questionnaire or an instrument that Fred Wolfe published about three or four years ago which are some of the items of the MHAQ which he called the Fibromyalgia HAQ. The problem is that no one has ever used either of these in a randomized, controlled trial of fibromyalgia. So there's absolutely no data on the MHAQ or this new measure that Fred developed with respect to using it in a randomized clinical trial.

I want to just talk briefly. You probably wouldn't imagine that I would come and talk to an FDA panel

on drugs, about cognitive-behavioral therapy and exercise, but I'm just going to briefly present the results of this study that were published in JAMA a couple months ago because I think it's very illustrative with respect to this dichotomy between function and symptoms and this spectrum of illness.

This study happened to have been done in returning Gulf War veterans, and for those of you who don't know the whole story of Gulf War Illness, Larry alluded earlier to the fact that multiple different names have been used to describe the spectrum of illness that we now call fibromyalgia. Things like shell shock and DeCosta syndrome, in fact, were terms that were used after World War I and World War II to describe the returning veterans from those conflicts who had chronic pain and chronic fatigue and other symptoms that we might in the year 2003 call fibromyalgia or chronic fatigue syndrome.

As we should have perhaps expected after the first Gulf War, a number of veterans returned with otherwise unexplained pain, fatigue, memory problems, and this constellation of symptoms that Leslie and Larry both talked about.

A number of different studies have been done looking at this constellation of symptoms and syndromes, and they've all concluded the same thing, that there's no

unique cluster of illness or syndrome that occurred in returning Gulf War veterans, that the cluster of symptoms that occurs in returning Gulf War veterans can also be found in the general population and the general population goes by names such as fibromyalgia, chronic fatigue syndrome, or somatoform disorders.

The other thing that these studies have found is that in fact after every war the U.S. has ever been involved in, there have been a subset of veterans who have returned with these symptoms and these complaints.

Then finally, with the exception of a single study suggesting that perhaps vaccines given right at the time of deployment might lead to a higher rate of this spectrum of illness in deployed Gulf War veterans. All of the other studies that have been done, now about $240 million worth of work that's been done in the United States, have all suggested that no single environmental exposure that occurred in the theater of operations in the first Gulf War could have been responsible for the symptoms that the returning Gulf War veterans returned with.

So the CDC late in the 1990s did this series of population-based studies, a couple of which Leslie alluded to, and coined the term chronic multi-symptom illness to describe this constellation of pain, fatigue, memory problems, that sometimes also includes mood disturbances,

but in fact affects about 10 to 15 percent of the population in the U.S. and in fact in most other developed countries that it's been looked at.

This is what makes up this umbrella of chronic multi-symptom illnesses. This includes diagnoses like fibromyalgia, multiple chemical sensitivity, chronic fatigue syndrome, somatoform disorders, and what I've euphemistically referred to here as exposure syndromes. The only way you can get Gulf War Illness is to have been deployed to the Gulf War. You can't get Gulf War Illness if you didn't go to the Gulf War, yet the symptoms that people experienced that came back from the Gulf War are exactly the same as the symptoms of those who have fibromyalgia or chronic fatigue syndrome.

I put silicone breast implants here just to make a point. Again, most of us in the rheumatology field know the story of silicone breast implants. This was an example where there was a false attribution between symptoms and exposure. People thought that there were symptoms of chronic pain and chronic fatigue and memory problems and the like that were, in fact, associated with silicone breast implants because there in fact were a lot of women in the country in the early 1990s who had both those symptoms and had silicone breast implants. But when the 14 or 15 different population-based studies that were

done looking at whether there was a true association between breast implants and those symptoms, by and large, they found that there was in fact no association, that those symptoms in fact were very common in middle-aged women and because there were two million women in the country that had breast implants, we would expect that 200,000 to 300,000 of those women would have symptoms of chronic pain and chronic fatigue, even if there was no causal association between breast implants and those symptoms.

So for this large study that was done in the VA Cooperative Trial Network that was specifically aimed at improving function in returning Gulf War veterans, we used the operational definition for chronic multi-symptom illness. We required that people have two of three of the following symptoms: pain, fatigue, and memory or mood difficulties. These had to begin at or after deployment and still be present in the late 1990s when the study was begun. I'm not going to go into all the details, but basically people were randomized to receive either cognitive-behavioral therapy alone, exercise alone, cognitive-behavioral therapy plus exercise, and all four groups got usual and customary care. Both exercise and CBT were given in group session, not in individual sessions.

The primary outcome measure, this is what's

important here. Those of us who were involved in designing this study thought that the most important thing we could do for our Gulf War veterans was improve their physical function, and because there was no disease-specific outcome measure, we chose the physical component summary scale of the SF-36 as the measure of physical function that should improve. And we required a 7-point improvement in the PCS to be clinically meaningful and that was based on published work by Ware and others suggesting that a 7-point movement in the PCS is both clinically meaningful and does not occur by chance. It exceeds the standard error of that measure if you give it over and over again.

Because these were veterans, the majority of these people were male rather than female, but as it turned out, 55 percent of the people in this trial met criteria for fibromyalgia, 45 percent met criteria for chronic fatigue syndrome. So even though these were primarily males, a substantial portion of them were tender enough and had chronic widespread pain, so they in fact would meet the criteria for fibromyalgia. They also had high rates of disability and high rates of axis 1 mood disorders which, as it turned out, the disability in particular was a big problem with respect to showing less of an effect of treatment than perhaps we otherwise would have.

I think this is really illustrative here.

These are the veterans in this study, the 1,100 veterans who were in this study. Their PCS score on the SF-36 was 33.7 which is almost 2 standard deviations below the population mean, and another study that was done by Lew Kazis that's not published yet looking at fibromyalgia in VA hospitals suggests that the average PCS score of veterans with the diagnosis of fibromyalgia is 28.7, more than 2 standard deviations below the population mean which is 50. You see here again, fibromyalgia or Gulf War Illness would be significantly lower on these functional status measures than these illnesses that we might intuitively think would be lower with respect to the burden that we know occurs in these illnesses.

This study was fairly disappointing with respect to the results, even though we targeted this cognitive-behavioral therapy specifically to improve physical function. We only showed a modest ability for the CBT to do that. 18.4 percent of the people who received cognitive-behavioral therapy or cognitive-behavioral therapy plus exercise had this 7-point improvement in their PCS score, whereas 11 percent of the veterans who had usual and customary care had this level of improvement.

Exercise alone led to symptomatic improvement in multiple domains of symptoms and there was no synergistic effect between exercise and CBT, which is

something again that was both disappointing and a little bit surprising.

But these are the data that are perhaps of most interest to this group. When we looked at the correlation between changes in symptoms and changes in function in this study that was specifically done to improve function, we found very modest correlations between the improvements in PCS score over this 12-month period and improvements in pain, improvements in fatigue, or improvements in cognitive dysfunction. Our values of .3 to .4 which would lead us to think that the percentage of the variants in physical function that could be explained by improvement in symptoms was perhaps 10 to 15 percent, that is, the r squared values.

Contrast this with the best review that I could find looking at the comparable data for osteoarthritis of the knee, where in osteoarthritis of the knee, the correlations between the different subscales of the WOMAC range in the .7 to .8 range which means that perhaps 50 or 60 percent of the variance in function can be predicted by improvement in symptoms in osteoarthritis of the knee and again the huge disparity between something like OA and something like fibromyalgia or chronic multi-symptom illnesses where there's just not nearly as big of a link between symptoms and function.

I'm not going to go through the conclusions.

So let me just try to explain why this might be. Because of this huge difference in self-report of physical function in individuals with fibromyalgia, our group and others have been very interested in trying to help sort of understand or explain why that might be occurring. One of the ways that you can try to get at this is to actually look at objective measures of activity, looking at things like activity monitors, and actually try to look at how these relate to self-report of physical function.

Actigraphy is actually very well validated as a surrogate measure of physical activity in that if you put people, for example, on a treadmill, you have an actigraph connected to them, you'll find that there's a quite linear relationship between what the actigraph shows and how many mats they're exercising on on the treadmill. This actually has been extrapolated to a number of different domains, and again actigraphy is fairly well accepted now as being a surrogate measure of activity per se. In fact, in the rheumatology literature in RA, there are modest correlations between activity as measured by activity monitoring and changes in the MHAQ over time in individuals in clinical trials of rheumatoid arthritis.

This happens to be the Actiwatch that we use.

There's a whole bunch of different ones on the market. One of the advantages of this is that you can actually not only collect activity, but people can actually enter their symptoms as well as activities. So at various times throughout the day, as we've been known to do and being annoying with our subjects, is these things beep and we ask them four or five times a day to record their pain, record their fatigue, record their levels of stress, to determine if those actually are related to activity or other measures in people with fibromyalgia.

This is an example of what an actigraph looks like. People fill out a diary. You can see here that the activity goes up when they're doing things like running. It goes down when they're doing things like sleeping. Although actigraphy has actually been used as sort of a surrogate measure of sleep efficiency because if people are thrashing around a lot during sleep, they're not getting as good a sleep as they are if they happen to, in fact, be resting. But again, an average look at what actigraphy will show you.

In this particular study, we had 30 people with fibromyalgia and 29 controls. The controls were specifically selected to be sedentary controls, not active exercising controls, and we were interested over this 5-day period not only what the activity levels were but how

activity related to symptoms in people with fibromyalgia.

Now, for any of the fibromyalgia skeptics that might be hiding in the room here, I'm not going to leave this slide up very long because this slide by itself will lead people to think that fibromyalgia isn't really real.

There was no difference at all between the patients in controls in either daytime activity or nighttime activity as measured by actigraphy, even though there was a 20-point difference in the physical component summary score in the people with fibromyalgia. So 2 standard deviations lower with respect to self-report activity, yet no difference whatsoever with respect to the mean activity levels in people with fibromyalgia.

However, what we did find is there were large differences in the peak activity levels in people with fibromyalgia. You see here the difference between the peak activity levels as well as the standard deviation or the variability of activity. What we basically found in people with fibromyalgia is they couldn't raise their activity. They couldn't meet different types of sort of daily demands. So what you find in fibromyalgia patients is that they didn't have the ability to go to these higher levels of peak activity that the normal controls did and you see this here depicted. Although they were very similar in the morning when they woke up, at midmorning, at afternoon, and

at evening, you see the much higher peak activity levels in the controls than you see here in the fibromyalgia subjects.

This is just actograms of the two different groups, a representative fibromyalgia patient and a representative control. You see in the control, all these high peaks where people can basically raise their activity, and you see in certain days in the fibromyalgia patients, there are certain hours where basically they have to be sedentary. And we would find fibromyalgia patients that for days at a time, they would basically be fairly sedentary, then they would do a little bit the next day and then have several days afterwards, again leading to equal means or averages between the groups but markedly different peaks between the two groups.

The other fascinating thing with respect to this study is that we didn't find any relationship between either peak or average ratings of pain, fatigue, or stress in the patient groups. So the level of symptoms they were having on that particular day did not correlate with what they did on that particular day, but we didn't find that in the control groups either, and the same held true for the fact that there was no relationship in either the patient or the control groups between self-report function, in this case as measured by the SF-36, and between objective

measures of activity in either patients or controls.

So I think what this study is telling us is a couple of things. One is that what seems to be most abnormal in people with fibromyalgia is sort of the ability to respond to demands of day-to-day life, not necessarily that they can't do sort of certain things from a day-to-day basis, and also that we have to really wonder what measures like the SF-36 and other functional status measures really are measuring if they're not measuring activity. What is it that we're capturing in these self-report questionnaires, if it's not actual objective activity that it is that we're capturing?

So to conclude, fibromyalgia patients rate their function as being very low. This domain has been very difficult to improve in clinical trials, even using behavioral interventions that are specifically designed to improve function. I happen to agree with what Larry said. I think that when we give cognitive-behavioral therapy in the setting of adequate pharmacologic therapy, cognitive-behavioral therapy will work a lot better, but that's a hypothesis that needs to be tested. And the dysfunction in fibromyalgia, perhaps most important to this group, is fundamentally different than dysfunction in other rheumatic diseases in that there's not as linear a relationship between symptoms and dysfunction in fibromyalgia as there

is in other rheumatic diseases.

I'm just going to talk briefly about some of the other outcome measures that have been considered in fibromyalgia. Patient global improvement --

DR. FIRESTEIN: Dr. Clauw?

DR. CLAUW: Yes?

DR. FIRESTEIN: Can you wrap up in just a couple minutes?

DR. CLAUW: Yes. Patient global improvement has been considered. It is a very valid measure but only a couple recent studies have actually looked at patient global as an outcome measure.

Fatigue. Again, this has been looked at over and over again. There are multidimensional assessments of fatigue that have been used. There are plain old visual analog scales that have been used, and I happen to agree with Fred Wolfe who has actually looked at this in depth, that the multidimensional measures give you more qualitative information about the type of fatigue that people have, but they're not any more responsive to change, that a VAS, a simple VAS is probably the best measure of fatigue to use in a clinical trial.

The same holds true with sleep. One of the things that you should understand about both sleep and cognitive dysfunction is that self-report measures of sleep

do not correlate very well at all with objective measures of sleep and self-report measures of cognitive dysfunction do not correlate very well with objective measures of cognitive dysfunction.

So when you are doing a clinical trial in fibromyalgia, what you probably would ask people if you thought that sleep and cognitive function were important domains is ask the person whether they thought these domains improved rather than trying to move towards looking at objective measures of sleep, like polysomnography or in the case of cognition neuropsychiatric testing, because in fact you don't find strong correlations between those more objective measures and subjective measures, either in fibromyalgia or in healthy normal individuals.

With respect to process measures or surrogate outcome measures, this is probably the only thing that I will say definitively, is that although our group does an awful lot of functional imaging, a lot of evoked pain testing, a lot of measures of autonomic function and hypothalamic-pituitary-adrenal function, none of these is ready for a clinical trial. None of these is ready to be used as a primary outcome measure in a randomized clinical trial because none of them are robust enough and the ones that we can get to change in highly-experimental settings, like in a GCRC, can't really be extrapolated to be used in

a large multicenter clinical trial.

So the last slide I have here is basically -- I think this is actually a relatively simple decision because there's only really only a couple answers to what should be the outcome measures in fibromyalgia. Where should we set the bar?

But if we set the bar at one place, we could say this is a legitimate syndrome with a large unmet need just as osteoarthritis or rheumatoid arthritis were 30 years ago, where there are no currently-approved drugs, and what we should do in fibromyalgia is improve pain.

Lynne will tell you in a couple minutes that that's probably what patients want, to improve pain, and as long as we use 2003 standards for randomized clinical trials, that is, we look at minimally clinically important differences, we look at intent-to-treat types of studies, that this might be a reasonable bar for a disease like fibromyalgia. This certainly would be comparable to the recent approvals for IBS drugs and migraine drugs, where improvement in a single domain which was pain in migraine and improvement in a single domain which was patient global in IBS led to approval of drugs in those different domains.

I actually happen to agree, though. I've heard Lee and Jim both say many times that we don't want to make pain better but make the patient worse. So perhaps the

next level at which we could set the bar would be that we show that people have both a clinically meaningful improvement in pain and an improvement in patient global. That would ensure us that the person as a whole is getting better as well as their pain getting better.

And then finally, the highest bar to set would be to require this sort of triple primary endpoint, and instead of improving function in fibromyalgia, because of the fact that we know function is difficult to improve, we perhaps could use an ACR 20 an ACR 50 responder analysis and lead to improvement in many domains.

The last thing I'll say and I'll close here is I think, because I can't talk any more after I get done talking now, is that what I would ask all of you to do is, at the end of the day, when you come up with an outcome measure for fibromyalgia, think of a drug that is an incredibly effective central analgesic but does nothing more than improve pain, and there will be such drugs. There will be drugs that are very good central analgesics, whether they're NMDA receptor blockers or substance P antagonists or whatever, that are very good at treating central pain but don't independently affect fatigue or other domains and just ask yourself two questions.

Number one, would fibromyalgia patients benefit from this drug? And number two, would the outcome measures

that we choose, the bar that we set, allow that drug to be approved?

There's not any such drug that's in the pipeline right now that's been tested, but that drug is likely to come on the scene, and again I think that my own personal view would be that fibromyalgia patients would benefit from that drug if it is safe. And as we think of these sort of multiple domains, we should look at that as sort of the acid test of whether a compound such as that in fact would be able to be approved in the setting of fibromyalgia.

Thank you.

(Applause.)

DR. FIRESTEIN: Thank you.

We have time for one question. This time Dr. Strand really did have a question or a comment.

DR. STRAND: I had a comment about the SF-36 and its use in RCTs and its correlation. Actually in RA, the PCS scores are virtually across all of our recent trials are about 30, 2 standard deviations from the norm, and the correlations proven in both the physical function domain and the PCS scores with the HAQ on the order of .7, .8 and .9, and we see improvements of about 10 points.

I think your definition of an improvement in PCS score of 7 was a bit high because most of the data we

have now from RA and also diabetes, OA, cardiovascular-pulmonary disease, suggests that the domain MCID scores are about 5 to 10, but that PCS being scored from 0 to 50 would be more like 2.5 to 5.

I wonder whether you might have seen a little bit better difference with the 5, the point being again also that physical function domains are positively scored in the PCS and are very low in RA and show a lot of change and that's ostensibly what you were looking for, change in your study with the vets.

DR. FIRESTEIN: Before you answer, Dr. Strand, I've been asked if you can identify yourself and indicate any potential conflicts.

DR. STRAND: I'm sorry. Strand, S-T-R-A-N-D, and I teach at Stanford. I'm a consultant and I'm here on my own.

DR. CLAUW: In answer to that question, we actually looked at different cut points because we were somewhat disappointed with the performance, and it didn't really matter in this particular trial. Using lower cut points wouldn't in this trial have done any better at separating the treatment groups from placebo.

I do agree with what you're saying. In retrospect, perhaps we set the bar a little bit too high with respect to the 7-point PCS score.

DR. FIRESTEIN: One last comment and then we're going to break.

DR. GIBOFSKY: Dr. Clauw, in his introductory remarks, Dr. Witter asked us to think about fibromyalgia either as a symptom or cluster of symptoms or as a complex disease state with varying clinical presentations. You suggest in some of your remarks that there might be a subset of patients for whom we should think of the claim as a way of life, that if the magical drug came on the market that eliminated the symptoms, I think you said we'd still be left with patients who have the disease.

I wonder if you could tease that out a bit more so I can understand a little bit better about how to structure the claim.

DR. CLAUW: Well, just to be clear, I didn't suggest the claim was a way of life. I suggested that in a subset of people with fibromyalgia that have high levels of psychological and behavioral co-morbidities, which most of the data suggests occur as a result of the fibromyalgia rather than they begin with, but even an effective drug -- again, these are sort of the classic tertiary care patients with fibromyalgia that probably make up a fairly small subgroup of the total universe of fibromyalgia patients. But even an effective drug, if administered to these individuals, might not lead to a great deal of improvement

in function because their dysfunction has occurred in large part as a result of the fact that they become isolated, they become depressed. Other things other than the primary symptoms of the fibromyalgia are driving their dysfunction.

Just to be clear, the same subset occurs in OA and RA, it's just not nearly as large a subset. We all have patients of ours with OA or RA that are on disability, that if we give them very effective drugs, we don't see as much of an improvement in their functional status as we might in someone who doesn't have that psychological and behavioral burden, if you will, because again these are people that, in addition to the underlying, in the case of RA, sort of immunobiology rather than neurobiology, just making that better doesn't make the entire person better.

So, hopefully, I clarified an issue or answered your question.

DR. FIRESTEIN: Dr. Anderson, you had one.

DR. ANDERSON: Yes. I just wanted to refer to your slides about effect sizes from meta-analysis and also ask you a question about pain.

There seemed to be quite a large number of trials done and perhaps there's data there that could be used in developing response criteria for fibromyalgia. The measures may be somewhat different but they fall in different clusters and they're similar enough that whoever

did the meta-analysis felt they could create effect sizes for them. So I'd like your comments on that, whether they would be usable for this purpose.

Also, about pain. You said a lot of things about how the VAS is not at all reliable and so forth. However, it has in a lot of contexts been found to be very responsive. And you end up saying for fibromyalgia that a VAS for fatigue was responsive. So maybe simple measures of pain could be useful.

DR. CLAUW: Let me answer the second question first. I think, as you know, there's a big difference between responsive and accurate/valid. The problem, I think, with VAS is not a responsive issue because in fact they're responsive. The issue, especially vis-a-vis diaries and things like that, is whether it's a valid response on the part of the patient or whether that recall bias, that filter that people use when they fill out a diary, when they backward fill or when they forward fill a diary and they try to guess what their pain -- that's more sort of a precision/validity issue than it is a responsiveness issue.

I did say that all of those measures, the electronic measures, the paper and pencil diaries, they all performed about the same with respect to responsiveness in the Cypress trial. So I'm not being critical of any of

these measures with respect to responsiveness. I am being somewhat critical. I think we just have to be circumspect about these measures with respect to sort of their accuracy and their validity.

With respect to your first question, I think that we have very good data that we could use to model something like an ACR 20, if the drug that was going to be used is a tricyclic drug. That ACR 20 might be totally the wrong instrument for a different compound that's acting on a different part of the central nervous system. Tricyclic drugs, for example, are sedating and in fact many of their side effects have to do with the sedating qualities of the tricyclics. A good drug for fibromyalgia might be a drug that is not a good sleep drug, that is an activating drug that improves fatigue and improves other symptoms, but doesn't do anything at all for sleep.

So again, if we had an ACR 20 that included sleep as a domain because we were modeling after tricyclics and because that was the largest effect size, it might not do very well for a compound that might, in fact, be a better compound but just doesn't happen to hit that domain. It doesn't happen to hit the sleep domains.

So I think that's the problem with an ACR 20 type of responder analysis, is it would have to incredible flexibility to capture all the different types of

pharmacologic agents that might be effective in treating subsets of people or subsets of symptoms in fibromyalgia. Maybe there is such an instrument that could be developed, but I guess I wonder whether that in fact is the case.

DR. FIRESTEIN: Before we break, I've been asked if Dr. Strand can disclose for the public record the relevant companies for which she consults, and you have a list. Would you please read the list for the record?

DR. STRAND: I don't have it with me. I will e-mail it to you. Would that be sufficient?

DR. FIRESTEIN: She will be e-mailing it. Okay.

And then for the record, we will no longer take comments from the public in order to avoid getting mired in this problem for the rest of the day.

So in that case, without further ado, we will break for 10 minutes. We'll start again at 11:10.

Thank you.

(Recess.)

DR. FIRESTEIN: Let's go ahead and get started.

So our first presentation of this part of the discussion will be by Lynne Matallana on a patient's perspective.

MS. MATALLANA: Good morning.

First of all, I would like to very much thank

the FDA for inviting me to be a part of this advisory committee. I know that the patients oftentimes have a lot of things that they would like to include in discussions of this sort, and I'm very pleased to be able to be here to represent that group of people.

I also am going to ask your indulgence as I'm going to sit because I don't want to fall over. So if you don't mind. If you can't see me from here, wave and I'll try to kind of move so that you can see me.

In 1993, I had a laparoscopy for endometriosis and woke up during the surgery, and at that point on, I started having very unusual symptoms. I was diagnosed about two years later with lupus and later rediagnosed with fibromyalgia.

In 1997, I started an organization at that time called the National Fibromyalgia Awareness Campaign, and our original intent was just to speak out on behalf of the patients, to let people know that this illness existed and that we needed help.

As time went by and the needs of the patient community as well as the medical community became more and more apparent to us, we became the National Fibromyalgia Association two years ago, and we now publish a national magazine which some of the committee members have in their packets that addresses issues that are very pertinent to

the patient community but also to the medical community, and we were very pleased that this publication has been received so well by the medical professionals.

I feel qualified to represent patients because I talk to thousands of patients every year through Internet, through phone calls, through meetings, and I also am very pleased that I have had the experience of working with many of you and many of the researchers and doctors. We have over 50 doctors who work with us as advisors. So we have quite a bit of input from them to know exactly what is going on in the clinical research area.

I've been asked to speak about the patient's perspective, and what I will be drawing from is obviously my own experiences, my own intuition, the anecdotal information that I have been given by other patients, and a survey.

I, unfortunately, was only appointed to this committee a couple of weeks ago, but I wanted to be able to bring some type of specific information from the patients. So we sent out a survey with about 20 questions to 16,000 fibromyalgia patients. To our surprise, in five days, we had 1,119 responses. Obviously, I was not able to tally all of that, and so we've taken a sample survey response group of about 200 people. So when I give my percentages, you can know that this is a group of about 200 people that

I am referring to.

One of the first things I want to address is the picture that you saw of the woman that looked like she was close to death and extremely miserable because this is something that most people with fibromyalgia feel at one time or another in their life. We do have, obviously, symptoms that wax and wane, but the majority of us go through a time where we are almost completely disabled, myself included. I spent two years in bed and four years at home.

But I feel that there is very much a belief in the patient community that with the right support, with the right medications and treatments and with the understanding that we are not crazy, that this is a true physical entity, that you can improve, and I think that part of the problem has been that many patients have not had the support or the educational information that they need in order to help improve and also have not had the opportunity to try certain medications that may be now in more of the experimental stages. So please keep in mind whenever I'm talking that I am talking about a group of people who are very distressed.

I'd like to answer several questions in my presentation today, the first being: what are the unmet needs of the fibromyalgia community?

One of the first things that we are faced with often is how many people have this illness. I think someone quoted 4 million to 10 million which is quite a deviation, and we do not have any true epidemiological studies that will talk about this issue, relate to this issue, look at geographic considerations, the illness in men versus women, different treatments. Many of you know that fibromyalgia patients react differently to certain treatments and why is that? We obviously have our lumpers and our splitters who look at fibromyalgia with subcategories and we need to look at that more specifically.

The other thing that I think is so important and you will hear constantly from people with fibromyalgia is the level of acceptance of the illness. Acceptance from society which includes their own families and employers and friends to the medical community, obviously having gone to doctors who have told them either there is nothing they can do for you or there is not an illness called fibromyalgia, and then also that feeling of having the plague. Dr. Clauw mentioned the isolation that people with fibromyalgia go through, and I think that this obviously then intensifies the symptoms. So with the acceptance and with the education, we can probably prevent a lot of that isolation.

Another concern is where to go for treatment

because many of the doctors do not believe in this illness and currently rheumatologists tend to be the main caregivers. However, as you know with the multiple symptoms that we have, many patients try to go to neurologists or different types of pain specialists or migraine specialists, gastroenterologists, and to have these groups of people who are very unfamiliar with the illness can be very detrimental. So we're also looking for continuing medical education and especially at the level of the family practice doctor because, as you know, diagnosis of fibromyalgia does usually take anywhere from two to five years. So if we could educate and help doctors in the family practice arena, we could probably cut the duration of time for diagnosis.

Also, it's very exciting to see fibromyalgia be taken so seriously and be moving forward at the federal government level. However, at the state and local level, that does not seem to be the case. We recently, in the state of California, worked to get a bill through that all it did was ask the Department of Health to recognize fibromyalgia and to include it in its list of illnesses that they are concerned about. Not only was the bill not passed but they placed another bill in its place that was approved so that the previous bill on fibromyalgia will not even be in the record. So state and local knowledge and

support of this illness is very much needed as well.

We've talked about diagnosis. As far as I think most patients are concerned, they feel that the tender point exam is a viable technique for diagnosis. We don't see too many people who have been told that they do meet these standards and that we don't feel have fibromyalgia. However, there is the problem with people not believing. So if there was a diagnostic test which was not subjective, it would help us in our plight to make people believe in this illness.

Also more research. Obviously, today the experts have presented so many different questions that need to be answered, and with the limited amount of research funding. The National Fibromyalgia Association is a non-profit organization that kind of squeaks by with the contributions of other patients, but we have so many doctors now coming to us, asking us for funding because they have viable research studies that they want to do, and it's very difficult for us to not be able to have that funding to help them. So funding is definitely a need.

Also, we are very thrilled with the people over the last 20 years who have been a part of the research of fibromyalgia. However, several of these people are starting to retire, and it's exciting when new people are becoming involved, but we'd like to see even more people

that have new ideas and are very much not afraid to look at a possible new paradigm for the causation of this illness.

As I mentioned about the diagnosis of fibromyalgia, a quantifiable test would help us in proving the existence of this illness and also could help cut down on the diagnostic time frame.

We also are interested in looking at some of these subgroups. It's interesting when certain patient organizations get behind a specific type of treatment, such as surgery for Chiari malformation or the use of guaifenesin and some of these other things. It's part of the patient group and yet it's something that needs to have medical evaluation. I know that, for example, on the guaifenesin, that Dr. Robert Bennett has done two tests which clinically prove that there is no treatment help from guaifenesin. However, when we do surveying, we still have a large percent, usually between 4 and 5 percent, of people who have felt that this has been the main product that has helped them in relieving symptoms.

The other thing that I think is important to look at is the onset of fibromyalgia. We have at times thought that it was about 40 percent of people that had onset because of trauma. However, in an anecdotal way of looking at this from talking to fibromyalgia patients, I would say at least 9 out of 10 patients do attribute the

onset of their illness due to some type of physical or emotional trauma, and I do think this could help us in learning how to possibly prevent or understand better what the cause of this illness is.

Also, the role of central sensitivity syndrome. The importance of being able to identify the overlapping conditions is very important because what I feel, although a lot of people would like to have a treatment specifically for their worst symptom, I think that oftentimes patients improve if they start with their easiest-to-treat symptom. So, for example, if they're suffering from migraine headaches and there are medical prescription drugs that help this, that even though that might not be their worst problem, to look at that as a possibility for treatment first and then work up to the more difficult symptoms.

DR. FIRESTEIN: Thank you.

Could you make a concluding remark?

MS. MATALLANA: Okay.

Well, what I have here now is going into the survey outcomes, and I guess what I'll have to do is just kind of give you an overview as far as--

DR. FIRESTEIN: Just a concluding remark, please.

MS. MATALLANA: Okay.

I would agree that pain is the most difficult

symptom and that 68 percent of people with fibromyalgia are interested in finding treatment for pain.

Thank you.

DR. FIRESTEIN: Thank you very much.

(Applause.)

DR. FIRESTEIN: Next, Dr. Wells will talk about outcomes: multi-system impact.

DR. WELLS: Thank you.

Just as some of the previous speakers, I'd like to also commend the committee and the FDA for holding these very timely and important meetings. Also, in terms of full disclosure, I'd like to indicate that I am 53 years old, so you can take Leslie's cognitive age curve and properly place me in that curve to know where I sit.

It's very difficult to speak after a patient and a consumer because they bring a real face to the issue.

I now have to go back and take an epidemiological and statistical perspective on looking at outcomes in this particular area. I'll try to do that as quickly as possible, also hopefully as informative as possible in that process.

I will quickly skip through the first two slides. These are the obligatory slides talking about what fibromyalgia is about, also the ACR criteria.

I will focus a little bit on the second slide,

though, to say that there are two controversies here really. First of all, there's the controversy of whether we're dealing with medicalization of unrelated symptoms, to a syndrome, to a defined disorder. The controversy I want to talk about right now is what is the most appropriate or combination, composite, appropriate outcome measures that we can select to look at this issue.

Now, to do that, I'm going to follow the following road map, and as I said, this is going to be very at times statistical, so I'll quickly go through some of these.

First of all, I want to give you an unsystematic review of the types of outcome measures that are used in fibromyalgia.

Second of all, I want to give you an intuitive feel for why we choose certain measures.

Next, the development and selection of outcomes. I do want to talk about issues, such as reliability, validity, sensitivity, which are very important, and people often confuse the terminology, so we have to be careful there.

We then are going to look at some overall response criteria. How can we go about this?

Next, the minimal clinically-important difference. I'll try to put a little bit different face on

that rather than just giving you the definition but also try to put it in context.

And then finally, something called low disease activity state. Earlier, we heard about ACR 20, 50, and 70. I suggest to you that if you're going to do something, you might as well as leapfrog and just not repeat what someone else has done but think further down the road and think of what the next step is, and I'm going to say to you that the next step is to look at entities called low disease activity states.

First of all, types of outcomes. This is my unsystematic review. I looked at three systematic reviews in the literature. Two of them were in the Cochrane Collaboration Review 2003 and 2002. I also looked at the review by Rossy in the Annals of Behavioral Medicine in 1999 and took a look at some of the outcomes that they viewed. I put them into different constructs, if you wish, and I found eight different areas, and I could add more. I could have added the economics and so on and so forth. But these are the eight.

When I look in pain, I can see everything from visual analog scales to ordinal scales to pain drawings. I also found a very interesting article by Fred Wolfe on looking at regional pain scales where he's trying to take a more quantitative look at this issue.

In tender points, we have the pain threshold and tenderness to thumb pressure.

In physical function, there is a host of different things we can look at. We have self-report of physical pain, the FIQ which Dan talked about, also the fibromyalgia HAQ which is the newer scale that was developed by Fred Wolfe. We also have musculoskeletal performance, various ways of measuring that, cardiorespiratory fitness and various ways of measuring that.

In terms of global well-being, we have the physician-rated things. We also have the overall score of the FIQ.

In terms of self-efficacy, there's the Arthritis Self-Efficacy Questionnaire.

In terms of fatigue and sleep, the FIQ Fatigue Subscale, the sleep VAS.

Psychological function, subscales again of the FIQ for depression and anxiety, but remember what Dan said, it was basically a visual analog scale and it wasn't really potentially tapping into all aspects.

Quality of life and generic functional status, Short Form 36, Sickness Impact Profile, and the HAQ, if you wish to view the HAQ as being more generic in this area.

Just to give you the background to the

Fibromyalgia Impact Questionnaire, it's a brief 10-item questionnaire. It measures a number of physical functions which are up there on the screen. It was developed in 1991 by Bennett. Basically, the questions are were you able to do some of these particular activities, and as was indicated earlier, many of these activities, people would not respond to today in terms of, for example, of washing dishes and so forth. There's also nine other questions. All of a sudden, I noticed it's changed to dots instead of numbers, but anyway, there's nine other questions and some of these questions are very specific, for example, to people who actually work. So you're going to find a lot of missing information. This is one of the reasons why Fred Wolfe in 2000 developed the FHAQ and he compared one to the other because he felt that some of these items would be missing too often for the FIQ to be useful and also some of the items would not be applicable today.

Now, choosing outcomes. Okay. First of all, just generalities. We like objective measurements. We'd like to, if we could, reduce or reverse disease. We'd like to improve quality of life. We'd like to reduce mortality. We'd like to have a good global impression, both in the patient and the physician. We'd like to improve symptomatology, and we'd like biochemical measures, if that was possible.

Now, from the patients, what do the patients want? To live as long as possible. That's your first D, death. To be normally functioning, so getting away from disability. To be free of pain, psychological, physical, social, and other symptoms, discomfort. To be free of problems from treatments, drugs, side effects, and so forth, and to remain solvent, the other D which is destitution, if you have to pay for some of these disorders. This is what the patient wants, just very globally what they would want.

There are other ways of identifying best outcomes, and let me just going to focus for a couple of seconds on what influences the physician's decision. The outcome measurements. This is a study that was actually done by Nick Bellamy in 1998 and 1999, and he asked the question: how often do you serially use the following assessment techniques for longitudinally monitoring the efficacy of antirheumatic drug therapy in your adult fibromyalgia and patient practice? He did Canada and he did Australia. Take a look at this. The quality of the sleep is usually and always of importance. Fatigue, usually and always of importance. The number of tender points, important but not as important, and skinfold thickness, not important at all, relatively speaking.

In Australia, when he did the study the

following year, he didn't include skinfold thickness, just stuck with the other three outcomes, and they all reflected something similar, except maybe a little bit less in terms of being "always" for the Australians.

So let's look at the development and selection of outcomes, and this is where I'll try to go through quickly so that we can save some time.

We have to look at the comprehensiveness or the content validity. We have to know that we've included the proper components of health. We have to look at credibility or face validity. What appears to be sensible and interpretable is there. We have to look at accuracy. Does it reflect the true clinical status of the patient? We have to look at sensitivity to change and also biological sense as a construct validity.

So the three key measurements are reliability, validity, and sensitivity to change, and it would be nice to take all the various outcomes that are around and take a look at their reliability, validity, and sensitivity to change. I'm going to go through a little bit of details on these, just to give you a sense of what each of these involves. The terminology that's used in this area is often not used properly, so we might as well get it correct right now.

Reliability is the reflection of the amount of

error, both random error and systematic, inherent to any measurement. It determines who reproducible the scale is under different conditions.

The reliability coefficient expresses the proportion of the true variation that you would see which is due to the subject's variability and not due to this measurement error. Reliability can either be reproducibility or internal consistency.

We use reproducibility when we want test/retest reliability to look at intra- and inter-rater reliabilities, which is very important for measure, or internal consistency if we have a scale and we want to see how consistent the items are within the scale. Some of the coefficients we can use for reproducibility are the intra-class correlation coefficient, the Pearson's r, we've seen a few of those this morning, Kendall's Index, kappa coefficient, and Bland and Altman plots.

Other considerations. If the test is always done by the same observer or if the test has different observers, then you've got to pay a bit of a price by putting that component in the denominator. So that's important when you're evaluating reliability.

Also, observer nested within the subjects. So if several subjects are being evaluated by several observers, you must take that into consideration. You must

use the right statistical techniques, in this case ANOVA, to do that.

You could have multiple observations on an individual, either because you've got several items on a questionnaire, several observers, a repeated use of an instrument, and again you have to accommodate that in your coefficient.

Internal consistency essentially means that are all the items that you're looking at within the scale agreeing with one another, are they going roughly in the same direction, and you would like to see correlations of that nature. Correlation coefficients could be item total, split-half, Kuder-Richardson, Cronbach's alpha. These are all standard ways of looking at internal consistencies.

We can improve reliability by reducing the error variance through good training, increase the true value by adding items, provided the items add information and just not replicate information.

Validity. The degree of confidence we can place on inferences being made on the scores in the scale.

We have something called content validity, so to cover all the domains of interest. When we look at a particular instrument, we want to ensure that patients and physicians are comfortable that the key components are being covered.

Then we have criterion validity which basically means we have a gold standard, a criterion which we can compare things to.

We also have construct validity. Construct validity is there's no gold standard but we're looking for circumstantial information, if you wish, and we look for situations where the instrument that we're looking at should correlate with other methods and does it, or divergent, whether the instrument we're looking at should not agree with something and it doesn't.

So we have criterion validity where you have a gold standard, and we have construct validity where you base everything on circumstantial evidence. These two concepts are constantly misinterpreted.

There's other more sophisticated ways of looking at construct validity through factorial analysis and multi-trait/multi-method analysis, and I won't go there.

To evaluate validity, we do it with correlations. We do it with receiver operator curves, and we can do it with using 2x2 tables on sensitivities and specificities.

Sensitivity to change. So this is the third. We've gone through liability. We've gone through validity. Now sensitivity to change. What is the ability of an

instrument to detect small but clinically important differences? That's what we're after. We can use three types. There's many types of measures. We could just simply do a t-test that compares baseline to follow-up to see if things have changed. We can use an effect size which is basically the difference of the mean and the follow-up at baseline to the standard deviation, or we can use an ROC curve. So there are different ways of looking at sensitivity to change.

I'm going to take the FIQ just to go through an exercise. It's the one that's been around since 1991 and you can see maybe some of these reliabilities, validities, and responsiveness to change in action. When they developed this instrument and published it, they said they had test/retest reliability because they looked at Pearson r correlations, and on repeated measurements between raters, they got between a .56 and a .95 Pearson relationship.

Content validity. They assessed the percent missing data, and this is really a concern because 11 percent did not answer the washing by hand, 20 percent did not answer the yard work, and 38 percent did not have jobs or did not work outside the house, and so those questions could not be answered as well.

They looked at construct validity by comparing

it to the AIMS in different items and scales, such as physical functioning, pain, depression, anxiety, and the values were not too bad. They also did a correlational analysis by looking at specific measures of the AIMS Impact Analog and Syndrome Activity and Tender Points and found for the various items some very, very low correlations and in other cases high, so it was quite a range, and they did a factor analysis which also proved to be not too bad.

They looked at responsiveness to perceived clinical outcome. It was done in a paper published in the Journal of Rheumatology in 2000. You can see that as an individual patient perceived, they went from improved to unchanged or worse. The FIQ did go in the right order as they indeed got worse, as the patient perceived they were getting worse. But Fred Wolfe, when he talked about the FHAQ, did note that the FIQ systematically underestimates the functional impairment because it doesn't handle activities not usually performed by the patients filling the form out.

6-minute walk in 2000. It was found when they looked at the 6-minute walk in the group who were before and after exercise, that they did find a statistical change in the 6-minute walk. They didn't find that the 6-minute walk was highly correlated with PVO2, so it wasn't doing a very good job as a valid predictor of cardiorespiratory

fitness. They did find, though, that it was highly related to the FIQ. So the 6-minute walk had some nice properties but it didn't really pick up on the cardiovascular, although it was responsive to change.

I won't go through this generic versus specific. I'll skip that.

Overall response criteria. So now we have a set of outcomes, outcomes that may be reliable, outcomes that may be valid, and outcomes that may be sensitive. And the question now as we're dealing with something that's multidimensional: is there some way that we can bring them together into a response or an improvement criteria? I'm going to give you the five steps. Again, those dots really aren't dots, they're numbers.

The first dot is number 1, where you would look at the outcome measures and you would look at all the various outcome measures that are used in the area that the patients, the physicians, and other stakeholders are interested in. You would look at the reliabilities, the sensitivities, and the validity issues. I quoted some papers there, but there are a lot of other papers that have been published over the last 10 to 12 years on some of these measures and some of those properties.

You would then conduct a survey of physicians. You would provide them with information on randomly

selected patients from clinical trials and the thresholds of what you think would be improvement. So basically you would take for outcome measures of interest, you would take data at the baseline. You'd take data at the end of the study. You'd take percent change provided for each patient. You would survey the clinicians and having them indicate whether they felt the patient was improved on the basis of the profile that you provided them with on the core outcomes that you're interested in, and then the analysis would then focus on the patients characterized by the vast majority as having improved.

Once you did that, you would do a statistical analysis of the clinical trial data for selecting definition of improvement, and this is the point where we would like to assemble appropriate placebo-controlled trials with very efficacious. I put "very" in quotes here. It obviously depends on the particular disorder you're looking at, and that also included the measures you're interested in. So the improvement criteria selected that best discriminates the efficacious intervention from the placebo would be further evaluated. You would evaluate them in large comparative data sets and then, finally, you do have to subject them to kind of that face validity evaluation at the end of the day. So again we take all the core measures that are reliable, sensitive, valid, of

varying degrees, come up with a core set, evaluate them in the data sets, survey the constituencies.

This is an example of one -- and I'm going to go through this very quickly -- that actually Simms and David Felson were involved with in 1991, taking preliminary criteria for response to treatment in fibromyalgia. They did look at a clinical trial where there appeared to be an efficacious difference. They took the treatment to be the proxy measure for response. So everybody in the active treatment was considered to be a responder, everybody in the other was not. They had outcome measures that included physician global, patient global, pain, fatigue, sleep, tender point score. They then used a number of statistical techniques to look at various combinations of outcome variables that they then subjected to receiver operator curve evaluation to find out the optimal sensitivity and specificity. They then applied these to an unreported trial.

Now, what they came out with at that time was a criteria that included physician global assessment was less than or equal to 4. You can see the scale being 0 to 10, from well to poor. Patient sleep, less than or equal to 6. Tender point score less than or equal to 14. The most important point that they made in the paper was that as more sensitive and clinically relevant outcomes are

developed, you can apply this methodology, which is really a working action of what I described in theory a little earlier, to refine the criteria or to develop more criteria.

Minimal clinically important difference. It will be so easy for me to in two sentences tell you what a minimal clinically important difference is and then move on and you'd have no concept any further than that. I'm going to try to put it in a little bit of a context. I'm going to go through this relatively quickly because it's really to the side of the types of issues that we want to deal with.

I'm going to give you minimal clinically important differences in terms of what are called studies of responsiveness. This is going to be a classification system on how we can put studies that look at responsiveness into context. I'm then going to tell you about a systematic review that we did looking at the various methods for minimally clinically important differences. This is very key to, obviously, evaluating various pharmacological and non-pharmacological treatments for this disorder.

Studies of responsiveness essentially are studies that evaluate the ability of an outcome measure to accurately detect change when change has occurred. Each

study defines the change. It can define it according to three key features. Is the change for an individual or is the change within the group? Which data is being compared? Are we interested in data that's within a group, between groups, or looking over time? What kind of change is being quantified, of which one of those changes will be the minimally clinically important difference?

So the setting is who's the focus? Group or individuals? Which scores are being contrasted? Differences between groups, changes within groups, or both, meaning that you're going to be looking at different scores between two different groups, or what kind of change? It goes all the way from minimally potentially detectable to detectable beyond error to observed in the population, something that's estimated to have changed as something that is important and estimated to have changed, and that's your minimal clinically important difference.

These three features all can be put at right angles to one another and then you could have this type of system. So the setting is the individual or the group, what are you looking at, differences between, within, or both, and then the type of change that you're doing.

Now, what's nice about the cube is that we can take a study of responsiveness and we can look in particular at minimal clinically important differences and

see where the holes are in the theory, see what's available to us when we wanted to apply it to such a problem that we're dealing with today. So let's take a look at that survey, and we're going to put it inside the cube.

So an MCID is considered as the smallest change or difference in an outcome measure that is perceived as beneficial and will lead to a change in the patients' management, assuming an absence of excessive side effects and costs, and that would be the two-line definition I would give you if I wasn't going through this process. We wanted to consider the different ways that people try to derive MCIDs and look at the different methods. We did the literature search. We read the articles, in particular the methods sections, and then we categorized it according to the cube, and this is what we ended up with.

On the right-hand side, you can see different types of methods appearing. There will be a little window here that's going to give you a three-step process of how it was done and then it's going to be dropped into these cells and what you're going to find is that most of the methods fall in this area which is basically that they're looking at groups. They're not looking at individuals. They're looking at groups and the changes within those groups to define minimal clinically important differences, whereas we should really try to look within the individual.

The methods may be more sensitive. So I'll just click away and you'll see.

So the first one is looking at patient perspectives, and it actually falls as changes within but within a group.

The next one is patient conversation. Again, it's looking at a group.

Clinical perspectives. We have two more, two different ways of looking at it, both of them comparing groups.

Clinical perspective again, patient scenario, comparing groups.

Patient scenario comparison, two different ways of looking at that but again within groups.

Finally, we get one that looks at the individual which is called a prognostic rating scale, a data-driven approach, discerning important improvement, improvement criteria, and then finally achieving treatment goals.

Again, these are the ways that you do it. These are the different methods that were there.

The bottom line of this whole process is that we do a lot with groups. We do not do enough with individuals, and we need to develop more important measures in that direction. So again, within this area, if we can

develop that within some of these measures as opposed to falling back on old technologies.

Low disease activity state. This is a relatively interesting concept, boring from trying to control hypertension. If we can keep blood pressure within a range that both the physicians and the patients are happy about, then we consider that we're in kind of a steady state. We're not looking at remission or anything like that. We're just saying that I'm happy where the patient is at, the patient is happy where he or she is at, and we feel that we have everything in control.

So we've had workshops on this and to meet many of the challenges that exist in trying to determine what we mean by low disease activity state, we've been concentrating in the area of rheumatoid arthritis, but this is where I'm saying that we should be a little bit more forward thinking and think about this as we're thinking about the responder criteria.

So the working definition is that it is a state that is deemed a useful treatment target by both patients and physicians. That's what our working definition of a low disease activity state would be. At this particular workshop, we obtained a large number of research agenda, all the way from looking at some of the core criteria within the core set for rheumatoid arthritis to including

fatigue and sleep within that criteria, and then the one I have highlighted is to design and conduct an opinion-based and observation approach for determining a low disease activity state for rheumatoid arthritis. So if you wish, this is going beyond the ACR 20. Then we wanted to finally then design and conduct a survey on how we should present this.

So in terms of the design and conduct of an opinion-based system, the steps are as follows. The opinions of the physicians and patients will be collected. Based on these opinions, we'll come up with candidate definitions. They'll be composed and they'll be tested in data sets. The results of this work will be collated and circulated to workshop participants, and at the workshop, we'll sit and we'll argue about it, both in plenary and in small group sessions, and probably come up with a number, hopefully a limited number, of top candidates that can then be validated in the following steps.

And Chair, I think that that's the end of the presentation.

(Applause.)

DR. FIRESTEIN: Are there any questions or comments for Dr. Wells? Yes?

DR. TURK: Thank you for the presentation.

I wondered if you'd care to comment about

norms, which you didn't seem to pay any attention to at all, as a lot of the measures that are available were never developed and standardized in the appropriate populations. Do you have any comment about that?

DR. WELLS: Yes. In particular, if you went with something, such as the -- I mean, if a measure has been properly developed, let's say the SF-36, where it's been normed to the particular population, so you can look at the deviation from the norm, I think a lot of the measures that we look at have not been and should be. I agree.

DR. FIRESTEIN: Thank you very much.

The next section was the open public hearing, but since there were no requests for time, we're then going to move on to Lee Simon who is going to charge us with something.

DR. SIMON: First, I have to get my computer to work. So I hope you'll indulge me for one second.

(Pause.)

DR. SIMON: Well, as it's coming up, I'd like to first thank the committee members for arriving here and bringing this on, as Dr. Witter noted. We are greatly appreciative of you taking your time out of your busy schedule to help inform us at the agency about this incredibly complicated arena.

Secondly, I'd like to take the opportunity as the first one at the end of all these invited speakers to say how grateful we are that you all came under sometimes unusual circumstances to give us your opinion about this particularly controversial area.

As Dan Clauw noted, I come from a different background than typically seen in the context of the fibromyalgia background. Having been at the bench for 15 years, I'm a little driven by evidence and I tried to be able to apply that over the years, and as a clinician, seeing patients for 25 years, always became very frustrated about seeing patients with fibromyalgia.

I think that the world has turned, however, and there seems to be a significant amount of science that is the underpinning of an understanding of what's really going on here. So everyone has mentioned the uniqueness of the moment, and it does appear that there's a bunch of things that are all coming together that allow us to finally begin to deal with this and give it the attention that it truly deserves, considering the number of people that have suffered with this disorder for such a long period of time.

You'll notice that I actually have changed my picture on my desktop. This is now a storm, and I actually kind of feel like I'm in the midst of a storm in my continuing career at the FDA. It's really quite

appropriate and also almost very appropriate for this particular discussion.

So what are the challenges in the development of the therapies for fibromyalgia? You've spent a significant amount of time actually looking at that particular question, and I'd like to point out a couple things historically, in addition to what you've already heard. In fact, however far we've come in understanding and divining the description of disease states and increasing the understanding of the biology of pain, the drugs that are presently available for chronic pain are basically the same drugs we had a hundred years ago. I point out that opioids, non-steroidal anti-inflammatory drugs and the congeners, sedatives, muscle relaxants, are those things that are still being used, and clearly that is just not adequate for our present understanding.

You've heard already that pain clearly is real, but it is also subjective. I've mentioned before in circumstances like this that in fact I need to be put to sleep to have my teeth cleaned, whereas my wife gets her teeth worked on with no novocaine. She claims that she has no pain. I walk into the dentist's office, my heart is racing, I'm sweating, and they haven't even touched me yet. So everyone learns the meaning of pain through experiences usually related to injuries in early life, and some

unpleasant experience or sensation becomes an emotional experience a la my childhood experiences with a dentist.

Pain is a significant stress physically and emotionally and you've heard much about what stress might do to certain genetic hosts that might lead to an establishment of a disease, such as fibromyalgia. So looking at ways to define chronic pain, and we've heard some of this but not all of it, we turned to the Merck Manual in 2002, the Centennial 17th Edition. In this edition, chronic pain is defined broadly and arbitrarily as pain which persists for greater than one month beyond any acute injury, and in this context of fibromyalgia, we may need to think about the acute injury as a stressful event. Perhaps it was going to the Gulf War in 1991, perhaps it is learning that your Medcat scores are not as good as you'd like.

Persistent and recurring pain for at least three months and pain expected to continue or progress may be associated or not associated with ongoing tissue injury. It has no adaptive role. It doesn't help one to survive. You just suffer with it.

And vegetative signs and depression may follow, and we've heard some of those issues, and in fact, Art Lipman has gone along and suggested in this construct that I'm going to show you that the psychosocial component must

be dealt with before depression becomes part of the clinical picture. Chronic pain should be recognized as a multifactorial disease state, requiring intervention at many levels, and he pictures it like this.

You heard from multiple speakers this morning that once it's happening and a patient is seen with this particular scenario in a tertiary care setting, it almost may be too late, that basically the construct that they presently are dealing with is just untreatable in the context of even alleviating their discomfort. So finding these patients earlier on, perhaps in a primary care arena, may allow us to obviate the eventual onset of some of these things as drawn here, where here is the pathologic process interacting with the physical factors, then going up the scaler over time, leading to psychological events, anxiety, depression, hostility, loneliness, thus isolation and those other social factors that play a role. Clearly, as you can see in this reference, this is for cancer nursing, but nonetheless can be easily applied to this particular scenario.

In addition, we at the agency have been grappling and have had some significant energetic debates with other divisions within the agency about how to describe chronic pain. We can think of lots of different ways and one of the really important ways is a la the 1992

Pain Guidance document which, for those of you that are interested, we've actually applied for it being removed from the docket so that people can't use this any longer.

What we are looking at here is the concept of mild, moderate, and severe pain. We all use this kind of jargon when we talk. We all kind of apply this in both talking to our patients and trying to understand ourselves suffering a particular injury and what it would mean. The problem, of course, is it's extraordinarily subjective. It's descriptive but does not provide rigor. Perhaps these should be used to modify the concept of chronic pain indication to allow patients to understand, but I'd like to challenge the committee to help us understand how you measure what is mild or moderate to severe. It's the bias of us as the agency to determine what might be that particular definition. It's the bias of the investigators. It's the bias of the sponsors that are developing the therapeutics, and of course, most importantly left off of here is the bias of the patient. How in the world can we determine what any one person thinks is moderate or severe or mild? Perhaps it's partly related to how they function, and of course function has already been overwhelming trashed repeatedly by many of the speakers as being something that's particularly applicable to understand this particular scenario.

So in thinking about fibromyalgia, we've heard a lot about the symptoms associated with fibromyalgia. We've thought about and heard about the fact that there are components of the disease, but in fact is fibromyalgia a painful syndrome with pain as we've heard from even the patient as the critical nature of the measure that should be looked at to determine outcome, but in fact is the disease a neuroendocrine disorder and pain just the primary or most important manifestation, or is it a painful condition with a neuroendocrine disorder associated with it? Is wind-up an epiphenomenon or is it causal, and if it's causal, is it important to measure? And if it's important to measure, can we use it as an indication for an outcome that you alter wind-up? Will that then change the fundamental chronic process that then would lead to not having chronic pain?

So that would take us to a concept where we ask this question. Internally, we've had the debate whether I should even ask this question of the committee. Is this improvement in the pain of fibromyalgia or is this improvement in fibromyalgia? It has enormous implications because one is dealing with the syndrome of fibromyalgia and perhaps its improvement, the other is dealing with just a painful state, one component of that. You may be able to measure a change, but is that actually improvement in the

whole scenario?

So many of you have seen these kinds of scalers before, and we have typically in the agency, at least in this division, thought about the concepts of what's important for pain domains, not to exclude all of these, but to actually think that these are the critical ones where you measure pain relief, pain-related function, and patient global. You heard this from Dr. Witter. You heard this from others this morning. Clearly, all these other things are very important, but what are the primary ways that one would determine a primary outcome?

So in looking at that context, we have seen these lists. Pain, patient global, health-related quality of life, and physical function measures, we believe are critically important in thinking about this as a scenario, as a syndrome, not just the pain of. However, obviously it's also important to know that perhaps these get better or at least do not worsen in the context of interventions. How to measure of these becomes important, and then listening to three of the last speakers, I would even go so far as to wonder whether or not we should be thinking about perhaps just one of these measures at any one time could be enough, as long as everything else didn't worsen, as we begin to learn more and more and more about critical measures associated with this particular scenario.

And then, obviously we don't want to ignore what Dr. Witter reminded us about, which is the mechanistic claim. Having heard some of the issues that Dr. Crofford brought up, there are so many different ways to be able to think about this in the context of the science that now could be measured, perhaps now we can begin to apply the mechanistic claim to some subsets of patients with fibromyalgia. So measuring an alteration in NMDA activity, which then might prevent wind-up, if that construct is true, may be important. Maybe it's important in some patients to reduce prostaglandin levels that you can actually measure either in the CSF or some other methodology that would be applicable, perhaps an imaging methodology that would be appropriate, other measurable biologic changes in chronic pain states that have not yet even been defined.

At one of the meetings that we participated in, Cliff Wolf presented extraordinary evidence in the animal about an acute and chronic pain scenario, about up regulation of 700 and something genes in the spinal cord and down regulation of 545 genes. Clearly, the animal is expending significant resources in these changes and that's probably important. What those changes are and what they represent elude us still, but that doesn't mean we shouldn't be looking at them.

And then, clearly we have another recurrent theme that comes up to us, which is, well, if you're actually going to be able to measure change in these chronic scenarios. Patients are not typically coming to these to get therapy without having already been on something, and thus could you measure a change in what they have been on, suggesting that in fact that's an improvement. In rheumatology, that has been traditionally looked at as glucocorticoid use, meaning you decrease the use of glucocorticoids, thus you're making improvement, perhaps if you decrease the use of non-steroidals or decrease the use of opioids in a measurable clinically important way, and that might be an important measure for a primary outcome.

Dr. Witter showed aspects of this slide, the ideal characteristics of a pain metric, and I want to remind you as we begin to grapple with this that we need to think about it in the context that it's easy and understandable by patients and clinicians. We've been struck by the fact that most clinicians don't read the label which is embarrassing since what the FDA mostly does is define itself by what's in the label and that's unfortunate. There's a lot of interesting material in the label.

And clearly whatever we use as an outcome needs

to be able to be explicable within that construct. It needs to be applicable across studies. Therefore, many studies are done to help establish what you're going to do for pivotal trials and under those circumstances, we need to be able to use these outcomes to facilitate full development, and as Dr. Clauw suggested, perhaps imaging of the brain is not something that's going to be applicable for a full drug development program as opposed to a proof of concept.

It defines a clinically meaningful result. It's valid, and I'm using the term "valid" in the context of what Dr. Wells suggested. And it measures response, again as per Dr. Wells, in a variety of pain conditions and therapies, and it's achievable with current meds. I would like to suggest, however, that that might be a wish. It may well be that the current meds that we're talking about are just around the corner and we need to be flexible to understand how to measure these particular outcomes. And it should be tiered to define important differences in drugs.

So we heard about this issue about choosing measurements of response and how it was done, and I'd just like to point out that in our division, there are two different models in the context of that, the OA model, the RA model. The OA model, which is a model of chronic pain

which is used and applied by our division, is mostly a local disease and presently requires these three co-primary outcomes for approval, the VAS scale for pain, WOMAC for function, and a patient global, and all three must win; whereas, the RA model, which is a systemic disease which may have local symptoms, is actually measured through a responder index and you actually saw the outcomes of this responder index.

I'd like to point out one particularly important aspect of this responder index is that in the first cut point here is tender and swollen joint counts. I'd like to point out that this was designed with lots of clinicians in mind, and we have learned something. What we have learned is that physicians like to believe they have an important impact on the measurement of outcome. Thus, the ACR 20 is actually somewhat sullied by this particular measure because the cut requires the physician input and then in fact these are the ones that are subjected to this particular outcome. I'd like to think that we've moved along here and recognize that patient-reported outcomes are equally as important as are the physician observations and thus maybe we should be thinking, if we're thinking about a responder index, that we don't distinguish the importance between the two and not think of a cut point in one versus another.

So also thinking about inclusion and exclusion criteria, in thinking about the homogeneity versus heterogeneity of the disease, one has to ask the question: so, if we're going to try to get real good outcome measures and we're going to apply them in a patient population that seems similar, should we think about the fact early on or later that patients who have a prominent component of depression should be excluded or should be included? And then, if they are included in the trial, how do we handle the antidepressants that are used that actually might have an impact on the outcome of fibromyalgia per se, and how do we control for that? Do we tier it? Do we stratify? How do we handle that? Should we include -- and Dr. Crofford and others have actually mentioned this this morning -- the patients that have secondary fibromyalgia, whatever that might mean? I don't mean to actually codify a scenario of primary and second, but we all know there are patients who have a disease as a stressor leading to symptoms of fibromyalgia, and thus do we treat rheumatoid arthritis patients who have fibromyalgia and then treat the rheumatoid arthritis and find that their fibromyalgia gets better, thus the treatments for rheumatoid arthritis should be approved for fibromyalgia? I don't think that that's really appropriate. So in learning this particular scenario and building the field, we may have to think about

excluding these patients.

How long should a trial be? It's actually quite interesting. I've actually just come back from Europe where I spent some time at the European League of Associations of Rheumatology Annual Meeting, and I actually walked around asking questions helter-skelter, kind of like how long should a fibromyalgia trial be, and I could get no consistent answers. Europe has a different opinion than the States.

In general, we would like to think of this longer than shorter because this is a scenario, this is a disease that's been around in the patient for a long time. We'd like to be able to see a substantial response that actually is maintained for a period of time, to know that something is an important modifier of that particular scenario. So we're thinking about at least three months, if not six months, and then guaranteeing at least a year of exposure for safety and recognizing that most published trials to date have been much shorter.

Should a patient have decreased symptoms and for how long and without therapies? So one could even imagine a scenario that if you have improvement over three months, can you think about low disease activity states a la Dr. Wells or a cure by stopping therapy? Should we require that a patient needs to have no therapy for a

period of time to be able to actually be improved with this particular scenario?

And then, the other question, of course, which comes up all the time is: what is the importance of the tender points? Do we use it as a measure of outcome? Should we use it as a criteria measure for inclusion, based on how much disease activity they have, and thus do we create a disease activity score as well as an outcome score?

And a la Dr. Clauw, is the FIQ an adequate measure of function or should, in fact, other outcome measures be developed, or should we begin to look at what's presently available, either in the FHAQ, the Fibromyalgia HAQ, or in the SF-36 and begin to apply that?

And then, fundamentally, the two questions really are represented by is it improvement in the pain of fibromyalgia or improvement in the disease? We'd like to think it's the latter and not just the pain of fibromyalgia.

And what would a cure require? I will not hold you to that question, but in fact it might be something you want to keep in the back of your mind.

Then the other question would be: in the context of doing and designing a clinical trial for outcome, what would be allowed concomitantly? Would

physical therapy be allowed? Would structured exercise be allowed? Would cognitive and behavioral therapies be allowed? You've already seen evidence that there's actually very good utility of cognitive and behavioral therapy. We would have to stratify thus in that kind of scenario, seriously increasing the number of patients in a clinical trial.

Would psychotherapy be allowed in the trial? Would ongoing therapy be allowed for patients who are already on therapy as they recruit? These issues then really do change whether or not you can recruit. How could you recruit people if you don't allow some of these issues? That's particularly true for the final one which is medical therapy for depression.

So in coming to conclusion, I'd like to point out that in fact what is the perfect drug and, a la Dr. Witter, the perfect drug is totally safe and totally effective. Unfortunately, none exist. Not one drug is totally effective and not one drug is totally safe. The problem with asking the question of what is safe, what is the benefit-to-risk ratio? And even more importantly, who should decide?

We unfortunately are living in a society that sometimes doesn't like to grapple with the important questions related to being diseased and in fact also

doesn't really understand and recognize all the time what it means to have a chronic scenario that alters your life. We have to make some decisions societally about what we will accept as therapeutics, that we'll accept the costs of those therapeutics, and part of the cost of those therapeutics is not just money but safety. I don't have any good answers to that.

But I do believe I feel like this slide, which I've shown before in this scenario, like this individual going to the diner and deciding, based on how much E.coli might be infecting my hamburger, that in fact I have to make the same kinds of decisions when I go to the counter and make decisions about how I would apply drugs to myself or to my patients, and I have to weigh the benefit-to-risk ratio in each circumstance and kind of apply that in the decision making process.

It's critical for us in our decision making to allow our patients to understand that we actually do this process on a regular basis and include them in that decision making so that they can actually feel part of that process in general.

So I think that what we're actually asking from you is to think about these issues. The questions we're going to be showing you are actually long. They have multiple components to them, but your input will be

critical for us to be able to make the next steps in thinking about fibromyalgia as a model of chronic pain and thus is a model that we can use in that scenario and/or is it also a disease state where we can determine a way to identify an outcome for the disease or syndrome of fibromyalgia.

So thank you very much.

(Applause.)

DR. FIRESTEIN: With that, we'll close the morning session, and we will have a sumptuous lunch, I'm sure. We will start again at 1:00. So that gives everybody 42 minutes for lunch. We'll see you at 1:00.

(Whereupon, at 12:18 p.m., the committee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:05 p.m.)

DR. FIRESTEIN: So why don't we go ahead and get started?

We have a list of seven questions that will guide the discussion, and I think the easiest way to do this is to just begin by reading the first question and that will get us into the discussion. If you don't have the questions, by the way, they're the back page of where the agenda is. It should be in your stack of papers over there.

The first question is fibromyalgia involves a constellation of symptoms. The ACR 1990 diagnostic criterion is based solely on the number of tender points. This definition may exclude patients who clearly have widespread pain, non-restorative sleep, fatigue, et cetera, but have 10 or fewer tender points.

Should an alternative definition be developed for fibromyalgia clinical trials with stratification by number of tender points?

So that's really two rather complicated questions. Thank you, Dr. Simon.

So perhaps somebody from the committee wants to begin. Yes, Dr. Williams?

DR. WILLIAMS: I'm not sure that they want to

start by trying to redefine it because those criteria were validated, and if you decide that you want to have a new set of criteria, you're going to have to validate them before you can use them. So even though it will eliminate some patients, we have the same problem with rheumatoid arthritis and lupus, that there are patients who have the disease who don't meet the criteria, but those who meet the criteria, everyone accepts. So I would not change the criteria.

DR. FIRESTEIN: Of course, one of the problems is that we now know, since the criteria were developed, that those specific trigger points aren't necessarily specific for fibromyalgia. As was pointed out, they define diffuse pain.

DR. WILLIAMS: They were not specific. However, when they did validate the criteria, they looked at a lot of different tender points and these were the most discriminating but they're not specific.

DR. FIRESTEIN: So is there general agreement that we should or should not redefine the disease at this point? Yes, Dr. Turk and Dr. Staud?

DR. STAUD: The question is with overlap. I think this is an important question. So when does someone become a patient with fibromyalgia and irritable bowel syndrome and migraine headaches and so on?

DR. FIRESTEIN: One of the questions is if we define solely by pain, then we have this overlap of the non-patient fibromyalgia patients or group of individuals versus the patients which were described earlier, that there are those individuals that have tender points and have pain who don't seek medical help and that would be included in a clinical trial and might be a potentially different population of patients.

Dr. Turk, did you have a comment?

DR. TURK: Just a comment. About eight months ago, there was an NIH meeting in which they brought together all the people who had NIH grants on fibromyalgia and part of this meeting was to identify what should be the directions for the future and for research, and the number one thing that came up at this meeting was we needed to have a new way of diagnosing or classifying people with fibromyalgia, that it's really not a very acceptable way that we're using right now. So it doesn't answer your question as far as right now what we should do. Larry, I think you were there. There were maybe 10 or 15 people at this meeting, all of whom agreed that the classification system is really inadequate.

DR. BRADLEY: Well, I guess maybe I'm not one of the 10 or 15. And granted, I think there's sort of a problem with error variance when you make a decision about

is 10 tender points and not 11 tender points error variance or is that something that's highly meaningful? But I think if we radically alter the definition, then essentially anything else that we produce in the future will be based on different criteria. It'll be an empirical question as to whether or not we're really talking about the same phenomenon.

I think what's really interesting is that there's a paper that came out in Pain several months ago, and I've forgotten, I believe the first author's last name was Corli, I believe. But in this paper, they compared responses to about five different pain sensitivity tasks in groups of patients ranging from patients with myofascial pain, regional myofascial pain, to fibromyalgia. There were about five groups of patients all in all. The most important finding was that the people who met the current criteria for fibromyalgia were sensitive to all five sets of sensitivity tasks using different stimuli.

So I think there is something about the use of the 18 trigger points that really distinguishes the phenomenon that we call fibromyalgia from other types of disorders that are characterized by chronic pain and feeling badly and so on. So I'm a little bit reluctant to advocate that we radically revise the criteria at this point.

DR. FIRESTEIN: Jack?

DR. CUSH: I, too, would argue strongly in favor of using the ACR criteria because it's the one thing that we do have that's rock solid, well tested, and it should be the primary and only indication to get into the study as fibromyalgia, whether you want other provisos on top, that's okay, but these criteria have nothing to do with what we're going to discuss henceforth, for which we have less rigorous guidelines and validations. So that's what I think is going to be the hard part of this discussion.

DR. FIRESTEIN: But maybe there should be two goals. One is in the short term use the current definition and in the long term try to develop a broader definition, in part because most of the things that we're planning on measuring as outcomes go beyond just simply counting trigger points or tender points.

DR. WILLIAMS: However, if you look at the frequency of tender points, that exceeds the frequency of inflammatory bowel disease or even chronic headaches. So if you start adding too many things, you're also going to start limiting your population.

DR. FIRESTEIN: Dr. Simon?

DR. SIMON: May I ask a modifying question? If tender points then are going to succeed and survive, do we

then convert it into a dolorimetric measure which is quantifiable rather than a finger measure which is dependent upon who does it and how it's done? If we believe that this is an important measure, should we be developing a better quantifiable way of approaching it?

DR. STAUD: This is one point that has been tried to be made in lots of different investigations and it has been shown to be very, very difficult. First of all, tender points are overlying very different tissues. Most of them are tendon insertion points but some of them are muscles. In most populations to identify pain threshold is a very difficult task. So most of these tests have failed. So the number of tender points seems to be the most solid measure.

DR. FIRESTEIN: But isn't that how the criteria that were developed, though?

DR. WILLIAMS: I think dolorimetry came in later. I think they just did the tender points initially.

DR. FIRESTEIN: But how many people have had the experience of going in to see a patient that the resident has seen and has said that there are no tender points, and then when we find the magic spots or push with a little bit more vigor, then it becomes quite obvious? So it's clearly operator-dependent. Is there not a better way of standardizing this?

I guess we'll start over here. Yes, Dr. Turk?

DR. TURK: There have been several attempts to develop procedures either dolorimetry or by patient reports, and there are a couple standardized approaches that have actually been published with standardized training tapes of how to actually perform the exam. It's called the Manual Tender Point Survey. I think Okifuji, Terry Starz, David Sinclair, and myself were involved in publishing some of those, and we showed they can be very reliable by both physical therapists as well as physicians performing a standardized protocol.

We also in that trial had patients not only say yes or no, it hurt, but to rate how severe the pain was and showed that the distribution of scores were much better if you use a quantitative score than an absolute number which was basically a normal distribution. If you use the absolute number of tender points, it was a very skewed distribution. So I think there is merit to consider whether there are some ways, whether it's dolorimetry or whether it's by patient ratings, that we can get much more sensitive measure than just the absolute number of tender points.

DR. FIRESTEIN: Dr. Katz and then Dr. Cush.

DR. KATZ: I think the other issue, though, is whether that might be more appropriate for phase II rather

than phase III studies. My own experience of trying to standardize dolorimetry in a multicenter study is that it's very difficult, very time-consuming. You can never train enough and there are always reliability problems.

However, if the distributions are better, there might be some use in phase II proof of concept trials, if there's an increase in sensitivity or responsiveness to be gained from all that additional effort, but in phase III, I would think that again you'd probably want something more generalizable to the doctor out there anyway who won't be doing dolorimetry. So I would be opposed myself to requiring it in those studies.

DR. FIRESTEIN: Could you just clarify? Do you mean for entry criteria or for following response to therapy or both?

DR. KATZ: Either one.

DR. FIRESTEIN: Jack?

DR. CUSH: I agree in that this has to be a tool which has parallels with real-life practice and dolorimetry would never be done in real-life practice, and Gary, when you say that we went in and found these trigger points, it really isn't because we pressed harder, it's because we knew where to go more often than not. It wasn't because we jumped on the patient, exerted 12 pounds per square inch, and I think it was just a simple blanch of the

finger pad. I think that it has to be a clinical skill.

If this is clinical skill, and it's to be part of the biometrics of clinical trials, then the clinical trial design has to account for that in some way with appropriate training and instruction at the outset of those who will be the assessors, and this is what we've done for RA trials. Especially in situations where the person doing the assessments may not be the investigator and may not be a rheumatologist, trying to standardize your assessors in some way through training, I think, is the best way to get around this without having to be too mechanistic about it.

DR. FIRESTEIN: Although we heard earlier that the location of the pain was not necessarily specific. So that, that would belie what you had just commented on.

DR. CUSH: But getting back to Jim's point, it is discriminatory, and it is part of the criteria. So that's why we're talking about these tender points as opposed to pain here, there, wherever. We know they hurt all over. We're only going to count these 18 spots.

DR. STAUD: One very important point, in order to decide if you want to do tender point counts or tender point scores, is the tender points per se or tender point scores do not really add anything to the overall examination of these patients because they mostly highly correlate with distress and not with measures that we're

actually trying to look at, like for example pain. So that's why in most trials, people have gone away from tender point scores. They just do tender point counts.

DR. FIRESTEIN: Do you mean gone away from tender points as an outcome or again as an entry criteria? Because most people do require it for entry criteria but you don't necessarily need to count changes in number of tender points as an outcome.

DR. STAUD: Actually, I was referring to using the tender point scores.

DR. BRADLEY: Just to beat the horse one more time, the dolorimeter is also operator-specific, and in our lab at least, it takes anywhere from three to six months to train a very bright graduate student to use the dolorimeter reliably with our master doloritress. So it's very difficult to use it for outcomes.

DR. KATZ: I'd like to raise a related point. We've been talking about which criteria to use for entry into the trial and we've been talking about the ACR criteria, but a separate issue is whether we should recommend that investigators further characterize their population in some way so we can understand exactly what type of fibromyalgia population they've studied. We've heard already today that different populations with fibromyalgia can really be on very wide range of disease

burden.

Should we require that we characterize the population in terms of what proportion have irritable bowel syndrome, have migraine, have some of these other features? Because that might make different trials comparable or not comparable. Should we require that there be some assessment of their severity of depression or mood disturbance at baseline, so that we can know whether we're comparing apples with apples when we look at different studies?

DR. FIRESTEIN: Jack?

DR. CUSH: To answer Nate's point, I would suggest that along with this entry, belief in this entry criteria, I think we should make strong statements about exclusions to try to again unify the population. I think that I wouldn't discount symptoms that may go along with the disease, but I would try to eliminate confounders of the disease. So whether that be uncontrolled psychiatric illness, for instance, patients who have over-reliance on narcotics. There are many issues that we may want to exclude at entry to try to unify the population, and I think that that's important and maybe even drugs might be a key exclusion to being in the study.

DR. FIRESTEIN: Lee?

DR. SIMON: Well, it's all very interesting

that you've now pointed these out, both Nate and Jack. So of those things that you would leave in, would you stratify for them, recognizing what that would mean from a numbers point of view and the implications of that? Obviously, to allow you to have a larger population, not a smaller population.

DR. KATZ: My own thought would be not to stratify. My own view of stratification is when you have robust knowledge that something is a clear-cut prognostic variable and you have some sense for in what way it might be prognostic, then it makes sense, but with these things, I think we have a general sense that people that are sicker will probably not do as well, but right now, it's just observational, I think.

DR. FIRESTEIN: Dr. Williams?

DR. WILLIAMS: I would agree. I think that if you start stratifying for these other various variables, that you're going to have unmanageable numbers required. At least in my population, pain is the most prominent feature, and if you're going to evaluate for pain, that's a whole different set of variables than if you're evaluating for irritable bowel.

MS. MATALLANA: Also, we hear from the patients quite often that they're upset that they are not able to participate in clinical trials because they're on certain

medications and things, and because of that, there's the fear that there are groups of people that maybe have more severe symptoms that are not being included in the clinical trials.

DR. CUSH: You might want to stratify for medicines, so people who are on tricyclics or SSRIs, that may be important because they may have some pain modifiers, but I think you have to decide whether you're going to allow pain modifiers. Should people who are on background amitriptyline or terazadone be allowed in a trial? That's an important factor, and I think that other clinical symptoms which are basically manifestations of disease and more severe disease will have more of those IBD or numbness or headache or back pain or TMJ, whatnot are not as important.

DR. FIRESTEIN: That question in terms of concomitant medicines is going to come up with one of the later questions. We'll probably discuss that because that's one of the major issues in terms of designing these studies.

But in terms of stratifying for number of tender points, I think, is there general agreement that that's not going to be particularly useful?

DR. WILLIAMS: I understood Lee's question not only stratifying by number of tender points but stratifying

by other associated conditions.

DR. FIRESTEIN: Right, although the actual question as originally stated was by tender points, and then the second question is whether or not one looks at different subpopulations as just pain or pain with concomitant syndromes, like cognitive impairment, et cetera.

Lee, did you have another comment or question?

DR. SIMON: No.

DR. FIRESTEIN: So.

DR. HOFFMAN: A question, Gary?

DR. FIRESTEIN: Yes.

DR. HOFFMAN: Not being someone who has studied fibromyalgia in a pharma way, a question for some of the panelists who have would be related to the specificity of the current ACR criteria.

What hasn't come up today is the patient who perhaps comes in with a dozen trigger points but perhaps not any of the specified 18 and these are non-articular and do not follow a pattern of peripheral inflammatory disease. What kind of specificity is lost if such people are included, if they have other characteristics that we've listed here, non-restorative sleep, fatigue, headaches? Are we losing from some of these studies a significant number of people who should be included?

DR. FIRESTEIN: Are there any comments?

DR. STAUD: Yes. I think really one of the hallmarks of fibromyalgia is widespread pain and widespread tenderness. So I think the distribution and number of tender points or the number of tender points really expresses the widespread distributions is extremely important. So we couldn't really cut back and say we don't care where tender points are measured or tender areas. It has to be in a widespread distribution as originally defined by the ACR criteria. It should be.

DR. CUSH: But I think adhering to the ACR criteria which are not dependent upon fatigue and cognitive impairment but instead are dependent upon widespread pain and its definition, if you meet that, then I think the stringency is not that different than what we have for RA, that you are going to get patients with more severe disease, but then again there may be patients with enough severity or enough pain that it's also modifiable by some intervention.

So while we're going to miss a lot of people in the real world -- they're poorly characterized but nonetheless are going to get treated in the real world -- I still think that sticking to more rigid criteria allow you to work with the data in a way that's going to either show the benefit or non-benefit of an intervention.

DR. FIRESTEIN: Well, the group has spoken.

DR. WITTER: Could I just ask maybe for a little bit more discussion, and it might be useful then for the other questions? If we are to evolve in terms of an approved outcome or inclusion criteria or definition for fibromyalgia, suggestions on how that would be done in trials that come to us? This might be a safe place to begin that discussion.

DR. CUSH: Could you rephrase that?

DR. WITTER: Well, it's nice to say that while we should come up and develop this, that, or the other thing, but I think in this area in particular, as we're moving forward, we don't have the luxury of the experiences that we had in RA or OA and that we may have to do more or less kind of real-time validation of new whatever it is.

Could you begin to discuss that maybe now? Is this the place? Would you like to entertain that? On how we on this side of the fence could encourage that kind of a process and not compromise what it is that we see?

DR. FIRESTEIN: Jack?

DR. CUSH: I think you have to go with our primary outcome variable, and with RA and other diseases, we have composite measures, and I think that this is a syndrome that has many facets to it, to stick to only pain as a single outcome variable by whatever measure would be a

major mistake. I think that we should invoke pain as a primary outcome that must be achieved but others as well, and so whether that is sleep, function, fatigue, I wouldn't go much beyond that. I wouldn't want to start listing headache and numbness and TMJ and IBS and all the other things that go along with it, but I would try to choose those features of the disease which are major -- they may be inter-related amongst each other. Pain and fatigue go together. Sleep and pain go together. Nonetheless, I think that they may also have their independent contributors to the disease.

So an intervention or set of interventions that could improve more than one domain is what I think we should be going after.

DR. FIRESTEIN: Dr. Katz?

DR. KATZ: Just a clarification, Jim. I heard you ask about developing improved diagnostic criteria, but I think Jack's point was addressing mainly developing outcome measures. So in terms of your question about entry criteria, I think we have to ask ourselves whether it's appropriate for us to require that sponsors of studies develop new diagnostic criteria for fibromyalgia.

As Dennis has already said, there are already efforts going on in that regard or that hopefully will go on at the NIH level, and obviously whatever we develop has

to be responsive to improve diagnostic criteria that develop. But as far as entry criteria go, I think we need to decide whether it's our role to require somebody to develop a new entry criteria.

Outcome measures, I totally agree with what Jack is saying. I think it would be more appropriate there to encourage sponsors of research to develop appropriate outcome measures for the medications that they're trying to get approved, but for entry criteria, I don't feel the same way.

DR. FIRESTEIN: But was your question primarily at entry criteria or outcomes?

DR. WITTER: It's really a general how-to question. Outcome variables, anything to move this disease in particular forward. It's really a question of, in terms of from our end, how do we do it? What are the ways that would not come up with undue burdens to the sponsors, would not be compromising what's going on in the research community in general. I think we're searching for ways that we can be helpful in the process but not be burdensome, and so I think it's a how-to question more than anything.

DR. FIRESTEIN: You're precisely right that it's going to end up being real time, and although we have acceptance of the ACR criteria, for instance, for RA, it is

still being re-evaluated constantly real time, and there's some discussion as to whether or not measuring tender and swollen joints adds anything to some of the other outcome measures.

So I think what in the end is going to happen is we take our best guess at what makes the most sense, and those would include a few different domains that have been discussed, including pain, patient global assessments, and perhaps some measure of patient function, and then use that to go forward and then have to, again, validate it real time.

Jim?

DR. BRADLEY: I think with regard to the question of function, I think expecting that a trial of a pharmacologic compound to change function over a very short period of time would be very unrealistic, and I think it would be overly restrictive in terms of measuring outcome. I think one has to remember that apart from the measurement problems of function that were described this morning, function in the patients who come for treatment and patients who would enter these trials, functional disability is in part determined by long periods of sitting and inactivity and it's a whole conglomeration of factors that influence current physical function.

So I think to expect any compound to change

function in a short period of time would be really unrealistic, and I think it'd really be much more appropriate to focus on alterations in pain and alterations in global assessment.

DR. FIRESTEIN: Lee?

DR. SIMON: So we've actually moved on to question 2.

DR. FIRESTEIN: I was going to say. We're well into question 2 right now, which relates to would it be reasonable to expect that a product that is truly as efficacious, but I assume you mean effective, --

DR. SIMON: Yes, but we don't use the term effective in this world.

DR. FIRESTEIN: I understand. For the treatment of the syndrome would show improvement in pain, some measures of physical function, and the patient global assessment, and then what would be the optimum duration? Because as you pointed out, a short duration trial might improve patient global assessment but might not have an impact on patient function.

DR. SIMON: And I'd like to address that particular issue since in fact we had a recent meeting in the rheumatoid arthritis arena to discuss the issue of physical function, and we presented evidence that within 16 weeks -- so thus 4 months and remember we're talking maybe

a 6-month trial here -- that in the context of a chronic disease with structural implications, you can actually against placebo measure differences in improvement in physical function. For those of you on the committee who will remember that discussion just two-three months ago.

That's actually a very important point. In OA and RA, there's a high correlation between pain and function. The functional outcomes are robust and well developed. Those measures are robust and well developed. The FIQ, you've already heard about here, has not been a terrific instrument, based on the particular activities that people are doing today and thus might need to be addressed. Nonetheless, we know at least using the FIQ that there isn't a great correlation between pain and function.

I find that a little weird. I think that in almost all other circumstances, there's a tremendous correlation between pain and function. So I don't understand if it's unique to fibromyalgia that there's not or it's just that it's a lousy functional measure and that's why there's no good correlation. So we at the agency are uncomfortable in thinking about an improvement in a scenario such as fibromyalgia that does not include some measure of function as pain improves.

We have actually had an example of a therapy,

based on trial design which was statistically significant improvement in pain of several millimeters in measurement, but in fact in the concept of function failed miserably in a traditional realm where function and pain are linked. So we are very uncomfortable in not looking at this as a gestalt rather than just the pain of.

Might we entertain a little discussion here about whether or not there is any linkage between pain and function, and if there is, should there be a requirement that we begin to work on a different kind of functional assessment that might be better or unique and give us a better correlation? Not because we're just trying to create the better correlation, because we're trying to measure the overall state of the patient.

DR. FIRESTEIN: Dr. Cush?

DR. CUSH: Lee, would you accept a quality of life measure as a functional measure as well? So like SF-36 in whole and then take out the physical component in part. What's your comment on that?

DR. SIMON: I think that I have been educated by any number of brilliant people to be convinced that health-related quality of life measures are similar to function but not always the same. SF-36 as a generic is not necessarily not applicable to specific diseases, and HAQ, which is supposedly non-generic, might be generic,

depending on the circumstances. So I think that this is an evolving field.

I think I've learned to think of the SF-36 as a very good measure, a very robust measure. You have to be specific about which components of it you can use. It has not been validated in all these diseases, but every time I look at it being applied to various different syndromes and diseases, when done correctly, it looks like it discriminates and is valid.

So under those circumstances, I would not distinguish, and I think that if a generic measure, such as the SF-36, is proven to be useful and have utility, I think that would be great.

DR. FIRESTEIN: One doesn't necessarily need to have an improvement in function in order to have a drug approved for rheumatoid arthritis.

DR. SIMON: No, and that's a very interesting point. From an educational point of view, we approve drugs for a separate indication, meaning there's the indication of signs and symptoms, there's the indication for x-ray progression, meaning inhibition of x-ray progression, and a separate indication that the sponsor has to go for for the improvement of physical function, and that's exactly right.

We could create the same scenario here and not just apply that in the context of improvement of outcome.

However, the caveat to that is the HAQ is now being considered as very important for even getting signs and symptoms, and we're actually evolving to consider that all studies in rheumatoid arthritis would have to include some physical function outcome, even though it may not be measured or expressed in the HAQ.

DR. FIRESTEIN: Does anybody have any comment on whether or not there should be a separate physical function component that's required for fibromyalgia? Yes?

DR. TURK: To answer part of your question, Lee, in back pain area as an example, there are lots of data to show that the correlation between function and pain is about .3 and there are studies in neuropathic pain to show that the relationship between pain and function is fairly low. So I don't think it's unique to fibromyalgia that there isn't a high correlation between pain and function. What that says to me is that function is an important outcome that should be considered, in addition to looking at pain.

Unlike Dan Clauw who's left, his last statement that if there was a treatment that was effective in reducing pain but had no beneficial effect on function, he would view that that's positive. My response would be to have someone who's a 45-year-old person with a 7-year history of fibromyalgia who had a statistically significant

improvement on pain but then said but I'm not doing anything any differently and not functioning any better, to me, that's not a great outcome.

Now, we could debate and I'm sure you might argue with me about that, but at least it does speak to my concern that I agree with you. I think that we should come up with some measure of function, whether it's the FIQ, we could again talk about that, but I don't think that we should take pain -- I disagree with Larry. I do think you could take functional changes because it depends on how you're defining function, Larry. If you're talking about lifting huge amounts or walking great distances, you might not expect to see that in a couple weeks, but if you're talking about improvement of sleep and improvement in ability to do things around the home, in fact, you might see those kinds of changes. So it really depends on how you're thinking of function.

DR. BRADLEY: Yes, I agree with you on that point, Dennis.

DR. FIRESTEIN: Lynne, Jack, and then Jim.

MS. MATALLANA: From the patient's viewpoint, our survey showed that even 20 percent improvement in pain would be a worthwhile outcome. I agree, that I don't think pain has as much of an effect on functionality. I think the fatigue issue does. But at this point, we don't have

many options for fatigue improvement. So if we can eliminate the human suffering of pain, I think that the benefits would be tremendous to the patient population.

DR. CUSH: I think that we have to sort of move forward. In the past, with all of the diseases we consider, we have always done short-term trials, single variable outcomes, mainly looking to improve a single symptom or a group of symptoms, and I think the trend has been at the FDA and as mandated or required by clinicians and researchers that we should go towards longer-term trials with multivariate outcomes which are more true to life that actually don't speak to symptom improvement, really to true disease improvement, and that that has long-term implications that impact on a patient's life and employability and whatnot.

I think that we should go toward a functional indication. I think that since we don't know which is the best, I think that the FDA should accept a group as being reasonable measures, whether it's the four being the FHAQ, SF-36, FIQ, or even WOMAC, and require a sponsor to do out of those four. And if you improve in one, that's good enough. Overall, it shouldn't be function and pain because, as has been said here before, there are people that may not improve their function, even in a 6-month trial.

So again, going towards a multivariate definition, we should require function as one of several measures that we may accept. Pain is first and we may accept some others as being part of some overall definition that we're going to call a response in fibromyalgia.

DR. WILLIAMS: I don't have a lot more to add, except I agree with both of them.

I have a question on what Jack said. I would not require long term on the initial studies. I would require 3 to 6 months with longer-term follow-up to see how long the response lasted, but I wouldn't require them to show benefit over a 1- or 2-year study like we do in RA now. And I agree that I think physical function is an important variable.

MS. McBRAIR: I also agree that physical function is important. You're talking about younger people. They have a long life ahead of them, and we need to see them make some progress in that area. However, as long as it's part of a number of variables like Dr. Cush mentioned, I think I could be comfortable with that.

DR. FIRESTEIN: Nobody is disputing that physical function is important. The question is: is that going to be a primary outcome? If you improve symptoms, for instance, is that good enough to get a drug approved? The gold standard would be that not only would symptoms

improve but also people would have improved function, go back to work or whatever, but is that going to be the standard to which anything that gets approved for myalgia be held?

Jim?

DR. WILLIAMS: I think pain has to be the primary outcome measure. That's what the patients are complaining of, but I think an important other measure would be physical function and patient global assessment which would include the fatigue and everything else.

DR. KATZ: I'd like to emphasize and maybe elaborate a little bit more on that proposal with an analogy.

If you think of something like pneumonia where somebody has chest pain, cough, fever, sputum production, whatever, if you give them morphine, it's going to help with their chest pain. It's going to reduce that symptom. It's going to reduce their cough, but you wouldn't call it a treatment for pneumonia. Yet, thank God, it's there and we should be applying it to people with pneumonia or something like it, codeine, dextromethorphan, what have you.

Likewise, if there's a treatment that improves the pain of fibromyalgia, I think that we should have some mechanism by which that medication can be made available to

the patients who just told us that they'd be happy to see something like that come down the pike. So my own thought is that we should have a label that says improves the pain of fibromyalgia, and I don't know, maybe we should even extend that to the fatigue of fibromyalgia or other things. I guess it could get complicated.

But then, in addition to that, recognize that there are treatments for pneumonia and if something does reduce the whole symptom complex of fibromyalgia, it reduces the patient's pain and fatigue, cognitive dysfunction, whatever, and we feel that by some biologically plausible mechanism, it's actually addressing the underlying disease, well, that should be further recognized by a label that says this is a treatment for fibromyalgia and, obviously, it will reduce the symptoms that go along with that disorder.

DR. FIRESTEIN: Dr. Anderson, and then Dr. Lasky.

DR. ANDERSON: I just wanted to say that although pain is of primary importance, the question before us is whether if a product is supposed to be truly efficacious for the treatment of the syndrome, you should expect it to show improvement in pain, physical function and patient global, and I would answer yes to that.

DR. LASKY: My concern would be the definition

of functionality because I've heard agreement around the table that certainly improvement in functionality is a positive outcome. There's no question about that. But without clear definitions of what would constitute functionality, I think the manufacturer would be at a specific disadvantage.

In addition, in terms of the length of the study, it's possible that pain relief may occur first and functionality later, and by continuously monitoring patients, the trials can continue after the drug has already come to market. But in order to make that claim for an indication, there has to be a line in the sand defining, in fact, what functionalities would be approvable by the FDA.

DR. FIRESTEIN: So, Lee, would the agency consider dividing things up as has been commented upon, where you have the pain and fatigue of fibromyalgia versus fibromyalgia as a global indication?

DR. SIMON: Well, I think that we'll consider anything that the committee suggests. That's why we're here. We have no preconceived notions. That's the other reason why we're here. A responder index might be exactly the way to go about doing this in the context of each of those areas, the pain of, the fatigue of, the blah-blah-blah of, and we are partial to that in a multidimensional,

multisystemic disorder, such as this one. It has a lot of logic to it.

What doesn't have a lot of logic is to have to create a bar where you have to win on multiple things that there's a lot of argument about.

DR. FIRESTEIN: I think most people would agree with that.

Yes, Jim?

DR. WITTER: Can I just have a bit of a discussion then on the pain metric itself in terms of, I had mentioned earlier, we're always concerned about overpowering of studies, that you can get a statistically important result, but it has no clinical meaning. John Farrar has come out recently with something suggesting that a 33 percent effect size is what you should shoot for in a chronic pain condition.

Could I have some discussion on if it's the pain component, what should that look like?

DR. FIRESTEIN: Sure. Who would like to comment on the pain component? Dr. Katz?

DR. KATZ: Dennis and I are having a secret visual communication.

(Laughter.)

DR. KATZ: We just finished having this IMMPACT meeting that has been alluded to several times, and I think

Jim, you were there, and just to reiterate for the rest of the group, that's a group of people who spent a lot of time reviewing all of the pain measures that have been used for chronic pain clinical trials. Basically the long and the short of it is that after that extensive review, that group came up with a recommendation of if we're looking for a unidimensional pain intensity measure, then a 10-point numerical rating scale was, for a variety of reasons, the recommendation.

DR. CUSH: How much improvement required?

DR. KATZ: The issue of what's a clinically significant improvement is a completely different question and to comment on that, it seems to me that the proportion of reduction of pain intensity that's clinically significant depends somewhat on the scenario. John Farrar has work related to neuropathic pain and also to cancer pain, just those two entities, but we don't have any evidence that those results necessarily extend to other areas.

My understanding of that same issue in the acute pain literature where people have tried to compare -- say, for example, with the stop watch techniques where you see when the patient clicks the watch is meaningful versus what the pain intensity difference is, my understanding is that it's closer to a 50-percent reduction in acute pain.

And in our own study on chronic low back pain, looking at a non-steroidal anti-inflammatory drug -- we haven't published this yet but we're working on it, and it looks also like it's more like about 50 percent relief. It correlates with the patient global improvement of meaningful.

So I think that if people wanted to find what the clinically significant differences are in fibromyalgia, it will have to be defined in the context of the specific field.

DR. STAUD: I was wondering if you could elaborate on this somewhat more, because I think most of us are aware of the problems with 10-point scales regarding linearity and comparison. So you could easily have someone who improved from a 9 to an 8, and the difference from 9 to 8 may be much less than a difference from a 4 to a 5. So I think for this reason, VAS scales have shown in multiple validation trials to have linearity and seem to be a better measure of change compared to 10-point scales.

DR. KATZ: Dennis, I don't know if you want to comment on that. My understanding is that there are some studies that suggest that the VAS is a ratio scale whereas the numerical scale doesn't have quite those ratio properties, but that in practice they both do exactly the same thing. Dennis, I don't know if you want to elaborate

on that.

DR. TURK: I'm not sure I want to elaborate, but the IMMPACT process did commission a background paper that addressed that particular issue, and in addition to raising the point that Nat just made about the linearity, and it looks like it's basically the same, whether you have a 10-point numerical scale or the visual analog scale.

There are several studies showing, especially with older populations, difficulty using visual analog scales and not understanding how to use mid-points and tend to use extremes. So the IMMPACT group recommended against using visual analog scales, mainly because of the difficulty with using it across populations of different ages.

DR. FIRESTEIN: Jim?

DR. WITTER: Could I press Nat a bit to expand upon your earlier comment then? If fibromyalgia should be viewed differently from other chronic pain models, I'll use that term, why should that be the case in terms of a 33 percent with, let's say, lower back pain? I mean, why should this be different?

DR. KATZ: Well, I think it's an empiric question. If the question is what percent reduction in pain intensity is best predictive of the patient global response as being good to excellent or better or meaningful

on a stop watch of wherever you decide the patient is going to report to you their own sense of whether their response is meaningful, to me, it's an empiric question as to whether that number is the same across multiple different disease entities. I don't think there's any reason to think that God made it that way and that it has to be the same across all different disease entities.

In terms of what data exists to address that empiric question, the only data that I'm aware of is John Farrar's work with the pregabalin in neuropathic pain and the work he did with the Actiq lozenge where he showed that if you use the metric of the patient's behavior of taking a second rescue dose as a sign of meaningful analgesia, a 33 percent reduction of the pain intensity that they started with at the time of that breakthrough episode was the degree of pain reduction that best predicted that the patient would not need to take a second rescue dose. So two different ways of getting at the clinical meaningfulness question. Both miraculously gave about a 33 percent reduction as the answer which is interesting that it's so consistent but still doesn't prove that it's going to be the same in other disorders, and we have these counter-examples.

My understanding in the acute pain scenario is that in fact it's not 33 percent but it's more like 50

percent, and our preliminary work with chronic low back pain and NSAIDs suggests that it's more like 50 percent.

The other issue is that we don't have any reason to believe that it's the same across drugs. The amount of reduction in pain intensity that may be associated with a patient rating of satisfaction may be different with opioids and with NSAIDs. My own sense of the literature, having looked at that informally, is that probably patient satisfaction may be associated with a lower pain intensity difference with the opioids which may independently modulate affective components of pain compared to the NSAIDs. So there's no reason to think that it's the same across all these different situations.

In fibromyalgia, if there's literature that directly assesses the degree of pain reduction that's best correlated with patient global assessments, I'm not aware of it, but it would have to stand on its own for fibromyalgia, I think.

DR. FIRESTEIN: Dr. Gibofsky?

DR. GIBOFSKY: I don't pretend to know what metric should be used to measure pain and since I don't know what metric should be used to measure pain, I don't know what the MCID for that metric should be, but the one thing I would argue strongly for -- and I'm influenced by what Ms. Matallana had to say -- is that whatever metric we

recommend should be one that can be simply applied and utilized by the non-specialists. Our patients are telling us that they want care from a non-specialist and most of the trials will be done by the non-specialists.

The incidence and prevalence data of fibromyalgia suggest that it's just not possible for all of our patients to be seen by any of the specialties represented here today, and so we need metrics that go beyond the sophistication of the specialists that can be easily applied.

The dichotomy between the devices that we determine for clinical trials and the actual data that we collect in clinical practice is often quite wide, and I think it would be problematic if we devise metrics for clinical trials that could not easily be adapted to clinical practice, particularly by non-specialists.

DR. FIRESTEIN: The number that came from your study was approximately a 20 percent improvement, and I think that's a reasonable place to start when trying to sort through. That is, what do patients find would be a clinically meaningful improvement in terms of at least pain? I mean, that number needs to be validated in some way obviously, but at least it's a reasonable starting place. You know, from an empiric perspective, amounts like 50 percent sound to me to be too high of a bar in terms of

trying to achieve in a clinical trial.

Jack?

DR. CUSH: I agree with those comments, and moreover, I think that the studies that I think Nat is talking about are using pain as primary outcome variables, and here, pain would be part of a composite definition, wherein such stringency is really not required. A lower level or minimum threshold of 20 percent could be reasonable if linked to a sequence of other "if" statements that then lends further credence to that initial 20 percent in pain improvement.

DR. FIRESTEIN: Dr. Witter?

DR. WITTER: Just two things on clarification. In acute pain, the discussion I think we should -- if we wander into acute pain, we should do so carefully. There's no argument, I think, from our end that in an acute pain setting, pain and function are essentially the same thing, and it's a very different setting, being post-op, I think you would agree, than having fibromyalgia. So I think we should wander into that carefully.

I just wanted a clarification. The 20 percent that we're referring to for fibromyalgia, that is the 200 responses from the 16,000 actually sent out?

MS. MATALLANA: We sent out 16,000. We had 1,119 responses, of which 200 we were able to tally, and of

that 200, 20 percent was the majority figure of needing to have improvement at that point.

DR. WITTER: Thank you.

DR. FIRESTEIN: I mean, that's obviously a very limited sample, but it does make some empiric sense that that's the general range that people might find useful in a treatment that had minimal side effects.

Just to come to the second part of the question in terms of the duration of clinical trials, most of the numbers that have been tossed about have been sort of in the 3- to 6-month range. Is there a lot of discussion on that? Of course, Dr. Cush.

DR. CUSH: I think to go anything less than 6 months would be a mistake, but at the same time, I do think that whatever guidelines we put forth, that they should be ones that are, A, meaningful but also, B, tend to promote investigation and drug development in this area, and so to develop too many hoops to jump through for studies that are too long, then who cares if there's 10 million people with the disease. We're just not going to go there. We'll go after simple pain indication and do it that way. So I think that again if 3 months actually improves the likelihood of that, then fine, but I think ideally 6 months should be the minimum.

DR. FIRESTEIN: Yes, I would agree with that.

Jennifer?

DR. ANDERSON: I'd just like to comment that I agree that 6 months is a good length, but for these sorts of trials, that you presumably would have multiple observations made during the trials, so you could determine how long it took for the drug to begin to be effective, so that the speed of action could also be determined.

DR. FIRESTEIN: Gary?

DR. HOFFMAN: I agree with Jack that 6 months seems like a reasonable minimal period of time, but the question is what would be the optimal duration, and given that this is a chronic disease and that the drugs that are going to be tested may be agents to which there is some adaptation and loss of effect over time, I think it'd be terribly important to know what the treatment response curve was over a more chronic period of time. So I'd be in favor in responding to the charge of what would be optimal duration to be thinking more in terms of a year.

DR. FIRESTEIN: Why don't we move on to the next question then, which is not posed with equipoise. It says: does the committee agree that placebo-controlled studies with analgesic rescue are a primary requirement in fibromyalgia?

I think placebo-controlled studies are a reasonable approach to this, Dr. Simon. Does anybody

disagree with that? Dr. Simon disagrees with his own question.

(Laughter.)

DR. SIMON: If we are to accept the possibility of true placebo-controlled trials, what does that mean to everybody around this table? What would be the background therapies that would be acceptable in that there is really no standard of care? Standard of care is very much up in the air and has a lot to do with components of treating aspects of the disease. There are many antidepressants, such as tricyclic antidepressants, that, as Nat previously noted, treat fundamentals of fibromyalgia, at the same time treating the depression.

So I would presume the committee is not really thinking about a 6-month trial of absolute real placebo compared to standard of care. So could someone comment about those implications?

DR. FIRESTEIN: That's not really the question. You didn't ask if this would be an add-on or not, but whether it's as an add-on or a single agent, I think everybody agrees that it should have a placebo control to it.

Now, that actually brings us to the next question, which is: what are the concomitant medicines and in particular those related to depression?

DR. WILLIAMS: Can I address question 3 first with analgesic rescue? Because we've done OA trials with analgesic rescue using 4 grams of acetaminophen and have patients who tolerated that. Now, whether fibromyalgia patients will do that or not, and to respond to the question as written, I would say you could have a placebo-controlled trial with acetaminophen rescue.

DR. SIMON: I'd just like to point out the caveat to that. There's a very famous study with hyaluronic acid with concomitant acetaminophen rescue where there was no evident capacity of the study drug to actually benefit the patient since they achieved appropriate analgesia with the acetaminophen. So one thinks of rescue in two different ways. Is analgesic rescue with acetaminophen withdrawal and failure of the study drug or is it concomitant therapy and background where then you're measuring from where you start off with with the analgesic background a la add-on trial, and then how do you ascertain the benefit? Would you then expect the same 20 percent improvement that you would with no background therapy?

So the first question is: would the analgesic rescue be failure of the study drug, thus withdrawal? And the second question is: if you're thinking about it as concomitant background therapy, would you then design a different kind of trial analysis defining a disease

activity score at the inception of the new study drug on the context of the background therapy and following and determining the outcome with the same disease activity measure subsequently?

DR. WILLIAMS: You make it a lot more complicated now. I think that if acetaminophen is going to complicate your response, then they don't need another drug. But you can't ask them to go on placebo without any benefit of anything else. So that, in the OA studies, using that as an example, we didn't expect acetaminophen to give total control, but we gave them some analgesic benefit if they needed it, and I think if that complicates the response to analgesia, then probably the drug doesn't offer a lot of extra benefit.

DR. FIRESTEIN: We'll now move on to the next question, which is related to treatment of depression and other concomitant medications.

So who would like -- Dr. Cush?

DR. CUSH: So the answer is no, patients with depression on full dose regular daily meds for depression should not be excluded. However, patients with uncontrolled depression with a BDI, Beck Depression Inventory, of a certain scale should be excluded as a measure of being uncontrolled. I think that would be reasonable.

I think con meds should be allowed, SSRIs. I think the real issue, I'd rather defer this to Nat and others who may know because my impression is that the use of tricyclics could clearly confound all this. Unless that were to be stratified for in trial design, I would not like/allow/want to have pain modifiers, such as tricyclics, in the trial.

DR. WILLIAMS: I would think if you're using pain as a primary outcome measure, you'd also want to excludes opiates.

DR. FIRESTEIN: Well, would opiates be written in as your analgesic rescue since NSAIDs are of marginal value?

DR. WILLIAMS: Well, previously, I said I'd use acetaminophen as analgesic rescue, and I wouldn't use NSAIDs, but I think that if you're using pain as your primary outcome measure, once you start using narcotics, you really complicate things because they may give you benefit with adding complications further down the road.

DR. FIRESTEIN: What about studies with either tricyclics or SSRIs or various combination drugs? How does one manage a clinical trial if they're being treated with an SSRI, for instance, or tricyclic for depression?

DR. WILLIAMS: I actually agree with Jack, that I think you do eliminate tricyclics, and I think if they

have depression that is controlled and you have to figure out how long you want it to be controlled. We do this with steroids in RA trials. They can be on steroids, if they've been on them for a period of time and they don't change. You could say that if they have depression and they're being treated with an SSRI or some other antidepressant drug, not a tricyclic, that if they've been controlled for X period of time, and that could be determined, and it doesn't change during the trial, then it's fine.

DR. FIRESTEIN: But if the mechanism of action of the clinical trial agent is related either to serotonin or norepinephrine or a variety of other --

DR. WILLIAMS: See, I'm not as convinced as some of you that SSRIs are as beneficial as tricyclics in fibromyalgia.

DR. KATZ: I think it's helpful to not lump all the kinds of clinical trials together and make blanket rules that cover both early proof of concept trials and late phase III trials because the goals of those trials are different. They're testing different hypotheses, and the risk to the trial of allowing potential confounders, such as concomitant depression or treatment for depression, is different in those two stages.

Clearly, all these drugs and the existence of concomitant co-morbidity, like moderate to severe

depression, is a potential confounder, and so for an early proof of concept trial, it might be prudent to exclude patients with all those issues and even maybe have a shorter duration trial where you're trying to just test your concept, whereas in later stages of development where you want to know -- and yes, the people out there in the world of fibromyalgia do have depression, are on these drugs, and yes, you may need to stratify it. So it may be appropriate to include those patients later on in drug development where the generalizability of earlier findings to those other populations becomes the question of relevance.

DR. BRADLEY: He convinced me.

DR. WITTER: I wonder if I could ask the chair to ask Drs. Crofford and Clauw to make comments on their opinion as to whether opioids are effective in the sense that we've been discussing today, effective for fibromyalgia in terms of treating pain.

DR. FIRESTEIN: In terms of rescue, you mean? Yes, not Dr. Clauw, but Dr. Crofford, I will immediately reflect that question without repeating it.

DR. CROFFORD: Thanks, Jim.

I actually don't think opioids are particularly effective in this syndrome, and I would agree completely with whomever it was, and I think it was a consensus of the

panel, that opioids should not be allowed as rescue nor do I think it's really necessary.

But I do think, if I could elaborate just briefly, if you want to do a monotherapy trial that's placebo-controlled, I think you should carefully consider whether 3 or 6 months may be the most appropriate duration of a trial in a condition where there's no approved drug and where therapies may not be particularly effective. Certainly I agree with everybody that the ideal is that it works forever and it stays the same and the effectiveness is maintained, but if you're considering a trial where you actually don't have concomitant meds or rescue meds, I think -- and you may ask your patient -- it may or may not be tolerable.

DR. FIRESTEIN: The ethics of placebo controls have been considered extensively in a variety of other disease states, and it's even more pertinent, for instance, in rheumatoid arthritis, for instance, where the window for being able to allow placebos has gotten narrower and narrower.

In this particular instance, unlike rheumatoid arthritis where there is now an alternative effect of therapy that can alter the natural history of the disease, there isn't really such a treatment right now for fibromyalgia, and my guess is that most patients, when they

enter a study such as this, will already have been tried on the standard available approaches. So I don't see a particular problem with, for instance, a 6-month clinical trial under those circumstances.

DR. CROFFORD: I'm not arguing against placebo control. Don't misunderstand what I'm saying. In fact, I'm not even arguing against a 6-month trial. I actually think a 6-month trial would be useful. I'm just hoping not to discourage people that may want to start clinical trials from actually doing them.

MS. MATALLANA: When we asked patients what was their first choice of treatment, the number one medication currently on the market was Ultram or Ultraset and following that was Vicodin, Oxycontin and Darvoset. But I personally feel that the reason why so many patients are on these narcotics is because doctors do not have many other options, and I know personally that I was put on a lot of heavy narcotic medication, weaned off of it and then put on basic Tylenol and Ultram and had quite a bit of improvement. So I think you definitely need to take them off these medications in order to see the efficacy of the new treatment.

DR. FIRESTEIN: Jack?

DR. CUSH: You could also say that people who responded to your survey were Ultraset, Ultram, Vicodin

users and not non-steroidal Tylenol responders.

DR. SIMON: I'd like to assure Leslie and others around the table that we would not be considering an active comparator trial for 6 months that would require true placebo in that.

I would like to reiterate Nat's point, that we would like to see at some stage in development a proof of concept that would demonstrate perhaps in only just 6 weeks, maybe even less, that there is a signal of improvement that would warrant going further in development to allow then the large pivotal trials to be appropriately designed that would allow patients to be in appropriately. So no one should think that we're withholding therapy for 6 months of a period of time.

But proof of concept is a very useful way to think about a short-term exposure that may allow us to get a real signal of real measurement that's not confounded and that's always very important to have, not just for efficacy but also for safety.

DR. FIRESTEIN: Lee, I think you have to be careful about referring to a placebo as withholding therapy.

DR. SIMON: Well taken.

DR. CUSH: Lee, were you intimating that you would consider an active comparator trial in an environment

when there is no reasonable active comparator, like proven efficacious standard of care, or would you have to go with, as your active comparator, a drug that's approved as a pain indication, for instance, albeit not for fibromyalgia?

DR. SIMON: Given the fact that this is an evolving field, we would be open to any suggestion that would be legitimate, that would be able to show a signal of improvement, and recognizing, of course, if you're doing an active comparator trial, you're going to need to be superior to your active comparator if your active comparator is not already labeled in that particular field. So that then becomes standard of care or "placebo." So it just depends on what you mean.

A non-inferiority trial which obviously would be very difficult to design in this construct, would require a comparator that's already approved on the market and thus accepted. Tricyclic antidepressants would not fulfill that requirement at this time.

DR. FIRESTEIN: Nat, did you have a comment?

DR. KATZ: I had a question for the group. I know that people who in their world of rheumatology have a lot of experience in considering the purpose and the methodology in analyzing these very long-duration trials. The pain trial tradition that I come from typically uses much shorter trials.

But my question would be if the purpose of the trial is to show that the effect, the analgesic effect is durable over time, it seems like there are a number of different techniques that one could consider for demonstrating that aside from having a prolonged comparison, and it would also seem to me that the prolonged placebo comparison as the primary means by which to judge the durability of therapy is fraught with all sorts of methodological issues. You've probably got much more dropouts in your placebo group, I would think, that on your active group, and you've got only the people in the placebo that are placebo responders. I would ask the group in rheumatology who do these sorts of things all the time whether you consider other alternative study designs for demonstrating durability of effect, like withdrawals down the line or other sorts of methods one could imagine.

DR. FIRESTEIN: Yes, we've considered them.

(Laughter.)

DR. FIRESTEIN: Well, I think most of our experience, in terms of these chronic disease states, suggests that you really do need to have prolonged treatment and that there are issues in terms of dropouts that can be statistically handled, and maybe Jennifer can comment on that in terms of using intention-to-treat analysis and making the appropriate corrections.

But the gold standard really has been long-term placebo-controlled studies for most of the agents that are currently approved for chronic rheumatic diseases. In particular, rheumatoid arthritis is where there's by far the most experience but also osteoarthritis.

DR. STAUD: I was wondering. In a disease where we have no short-term knowledge of effectiveness of most analgesic therapies, why we would initially go and require such long-term effectiveness and not say we are already happy if there is effects for 3 months instead of 6 months.

DR. FIRESTEIN: Well, in part, because of the rather prominent placebo effect that can occur and the lack of durability of many placebo effects.

DR. STAUD: I understand this, but we assume that the trial drug will be more effective than placebo.

DR. FIRESTEIN: Well, we don't assume that actually. That's what the purpose of the study is.

DR. STAUD: I know.

DR. ANDERSON: I could make some comments about this. Using the term "placebo-controlled trial" isn't meant to mean that all therapies are withheld from the placebo group because placebo, as has been discussed here already, includes some background medication generally these days. So although one might anticipate that there

would be more dropouts from the placebo group, if you're really going to do an intent-to-treat analysis and get a handle on the effectiveness of the new therapy that you're looking at as distinct from its efficacy, you have to include all patients for the full duration of the trial. So even if people "drop out" in the sense that they're no longer taking the therapy that they began with -- and this applies to the intervention group and the control group -- you have to continue. The group that's doing the trial, the sponsor, whomever, has to make every possible effort to continue to get information at the appropriate time points from all of the participants, so that you can really do an intent-to-treat analysis. So that's my shtick.

I don't know whether I addressed what you wanted me to address or not.

DR. FIRESTEIN: Jim?

DR. WITTER: Maybe, could you just expand a bit? To some extent, there's almost some magical thinking when it comes to rescue medications, even the term "rescue," and I think one of the ways that we need to fix that, to use that term, is to keep analyzing the patients, even after they start taking this rescue, to give us an idea of did it work, did it rescue. Could you maybe comment on that strategy to kind of help us fill in some of these blanks?

DR. ANDERSON: Well, from what I've seen of the write-ups of clinical trials, there has been a tendency to just stop collecting any information on the patients once they're "rescued" or deviate in any way from the desired protocol. But I guess my point is that you really do need to keep getting the reports from them and making the measurements on them, so as to do the efficacy analysis and so that you can do what you're referring to, to see whether this rescue was really a rescue, and you can learn a lot and maybe it isn't all together in favor of -- well, I don't know. Who knows what it's going to show, but I don't think the sponsors should be scared of doing these analyses.

DR. WITTER: Should we be asking then sponsors to do that in the trials as they propose, that they look at this, even if patients are rescued, they continue to look at these outcomes, particularly pain?

DR. ANDERSON: Yes, yes.

DR. FIRESTEIN: Just to come back to the questions, are there any concomitant therapies that should definitely be excluded? I think we talked a little bit about this, but should tricyclics be excluded, for instance?

DR. WILLIAMS: Well, I think Jack and I both have said that we thought tricyclics ought to be excluded,

opiates ought to be excluded, and there was some discussion about whether SSRIs should be excluded.

DR. FIRESTEIN: Are there other comments from the committee with regard to SSRIs, for instance?

DR. CUSH: I would modify it according to what Nat said earlier, that in the short term, yes, more rigid, but in the long term, no, because it's more real life. I think that patients on antipsychotics should be excluded. I think patients with primary CNS issues, whether it was meningoencephalitis, head trauma as an inciter, inciting events getting in, should be excluded. I have another exclusion somewhere but I can't find it right now.

DR. FIRESTEIN: Yes?

DR. TURK: Just a caution for us as we think about excluding antidepressants or depressed patients. I work in research in a tertiary care rehabilitation center, so obviously it's a select sample, but somewhere in the neighborhood of 50 to 60 percent of those patients are coming into us and they're receiving antidepressant medication which would mean that if we were using them in clinical trials, we're basically chopping off half of the sample of patients who are being treated in at least that type of facility. So what you're left with is a potentially unusual subsample of people with fibromyalgia.

DR. FIRESTEIN: Is there disagreement about

concomitant use of tricyclics? For instance, you would exclude tricyclics?

DR. WILLIAMS: I would exclude tricyclics. I actually like Nate's approach where we have proof of concept and then later on, you can add some of these other drugs in on stable doses and see what happens with that, but I think that for initial demonstration that you've got an effective drug, you have to exclude tricyclics.

DR. FIRESTEIN: Right. But for registration purposes later on? For phase III studies, I think it would be very difficult --

DR. WILLIAMS: -- to show you've got some benefit.

DR. FIRESTEIN: One assumes that you're already done a short-term proof of concept study. At that point, it would be very difficult to --

DR. WILLIAMS: I think there are two studies. One, you have to do without tricyclics and one you do with stable tricyclics.

DR. BRADLEY: I would agree. I think especially over time, I think there's a number of trials, particularly Carette's trials, in the early 1990s showing that the effects of the tricyclics really do fade over time. After about 3 months, they really tend to fade out. So when you get to the longer trials, I think then it's

appropriate. You can include tricyclic use.

The other issue with regard to other exclusionary criteria. I'm concerned about including people in trials who have had maybe even one but certainly multiple spinal surgeries, spinal fusions. I'm not sure that the pain that those people experience is exactly the same as the fibromyalgia syndrome, and I would be careful about these people with really dramatic trauma done to their spines.

DR. FIRESTEIN: The point you make about the duration of response to tricyclics also, by the way, is again one of the reasons why it's important to have a longer duration study.

Well, the next question relates to ancillary therapies, such as physical therapy, exercise, behavioral therapy, psychotherapy, particularly for people requiring dental procedures.

(Laughter.)

DR. FIRESTEIN: Should that be allowed during the trial?

I think from my perspective, these things are all reasonable to include.

DR. WILLIAMS: I think it's very analogous to using steroids in rheumatoid arthritis. You have them on a background, but they have to be stable on that background

before you start the study. You can't start the exercise therapy at the same time you start your intervention. So as long as they're stable on those backgrounds and they don't change.

DR. FIRESTEIN: Yes?

DR. ANDERSON: But in rheumatoid arthritis trials, are people prevented from taking an exercise class or something during the trial? Does anybody notice?

DR. WILLIAMS: No. Often, we don't ever discuss physical therapy in rheumatoid arthritis because we don't think it changes the course of the disease. It may change long-term mobility of the joints and so forth, but it doesn't change the arthritis.

I was more using the analogy of corticosteroids, where that is an effective therapy, but as long as they're on a stable dose and it's been stable for 2 months and you don't change it during the course of the disease, that it's allowed, and I would say if these people are on these interventions mentioned here and they were stable on those interventions, you can add in another intervention for your trial, as long as these didn't change.

You're the statistician. You look troubled.

DR. ANDERSON: Well, I just think that -- and I'm not sure that this is from a statistical point of view.

I don't think you should say that none of these should be allowed to be started during a trial. I guess if somebody starts to feel better, they may want to start doing some exercise or something like that and to be prevented from doing it because it's during a trial, I think, is a problem. I just think that any of these therapies that people decide to do should be noted and the information should be there that they've been doing them and for how long as part of reporting on the trial and finding out and looking at the results.

DR. FIRESTEIN: Dr. Hoffman, then Dr. Staud.

DR. HOFFMAN: I would agree with those comments. I think it has to be approached the same way an adjunctive pharmaceutical therapy would be approached, that if the people providing the study design feel that exercise is an important adjunct to treatment, then the same guidelines for exercise should be provided for everyone. Everybody is being randomized to both groups. It shouldn't then be a confounder.

DR. STAUD: Yes. I can see this only works if the adjunctive therapies are standardized across the trial which I think is very difficult for psychotherapy, behavioral therapy and so on, and so for this purpose, it will pose a major problem.

DR. FIRESTEIN: You think that it's a major

problem, did you say?

DR. STAUD: Yes, because I think the standardization of these interventions across the trial is very difficult, and so what was mentioned here, this would have been part of the trial itself, that it could not be just something that these subjects do on the side.

DR. FIRESTEIN: But do you think any of these have a significant impact on the disease in a short-term or relatively short-term trial, like 6 months? Psychotherapy for 6 months?

DR. STAUD: CBT does. Acupuncture does. So I think all these things need to be considered.

DR. WILLIAMS: I think exercise can.

DR. FIRESTEIN: But again, it will be very difficult to strap patients into a couch with a remote control for the duration of the study, if part of the response to the treatment would lead them to want to exercise more. It would be very difficult to build in a lack of exercise requirement.

Jack?

DR. CUSH: I agree with Roland. I think that this is fraught with difficulty because you can require them to have a stable course of whatever these therapies are for 2 or 3 three months at entry, but more importantly, you're going to have to continue those same therapies

throughout the trial, otherwise the patient is in violation of the protocol and would have to be dropped, and so the wording should almost be written to discourage such patients but you should allow them in.

The problem in reality is that if I can get my patients to go to CBT or to go to yoga to Tai Chi or to go to a pool program, they'll do it and they'll do it for a few months and then they stop doing it. They stop doing it for the most minor of reasons, because they got a little bit of benefit, they don't want to go any more, the bathing suit doesn't fit, whatever, and they stop going. So they become actually quite noncompliant with a regimen that has been shown to work, and you don't want to have that happen in the context of the trial.

So while you may let them in, that's well and fine. One thing we didn't discuss earlier on is what's the criteria by which they actually get into the study, meaning we talked about ACR criteria, fine, but what's the activity measure that allows them to get in and that's going to be an important part. So is it going to be as simple as a VAS of greater than 4 on a 10-centimeter scale. That's an important and difficult issue.

DR. SIMON: Yes. In thinking about this question, it was actually a little trick question here because we actually think that cognitive and behavioral

therapy is not the same thing as even standardized exercise. I think that we think that cognitive and behavioral therapy is as therapeutic as is a tricyclic antidepressant in this particular realm. I know it's hard for anybody to believe that I actually might say that. So under those circumstances, I think that we would likely either stratify for that or not allow it as part of the component.

The other components, one might think about this slightly differently. Perhaps if a population begins to exercise, perhaps that's a positive outcome and maybe it's a measurable positive outcome, how much exercise they actually can do. We've actually thought about turning that question around and using that as an additive outcome to be determined. So we're actually not adverse to that, but we are a little adverse to leaving in cognitive and behavioral therapy.

DR. FIRESTEIN: But you're quite right, it was not on your list of alternative therapies that would be available.

Were there a couple other comments?

DR. BRADLEY: I guess with regard to the exercise question, actually I think that perhaps it's the same sort of situation that we talked before, the difference between a short-term trial just as a

demonstration versus a longer-term trial. I think, for example, it's almost like a forward pass in Woody Hayes' point of view. Multiple things can go wrong. If you have someone who begins exercise at the start of a short demonstration trial for a pharmacologic agent, one might be that exercise might make the person feel better and then you obscure the effect of the agent. The other is, is that, oftentimes people with fibromyalgia, when they begin to exercise, actually feel worse at first, and then you might actually have a negative effect on your agent. So I think we have to sort of make some decisions about the short-term projects versus the longer-term projects.

DR. HOFFMAN: I'm not sure adding in the exercise variable really presents a problem because patients are being randomized between groups, and if they're randomized at each site, then the same standard of care is being provided, except for those exclusions that you would want to list otherwise. So those in the placebo group and those in what you hope is the active drug, the test drug group, have equal access to that modality and that should even out in the final analysis.

DR. STAUD: I think exercise is not the same as study application. This can vary within one subject so dramatically over time that I think it's going to be a very difficult variable to consider in this trial.

DR. FIRESTEIN: I'm confused as to why it's more difficult than in any other of the clinical trials that have been evaluated. For instance, again we don't prevent patients with rheumatoid arthritis from walking on a treadmill during a study with other anti-inflammatory agents. We don't prevent them from doing that in osteoarthritis. Why would we entertain that in fibromyalgia? That's different from again cognitive-behavioral therapy. This is again part of activities of daily living plus.

DR. STAUD: I mean, part of it is that the effect of short-term exercise is very unpredictable in this patient population. So that's the main reason. So I think long-term exercise, doing it steadily, I think it will have not dramatic impact on trials but short-term starting and stopping, I could see that happening.

DR. FIRESTEIN: Right. But we live in a real world and we have to let patients seek their own level in terms of activity, and if they're feeling better and they want -- there will be some potentially confounding issues if people are exercising more and that causes more pain for other reasons because they're deconditioned or other things that can cause some confounding issues, but overall, this has got to be a real world trial for the same reason it has to be real world with regard to concomitant medications as

we've talked about.

So one or two more quick comments and then we'll go on to question 6.

MS. McBRAIR: I agree on the issue of exercise. We need to allow patients to do whatever they can do to help themselves, and as long as that's documented, what has happened, I think we can look at it more closely. But to say someone couldn't exercise or couldn't do more and we're looking for increased function as one of the things we'd like to see happen, I think would be a wrong message for the patients.

DR. FIRESTEIN: The next question really relates to fibromyalgia with overlap diseases and how one decides clinical studies. Should patients with rheumatoid arthritis, lupus, Sjogren's, etc., be excluded from these clinical trials?

DR. WILLIAMS: If pain is your primary outcome measure, these are diseases that cause pain by a different mechanism, and I would exclude them.

DR. FIRESTEIN: I would agree with that. It just makes it too complicated to assess. That can be something that can be done later on, but if you're looking for efficacy in fibromyalgia, it will make it hopelessly complicated, I think. Everybody agrees with that.

DR. WILLIAMS: If you prove its effective in

fibromyalgia, it'll be used in these patients anyway.

DR. FIRESTEIN: The last question is: which of the available instruments appear most appropriate for evaluation of physical function, sleep disturbances, cognitive impairment, and fatigue?

I would open it up. We had a number of these sorts of things discussed. Anybody want to comment on this?

DR. WILLIAMS: We really discussed physical function earlier, and I don't know that there's a better one than the SF-36 right now for this particular disease. For sleep disturbance, it was Dr. Wells that suggested the VAS was as effective as anything. I'm not sure I can tell you anything about cognitive dysfunction as a good instrument. And for fatigue, I'd use the VAS.

DR. FIRESTEIN: Any other -- yes?

DR. TURK: At the IMMPACT meeting, when we looked at the question of functional measures, we separated it into disease-specific or general measures, and within the general measures, we recommend that the interference scale of the Multidimensional Pain Inventory was as good, if not the best, measure to use, followed by the BPI, or the Brief Pain Inventory. Now, the Brief Pain Inventory is a pain-specific measure. The Sickness Impact Profile, the reason we had concerns with that is because the literature

on its sensitivity to change is pretty poor and therefore it might not be the best outcome measure to use.

DR. CUSH: Of these, I would have physical function and sleep disturbance in there. I would not do cognitive impairment. I think fatigue is up in the air because I think that at some point, they're all inter-related. You might as well add headache and irritable bowel and everything else onto this. It gets a little crazy with 54 visual analog scales to come up with what's going on in fibromyalgia.

I think that we should go towards a responsiveness, an FM-20, if you will, that goes after three domains. You must meet pain and any one of two or three others. Certainly two that are potential areas are pain and fatigue and quality of life or function, and to improve in pain plus something else would be enough.

Now, what you choose for each of these domains has got to be left up to whatever the state of the art is, and I think that we've heard what's reasonable as far as function. I think that there are sleep scales that can be used or as simple as a visual analog scale. I don't know that you improve things more than the visual analog scale for pain and then for fatigue. There are specific fatigue questionnaires, not well worked out, I don't think, in fibromyalgia, but in other diseases they have been, like

cancer and whatnot.

So they're there, and to go with, again, a composite definition of response is reasonable, both for short term or long term, and I think it would be a major advantage or major leap forward in trying to promote drug development. Again, the idea is to go after not just symptom improvement but actual disease improvement, as Lee suggested earlier.

DR. FIRESTEIN: But with symptom improvement alone, would that not be a contribution?

DR. CUSH: Not much more than what we've done in the past or what we're currently doing because then you're always talking about single symptom improvement, and I think that that's a major step backwards. I think that maybe we're limited by our lack of understanding of disease. Nat's correlation with pneumonia was interesting, but also we're in the era where we truly understand the pathogenesis of pneumonia, the bugs that are involved, and the consequences of pneumonia and whatnot. If we were in the 18th Century, giving opium for pneumonia would probably make a great deal of sense, and I think that we may well be in the 18th Century with regard to fibromyalgia.

DR. FIRESTEIN: Well, again --

DR. CUSH: It's a little strong, I know.

DR. FIRESTEIN: It is a little bit strong, and

it's because in the end, we are in the 18th Century because we don't have a specific therapy, unlike pneumococcal pneumonia, and so treating symptoms alone, which by the way was a gold standard for rheumatoid arthritis for a long, long time -- except for injectable gold, there were no disease-modifying agents, and we know how good an agent injectable gold was. So just signs and symptoms was good enough without having a specific treatment for rheumatoid arthritis, and I think the same thing might be true for improving the lives of patients with fibromyalgia. Just improving the symptoms may well be a significant contribution.

Nat?

DR. KATZ: I would just re-agree with myself and with you now.

(Laughter.)

DR. FIRESTEIN: Unlike Lee who argues with himself.

(Laughter.)

DR. KATZ: Before someone looks up the rules. I mean, we just should keep in mind that there's been this traditional discordance between what's important to patients and what's important to physicians. I think we all have had pain at one time or another. If you can recall back to when you've had pain, you'd look at pain

relief as being a godsend, regardless whether it improved some other parameter that interested your doctor and more than interested you.

Now, again, I'm not disagreeing. I also feel that ultimately, there is a notion of treatment of disease that obviously is the long-term goal of drug development. Maybe one day, we'll understand this disease better and we'll have treatments and maybe that'll be in 5 years, maybe that'll be in 50 years. But in the meantime, if there are agents available that can treat symptoms, that's what patients are really looking for.

It's worth keeping in mind that drug development has been going on for thousands of years and effective drugs have been developed. In fact, the ones that we still use for pain have been developed long before anybody understood anything about the diseases that were being treated and anything about the mechanisms of the drug and that's how these what are regarded as boons to mankind have been developed.

So to minimize the importance of treatment of individual symptoms that occur in the constellation of all sorts of diseases would be, I think, a terrible mistake.

DR. FIRESTEIN: Steve, and then Lee.

DR. ABRAMSON: Yes, I would agree, and I think what we're really talking about is to have an isolated pain

indication is not necessarily unacceptable, but to mandate that in all of these studies that function and quality of life and all of these studies be standardized so that information is captured, maybe you don't have to win on all three domains, but you need to know that this drug works for pain but not for function. I think over time, that will be very important as these drugs sort out in the market.

I think there would be a hazard of a company going just for a pain indication. I think we'll lose a lot of information. So I think capturing information but having separate indications is still important.

DR. SIMON: Just actually as an extension, not to be terribly concrete, but for those of you that have had experience with the Krupp Fatigue Scale as opposed to a VAS scale for fatigue, might you comment on a multidimensional fatigue outcome versus just are you tired or how you ask the question to be dependent upon one question? Is there any comment about that in such an issue as fatigue?

DR. KATZ: Since it doesn't seem like anybody else knows the answer, I'll chime in with this tiny amount of information I have. There has been a lot of instrument development work that's gone on in the fatigue world. Talk to anybody at Ortho-McNeil Pharmaceuticals and they'll tell you all about it. Initially, they started with large

fatigue inventories and then ultimately at least their one was reduced down to the so-called Brief Fatigue Inventory that's commonly used, and so in their psychometric process, they were not able to effectively reduce their instrument down to one item.

DR. FIRESTEIN: Are there any other comments on these various instruments? I don't have any.

Jim?

DR. WITTER: Can I recue up my question then from earlier in terms of developing new instruments? Dennis is here and he can comment. One of the issues, for example, from IMMPACT is that even though we may not have an instrument, we still want the domain to be measured and that was the same message from the NIH conference that I discussed earlier. So just because we don't have something doesn't mean we don't need something in the long run.

So how would you suggest as a part of the discussion that we would encourage and facilitate, whatever the proper term is, to get these endpoints and get them validated and developed for the next generation of sufferers of this condition?

DR. FIRESTEIN: I guess you could mandate it. That's what you do.

Yes, I mean, as long as it's clear that it will not be used as a club to beat them over the head with later

if they don't hit a predetermined mark, then I think it's entirely reasonable to ask for the data to be collected, but it does mean that the primary endpoints are going to probably have to exclude that domain. But on the other hand, pain and patient global is not a bad place to start with fibromyalgia. Really, the question has been in terms of functional indices. We don't really know what to ask yet.

DR. KATZ: It sounds like we're all agreeing that ultimately we want to be able to measure the critical components of this syndrome of fibromyalgia in clinical trials, even if we don't necessarily require that one win on all the different components. It seems like the conversation has left off is that while we think that this functional measure might be a good one to throw in there and maybe this fatigue measure might be a good one to throw in there and somehow we'll guess at what might be an appropriate responder index, but the fact is, as you all well know in rheumatology better than I, developing such instruments and such responder indices is an empiric process that requires a concerted and directed effort.

It seems reasonable to me that as part of the development process of these medications, the agency is in a reasonable position to require that some sort of responder index be provided which to me seems like it needs

to be specifically developed.

DR. FIRESTEIN: But again, with the proviso being that it's not going to be used as one of the criteria for having a drug approved because you can't collect the data and then retrospectively validate it and then say that you either hit or miss based on those data.

DR. KATZ: Absolutely. It has to be reasonable.

DR. STAUD: I also wanted to bring up one point in the discussion that we haven't really done. This is measurements of disease processes that are relevant to the syndrome, and as we know, the process that is relevant is called central sensitization, central sensitization of particularly spinal cord elements as well as probably higher brain centers, and currently the only measure that gets even close to this is tender points that we talked about.

I think we have better measures these days that we could request from companies to use as criteria in these trials, even if they don't make the primary criteria, to look at these measures because they have impact most likely on the evaluation of the disease and its course.

DR. CUSH: I think it's a good opportunity for the FDA to hear from us who are practicing clinicians what would be valuable and reasonable in the construct of trials

and indications, but I also think that a parallel process should go on between the FDA and the NIH as far as developing a consensus group which will involve the experts in the field as to what would be the most discriminate values. And they'll be able to look at ongoing data collection and basically do the same as the way OMERACT has functioned to help rheumatoid arthritis.

One of the problems and one of the hindrances of that is that you bring together the best minds in fibromyalgia research who are very biometrically oriented and in the end, you get so far away from real life as far as what you're requiring for outcomes, that it's only good for trials and drug development and it has no utility to what I'm doing in my practice with my patients and the extrapolatability of the information from that new trial with its design to what I'm going to tell my patient and what he or she may expect.

So I do think that the input of this body at this point is important. I think we should push forward what we think should happen, whether it's how many domains, which domains, single domains, combinations of domains. I think it's important that you hear, but I also think that another process has to complement this.

DR. FIRESTEIN: So we've reached the end of your questions. Never mind. Yes, Wendy?

MS. McBRAIR: This isn't a question, just a comment. I work with a lot of fibromyalgia patients and they are looking for some answers and they are looking for some help. So I really commend the FDA on even bringing up this discussion and starting to look for answers and guidance. Along with medication control and learning more about what we can do to help folks, we certainly need to continue to look at what the cause is of fibromyalgia and hopefully some companies will continue to work on that as well as some scientific researchers.

It's very frustrating for patients to get the runaround and then also to find out what they have but not to learn that there's some real help out there. So I hope that we continue this conversation.

DR. FIRESTEIN: Dr. Simon?

DR. SIMON: Yes, we are assuaged. We want to thank everybody here. We tried to construct a committee that was part skeptic, part expert, part experience, and I think we really achieved that. Some people came totally disbelieving there was any reason to have this discussion, I think, and I think that there were good things that were brought up. And most importantly, you really gave us wonderful advice about what we truly are grappling with on a daily basis because in fact there are promising therapies that are in front of us and we just didn't know the kind of

questions to ask, and you've helped us to be able to do that.

DR. FIRESTEIN: Thank you very much, everybody. This meeting is now adjourned.

(Whereupon, at 2:54 p.m., the committee was recessed, to reconvene at 8:00 a.m., Tuesday, June 24, 2003.)