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SCIENTIFIC WORKSHOP ON

FEMALE SEXUAL INTEREST/

AROUSAL DISORDER

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TABLE OF CONTENTS

TABLE OF CONTENTS

(Continued)

TABLE OF CONTENTS

(Continued)

TABLE OF CONTENTS

(Continued)

TABLE OF CONTENTS

(Continued)

P R O C E E D I N G S

DR. CHANG: Good morning everyone. We're going to get ready to get started because we have a very full day, so I wanted to invite Marsha Henderson who is the Assistant Commissioner for Women's Health to welcome our -- to open our meeting today.

MS. HENDERSON: Good morning. I'm Marsha Henderson. I'm the Assistant Commissioner for Women's Health here at the Food and Drug Administration in the Office of Women's Health, and it is with great pleasure that I welcome you here today for our scientific workshop focusing on the topic of female sexual interest and arousal disorder.

Workshops such as today's will help FDA gain needed input into this complex disorder. Yesterday we heard compelling stories from women and men who are struggling with this condition. They gave voice to some of the challenges that surround diagnosing, assessing, and measuring treatment effects. Today we will hear from scientific experts who represent a variety of clinical disciplines such as urology, sexual medicine, endocrinology, obstetrics and

gynecology, psychiatry and psychology to discuss the challenges and explore solutions. I am confident that by looking through the many different lenses of expertise and personal experience, we will have an even stronger evidence base on which to review future product applications.

So without further delay, thank you so much for joining us again today and I invite Dr. Christina Chang back to the podium.

(Applause.)

DR. CHANG: Thank you, Marsha. Good morning again and welcome to the scientific workshop on female sexual interest and arousal disorder. My name is Christy Chang, again, and I'm a Clinical Team Leader in the Division of Bone, Reproductive and Urologic Produces here in FDA and CDER. For those who do not know, my division reviews drugs intended to treat female sexual dysfunction, and my team is specifically charged to review any clinical data that are submitted in support of these drug applications.

And I understand that there are a lot of folks who are joining us via the webcast so welcome,

everyone, and I'm just very thrilled to see that there is an excellent turnout for this workshop.

And first, I want to thank all the patients who spoke eloquently yesterday about how their lives had been impacted by the condition. We learned an incredible amount from these women who courageously shared their personal stories and we really appreciate it. So we recognize that sexual dysfunction can significantly impact a woman's quality of life so this is an important area for FDA to have dialogue with all the key stakeholders.

And having heard from the patients, now we want to turn our attention to the scientific workshop being held, and this is part of a larger two-day effort for FDA to hear from the experts in the field of female sexual dysfunction. And the experts are those who are in academia, who are studying the condition, and those who have conducted clinical research in this area as well as a representative of the pharmaceutical industry. Given the limited time we have and the complexity of the female sexual dysfunction overall, we want to also, like yesterday,

focus today's workshop specifically on FSIAD, or female sexual interest and arousal disorder because there is no FDA-approved pharmacotherapy currently for treating FSIAD.

We have assembled a panel of experts with impressive scientific credentials representing diverse viewpoints, and this is a great opportunity for FDA to gain more clarity on the questions that we've had in terms of being able to accurately make a diagnoses and for both enrollment in clinical trials and ultimately in clinical practice. So in addition, we also hope to have conversations about which clinical endpoints may be most meaningful to patients and about getting valid patient-reported outcome measures that really be useful for the key efficacy endpoints in clinical trials.

So now allow me to give you a brief overview of the agenda today. The first half of the morning will be devoted to five presentation and we'll start off and end with two FDA presentations. Dr. Marcia Whitaker from our division will review our current approaches to evaluating clinical data and clinical

trials for drugs intended to treat FSD, and Dr. Ashley Slagle will discuss how FDA has reviewed the PROP instruments that are frequently used in this area.

And flanked in the middle of these two talks are three external presentations from our experts. The first is Dr. Rosemary Basson who will talk about the female sexual response, and then Dr. Cindy Meston will discuss the diagnosis criteria as outlined in both DSM-IV and DSM-5. And given the recent combination of HSDD and FSAD into FSIAD, we think t his will be a good opportunity to hear both. The last external presentation will be from Dr. Leonard DeRogatis who will share with us his perspective on the PRO instruments.

And these presentations will serve to provide a foundation on which to launch into the three sessions where FDA has specific questions for the entire panel. And as for our distinguished panel, the roster is included in the meeting material, and we'll ask each panel member to introduce him or herself when we get into panel discussions later. And please note that we have asked all the panelists to disclose

potential conflicts of interest which are also included in the meeting materials.

And so now I want to go over a few ground rules. We tried very hard to make the discussion topics non-biased and the questions open-ended to get diverse opinions, and we certainly welcome feedback and questions from the audience.

After the morning presentations, we -- and the audience are welcome to ask clarifying questions as well as the panel of the presenters. I'll let the panel go first and as to the audience, we're going to ask the audience to write down their questions on index cards. We'll be collecting those so we can group the similar questions that are posed by the audience to move things along.

And following each of the discussion topics, there's also an opportunity for the audience members to directly pose questions to the panel, but we ask that these questions or comments be limited to a minute or two to allow everyone a chance to share their viewpoints. And I just request that for any audience members who come up to speak before asking

your question or before making your comments, please state your name, the organization that you're affiliated with, or -- and as well as whether you're travel is being funded by any of these organizations that may have an interest in today's discussion.

So if we don't have too many questions from the audience later on, then we will just move along in our agenda.

And so again, a very warm welcome to everyone here and thank you all for traveling to the FDA. And I also want to thank all the members of our panel in advance for sharing their insights with us.

And finally, please know that our discussion will not focus on any particular drug products and that no regulatory policies or decisions will be made today. FDA will take back all the comments that we hear from both days of the workshop and carefully review them so that we may take the next step forward.

And I'll now turn over to our first presentation, Dr. Marcea Whitaker who is going to discuss the regulatory paradigm for evaluating drugs intended for the treatment of female sexual interest

and arousal disorder. Dr. Whitaker.

DR. WHITAKER: Thank you, Dr. Chang, and good morning. My name is Marcea Whitaker and I am a Medical Officer in the Division of Bone, Reproductive and Urologic Products here at the FDA, and I will be giving the overview of the current regulatory framework for female sexual interest and arousal disorder, or FSIAD.ddd

As you will hear from Dr. Meston a little later, FSIAD is a relatively new diagnosis in the 5th edition of the DSM, referred to as DSM-5 which was published last year. It's a merging of two separate and more well-known diagnoses, the hypoactive sexual desire disorder, or HSDD, and the female sexual arousal disorder, or FSAD in the previous DSM versions. Because the clinical experience with FSIAD is limited, we are interested in hearing and getting some clarity from the panel on some of the unresolved questions we have relating to its diagnosis.

Per the DSM-5, FSIAD is diagnosed by the absence or the reduction in sexual interest or arousal for at least six months duration that includes at

least three of the six listed symptoms. The first three and the fifth symptoms relate to desire and the last three relate to arousal. The symptoms refer to the absence or reduced interest in sexual activity, thoughts or fantasies, initiation or responsiveness to a partner's initiation, excitement during sexual activity, response to sexual cues, and genital and non-genital sensations during sexual activity. In addition, the problem must cause significant distress and other causes of sexual function such as mental disorders, relationship distress, substance abuse, medication side effects or other medical disorders must have been ruled out. Primary care physicians are often the first line of contact for these patients. However, other specialists such as psychiatrists, urologists, psychologists, and sex and couples therapists may also make the diagnosis.

As we transition from HSDD and FSAD to the combined diagnosis of FSIAD, the Division understands that there will be some challenges when it comes to designing and interpreting the results of clinical trials. For example, how should the new diagnostic

criteria be applied to enrolling patients in clinical trials; what combination of symptoms should be used. I refer you back to the previous slide where it listed the six symptoms of FSIAD. So what if a patient has two desire symptoms and one arousal symptom and another patient has one desire symptom and two arousal symptoms? Both the patients have three symptoms that qualify them for the FSIAD diagnosis but are their profiles similar enough to justify being included in the same clinical trial?

Another challenge is that low desire and low arousal may have different etiologies. So how would we differentia whether a particular product treats primarily desire symptoms or primarily arousal symptoms in one clinical trial? And how should these products be labeled if most patients in the trial have, for example, only low desire and not low arousal? And which patient-reported outcome or PRO instrument is best to use? These are just some of the questions that we want the panel to consider during this workshop. Until we address these questions and other related concerns, it will be difficult for the

Division to provide more definitive recommendations on the design and the conduct of clinical trials in FSIAD. Some of these questions that are raised also apply to HSDD and FSAD indications.

As a result, what we can offer are very limited general recommendations for clinical trials; Mainly, that patients enrolled should be sexually active women who are at least 18 years of age with documented personal distress related to low desire or arousal difficulties. Sponsors should define the targeted patient population, provide a justification for the patient population that is selected and also provide sufficient details of the enrollment criteria.

We do encourage sponsors to study both pre and post menopausal women in the clinical development program. Ideally, these two groups of women should be evaluated separately. However, if pre and post menopausal women are included in one trial, the study should be powered for each subgroup due to the possible differences in the physiologic response to treatment as well as any potential differences in the safety profile. Because of these potential

differences and their potential impact on efficacy and safety, labeling will reflect only the populations studied. We do refer sponsors to the estrogen and vasomotor symptoms guidance listed here for further definition of these populations.

As with any application, FDA usually requires two adequate and well-controlled studies for approval. For FSD-related indications, we also require that these studies be conducted in North America, either in the United States or in Canada because we believe that there are enough differences in the diagnosis and the practice of medicine in other regions of the world. We also believe that there are sufficient differences in how patients view their disease based on cultural or religious influences and how they respond when asked about their symptoms. Due to the subjective nature of these conditions and how they may be diagnosed, the North American requirement ensures that the results are applicable to the U.S. population.

We have also requested that the phase three studies be at least 24 weeks in duration in order to

assess both efficacy and safety. Additional data such as extension studies that provide total exposure for at least 52 weeks will also be needed to better characterize the total exposure -- to better characterize the exposure following 52 weeks or chronic use as well as to satisfy other requirements such as for new molecular entities.

Additional topics such as differences related to as needed versus daily use of these medications may also need consideration and will be discussed during the workshop.

The selection of meaningful clinical endpoints for these trials as well as the development and validation of instruments to assess these endpoints has been challenging. The Division has recommended two co-primary endpoints to date which we recognize may have limitations. The first is the number of satisfactory sexual events, or SSEs, determined by the patients themselves. SSEs are discreet observable events that can serve as objective measures of effectiveness. And the second, which is a subjective measure, is the change in sexual desire or

arousal.

A key secondary endpoint, distress related to sexual function is also a subjective measure. To measure distress, we have accepted the patient-reported distress level as measured by question 13 of the revised female sexual distress scale.

The pros and cons of the instruments used and the timing of their assessments will be discussed in the following presentations.

So when we look at the results of these and other endpoints, efficacy should be based both on the statistical as well as the clinically significant improvement in the outcomes of interest. But we must also consider the magnitude of the treatment effect, the applicability of existing instruments such as the female sexual function index, or the FSFI, and the setting of things such as the changing diagnostic criteria, the appropriate recall period, and the utility of multi-barreled questions.

We must also consider time constraints and other limitations seen in the primary care setting and the potential physiologic differences between

populations and their impact on efficacy and safety.

At the end of the day, the risk-benefit relationship must be considered taking into account the generalizability of the trial results to patients with other comorbidities such as psychiatric or medical conditions, potential interactions with drugs or alcohol, and the spectrum of adverse events. Because of the potentially large patient population of affected individuals with sexual desire and arousal disorders, widespread use could mean that even uncommon side effects could have a sizeable adverse impact on public health.

Thank you and I will now turn the podium over to Dr. Rosemary Basson who is joining via videoconference. Dr. Basson is a professor of psychiatry and the Director of the Sexual Medicine Program at the University of British Columbia. Dr Basson will discuss the female sexual response. Her presentation has been pre-recorded due to the three-hour time difference on the West Coast, and she will be joining us live during the question and answer sessions. Dr. Basson.

DR. BASSON: Thank you so much for inviting me to discuss women's sexual response and some of their sexual problems with view to considering potential pharmacological interventions for dysfunctional response.

Likely, any model to portray the complex and highly variable experience we call sexual response is simplistic, sexual activity so much more than vaginal penetration of any sort including intercourse, and sexual response is so much more than sexual activity. And attempting to include the emotions, physical changes, sensations, and to allow variation to avoid pathologizing is daunting. Now models of sexual response followed the work of Masters, Johnson, Lief and Kaplan in the 60's and 70's and this work informed the APA's definitions of sexual disorders and also the diagnostic instruments and inclusion criteria, and endpoints of randomized control trials

But very unfortunately, two components were subsequently neglected. Firstly, Helen Kaplan spoke of desire as having both intrinsic and extrinsic responsive component. And secondly, Masters and

Johnson spoke of subjective arousal as well as genital congestion, i.e., male erection and female vaginal lubrication involving swelling. But by the 1980's, the extrinsic or responsive component to desire got lost and the subjective component of arousal neglected. So that's what's created the well-known linear genitally-focused entity that was devoid of any external triggers to allow Kaplan's result, responsive desire, to emerge.

In contrast, desire was said to be necessary at the outside, presumably in both partners simultaneously and arousal became more or less equated to erection and vaginal lubrication. Now this was not in keeping either with clinical experience of psychophysiological research and so other models emerged and their empirical validation followed. But the consequences of these omissions were profound. Initial seemingly spontaneous desire became the focus of assessment of sexual desire and its absence implied disorder, and women reporting responsive desire but less frequent intrinsic spontaneous desire would those be deemed as functional. But this is not in keeping

with the evidence.

For instance, studying 3,200 mid-life women, the vast majority reporting sexual satisfaction, a sense of desire at the outset and in between encounters was rare or absent in most. And as we'll be hearing shortly from Dr. Meston the wanting or motivation for sex is very complex and awareness of sexual desire or urge is not the most common reason that women have sex.

Also, a number of studies have shown that the seemingly spontaneous desire reduces with age and with relationship duration. Nevertheless, at the same time, sexual satisfaction progressively increases.

Now the consequences of the second omission include the fact that genital swelling and lubrication became the focus of any assessment or enhancement attempt of sexual arousal. And until DSM-5, subjective arousal and excitement in the mind was ignored and this, too, is not in keeping with the evidence multiple studies have shown over the last three decades to confirm that vaginal lubrication correlates poorly with subjective arousal, i.e.,

sexual excitement and pleasurable sexual sensations. And this is true for both women with and without sexual problems. Also, vaginal changes correlate very poorly with brain activation during visual erotic stimulation.

So currently, an incentives or motivation-based sexual response cycle is thought to underlie the and reflect the human experience. Now some reasons for sex are not strictly sexual. Often they're to do with promoting or confirming emotional intimacy, but the expectation is that the experience will ultimately be sexually rewarding even if that's not the prime motivation. The person's expecting to become sexually aroused and that arousal, in time, will trigger desire and more intense arousal, the two of them being quite difficult to distinguish and the whole experience being ultimately physically and emotionally satisfying with or without one or many orgasms and without pain so that there will be incentive to repeat this experience in the new or more distant future.

Now the tricky part is moving from having one or many of these needs to be sexual and actually

experiencing that arousal. Well, clearly, stimuli are needed to elicit a response and an appropriate context is necessary and for many, emotional closeness is a prerequisite as well as a willingness to guide the partner both generally and in the moment. We know that women's need to stimuli are highly variable and not necessarily physical. Actually, a woman who was previously labeled with the very derogatory term "frigid" explained to me that she could become highly aroused but it would really only be after an argument with her long-term husband and it had to be an argument that was political and she had to win.

(Laughter.)

DR. WHITAKER: She had to truly win. If he just kind of let her win, that didn't work. So she doesn't mind me using her as a kind of unusual example just to note that it's not always a physical stimulus that we need. Now the stimuli need to be appraised in the brain such that the neural networks that usually constantly suppress our sexual responses can be switched off and arousal allowed to develop. Now this sexual information processing by the brain is not only

a major component of the sexual response cycle but it's the areas where difficulties most commonly arise.

Now focusing a little more on arousal, it's important to notice its components. Firstly, there's that mental excitement and then the physical congestion, particularly genital congestion, but there's also an increase in physical sexual sensitivity not only of the genitalia but also the breasts and elsewhere in the body. But you might say what about that initial sexual urging or hunger or those sexual fantasies whose absence feature so much in the definition of hypoactive sexual desire disorder, or HSDD of DSM-4. Well, if they are present initially, seemingly spontaneously and not triggered, they can indeed reinforce the other reasons to be sexual. They can increase the willingness to go ahead with a sexual experience, and they can positively affect that information processing in the mind.

So what we can say is that some seemingly innate sense of desire is helpful but by no means mandatory. And I must include the fact that some people in this field really do maintain that no desire

is truly spontaneous. All of it is triggered by stimuli even if subliminally.

Now, importantly, a little arousal will allow a woman to permit ask for much more specifically sexual touch. Women typically do not enjoy genital or breast touched too early and mostly, they prefer genital touching that's not penetrative before there's any penetration. So in other words, some arousal allows a willingness to experience more intense stimulation and hence more intense arousal.

Now, when a woman says "I don't feel anything" or "there's no response" or "nothing arouses me," well, she may mean that there's no mental excitement. Maybe she means there's no sexual sensations, either genital or breast or elsewhere, and there's a tingling or throbbing that perhaps she once experienced in her youth. Or perhaps there's no awareness that genital structures become wet or swollen. Very often she's meaning an absence of sexual sensations that are pleasant and arising from direct genital or direct breast stimulation. So in other words, there's, firstly, subjective mental

arousal and secondly, a very composite physical genital arousal.

So just a moment to focus a little more on sexual satisfaction, difficult to know what women mean by this but qualitative study is just beginning, and we do know that it's not equivalent to just an absence of dysfunction but much more to do with mutual pleasure, intimacy, and interestingly, if a couple is reporting particularly high sexual satisfaction, there's no focus on performance there, no focus on the act of intercourse.

So, what are the consequences of accepting an evidence-based model that allows responsive desire to be just as normal as the seemingly spontaneous desire typical of new relationships and the model that notes the requirements of sexual stimuli and context? Well, it's explanation can actually constitute the therapy. It's a really typical response from a woman. "Well, there's nothing wrong with me. I don't have to feel lust before I start and it's okay to need emotional intimacy first" and then feeling less abnormal, now she has motivation to make whatever

necessary changes there are to make sex more rewarding. But, the HSDD criteria have designated pathology and they have been used as the recruitment criteria for the randomized controlled trials, medications then we might say have been trialed on women who may have been completely sexually healthy by today's standards and understanding.

So we have a dilemma today as illustrated by the rather confusing recent Endocrine Society guidelines that were designed to temper the widespread use of compounded and male formulations of testosterone, a kind of harm reduction enterprise. We see many caveats in that guideline due to the inclusion criteria of the testosterone studies and due to the fact that HSDD is now discredited.

The committee noted the recruited women in the studies already had two to three rewarding sexual events at baseline. They noted that an absence of desire when not sexually engaged and initially before engagement process was well within normal experience. And they noted that desire is just one of many reasons for sex, and they noted the studies that are still

needed.

So now just moving on to where the cycle can be interrupted. The main sorts of difficulty in that information-processing in the mind. In other words, by the time a woman is really seeking professional help, usually there is reasonable stimulation when she's engaging with her partner and the context is reasonable and yet she's not experiencing arousal. So considerable research is currently focused on the factors influencing the mind's appraisal of sexual stimuli such that arousal is or is not experienced.

Brain imaging during erotic visual stimulation identifies brain areas that become activated but it also identifies other areas that must be deactivated to allow the experience of arousal. So what interrupts this process? Well, commonly, mood disorders, medications, fatigue, and distractions, whether they are to do with women checking their own responses and worrying if they're sufficient. Truly, it's not possible to be open and vulnerable such that arousal just takes over. This is a need to look or react in a certain way or if there's a need to be in

control of one's emotional and physical reactions. Maybe she's unable to free her mind from thoughts and stresses that are quite irrelevant to sex. So often do we hear "I have such a busy mind. Mostly, I just can't turn it off." Or maybe she has little expectation of that emotional closeness that can be so profound both during and particularly after a sexual encounter.

And empirical research now confirms the power of such negative cognitions and negative emotions to limit arousal. And this concept of inhibition proneness has led to a useful dual control model which has identified the major factors inhibiting women's arousal.

Now ongoing distressing sexual difficulties are thought to affect perhaps some 10 percent of women. And their etiology is typically multi-factorial with robust evidence linking these problems to mood disorders and to other psychological factors. Now the etiological role of biological factors is clear in clinical depression and in sexual dysfunction associated with medications and certainly in genital

problems related to estrogen deficit and very -- that's commonly but also due to the over production of prolactin.

However, it's important to note that biological factors have not been confirmed where we might have thought they were etiologically important; that's to say in the context of women's chronic illness such as diabetes or renal failure, multiple sclerosis. In these kind of situations, research repeatedly confirms that it's the presence of comorbid depression plus some relationship factors that determine dysfunction.

And also, to emphasize, we have no correlation of dysfunction with testosterone deficit. However, we try and measure the testosterone activity. And, of course, past research has been confounded by uncertainty regarding the quality of testosterone acids and also by the fact that testosterone produced within the cells is not reflected in the serum. However, just recently, using mass-spectrometry methods, serum levels of testosterone and serum levels of androgen metabolites and the latter reflects both

ovarian testosterone and that testosterone that's produced within cells from precursors Include DHEA. All these levels were similar in 250 women. Half of them had low sexual desire concerns and half of them did not.

And while it's certainly true that sexual function can be altered by medication that affects serotonin, dopamine, noradrenaline receptors, we've no evidence of an intrinsic aberration of these neurotransmitters underlying the sexual dysfunction. Of course, brain imaging while viewing erotica will be different in women with and without desire complaints, given all we know about the impact of their negative thoughts, their self-monitoring, negative emotions, their distractions; however, this does not denote an intrinsic brain disorder.

So moving on, what are the common sexual problems? Well, a very common difficulty is absent or reduced arousal and thus usually infrequent or absent orgasm. Usually, neither mental stimuli nor direct physical stimulation causes any excitement or subjective arousal. This commonly is only genital

stimulation that's ineffective, the so-called genital sexual arousal disorder, backwards definitions. Also, pain with penetrative sex affects perhaps some 15 percent of premenopausal women where the diagnosis is usually provided vestibulodynia which is a chronic pain syndrome often associated with other pain syndromes, and pain is also present in some post menopausal women related to estrogen deficiency. And then as well, there's absent orgasm despite high arousal and a feeling of being very close to orgasm and this is often lifelong unless it's associated with medication, typically an SSRI. Now importantly, in the majority of cases, all of these symptoms gradually all, even very quickly, lead to a loss of sexual interest and motivation.

So, as a clinician, what would my list be for pharmacological therapies? Well, I cannot overemphasize the need for effective but sexually neutral antidepressants and antianxiety agents. The common complaint of little arousal, therefore, little triggering of any desire during the sexual experience is typically voiced by women with current or past

depression. We noted that some 90 percent of women referred to our clinic for low interest and low arousal were currently either taking an antidepressant -- that was the majority then -- or the remainder screened positive for depression. As well, there is marked comorbidity between provoked vestibulodynia and anxiety and to a lesser extent with depression.

Secondly, a medication to augment the help from cognitive therapy for the management of chronic dyspareunia provoked vestibulodynia would be welcome.

And then for post menopausal women, we have a particularly difficult problem; that's to say women who are not allowed to take any form of estrogen, even a vaginal preparation for fear that there might be some systemic absorption given they have a history of estrogen-sensitive cancer, so a selective estrogen receptor modulator is needed and also, any medication, probably it would be hormonal, would be welcome to address that loss of sexual sensitivity that can occur post menopause.

But here's the very difficult question.

Could there be a medication that could assist that very common lack of interest that's arisen because of decreased or absent arousal, where there's no arousal either from physical or mental stimuli? Well, we've briefly looked at the complexity of processing sexual stimuli in the brain and we've noted the strong link with these kind of difficulties with mood disorder. And the assessment of women with these complaints frequently indicate that their lack of arousal is actually adapted to psychological factors from the past, often the women's personal psychology. For instance, a state of sexual arousal may be just too vulnerable, too difficult given her need to be in control, perhaps all of this stemming from earlier childhood and adolescence.

Now meta analysis recently has supported the use of psychological methods. This would include CBT and sex therapy so that the couple can learn true communication and attention to sexual sensations. And very recently the benefit of mindfulness based cognitive therapy has been shown to benefit low self image, mood, stress, a tendency to follow distractions

and also to foster an acceptance instead of evaluation and criticism for one's own response, so with all of that experience, I would say probably not.

Nevertheless, we do know medications can induce this kind of dysfunction so, at least theoretically, medications with opposite action could provide a pharmacological approach. Well, at this time that is theoretical only because the control trials today for medications for low desire have not recruited these women. You recall that the RCTs basically recruit women who, on average, report two to three sexually satisfying events each month at the baseline. So in other words, the women reporting infrequent sex due to zero satisfying events per month or even for a year simply have not been studied.

So in conclusion, we now recognize an incentive motivation-based model of sexual response and for women, intimacy and senses predominate. Responsive desire and subjective arousal, and once again, acknowledged as integral components of a healthy sexual response, and innate seemingly spontaneous desire seems to be apparent, particularly

early on in relationships and often fades with the relationship duration and with age but sexual satisfaction mostly increases. Thank you so much.

(Applause.)

DR. CHANG: Thank you, Dr. Basson. I'm going to ask the audience and the panel to hold the questions for each -- for the individual presenters until all of them are done because the -- it's 8:44 now and it's only 5:44 for Dr. Basson.

So next up I want to invite Dr. Cindy Meston to talk about transitioning from DSM-4 to DSM-5 for diagnosis.

DR. MESTON: Thank you. It's an honor to be here. I'm a professor of clinical psychology at the University of Texas at Austin and Director of the Female Sexual Psychophysiology Laboratory. My travel was paid for by the FDA and I am on S1 Biopharma Advisory Board.

So today I am going to review the criticisms of the DSM-4 criteria for hypoactive sexual desire order and female sexual arousal disorder. I'll provide the justification given for combining these

disorders into female sexual interest and arousal disorder in the DSM-5 as well as the criticisms of that decision and end with discussing briefly some practical implications for diagnosing desire and arousal problems with the DSM-5.

Hypoactive sexual desire disorder was described in the DSM-4 as follows, and I'll just focus on criterion a because of time constraints: persistently or recurrently deficient or absent sexual fantasies and desire for sexual activity. The judgment of deficiency or absence is made by the clinician taking into account factors that affect sexual functioning such as age and the context of the person's life.

There are two main criticisms of this criterion. One pertains to the reliance on sexual fantasies as a defining characteristic when we know from the literature there are significant gender differences in the frequency of sexual fantasies. With women, there are actually very low base rates of sexual thoughts and fantasies, particularly in longer term relationships. So it may be a construct that

applies more to male sexual desire and as several have suggested, it seems that sexual fantasies are something women are more likely to use as a way to trigger sexual desire or maintain arousal as opposed to being a defining characteristics.

The second criticism pertains to the wording "desire for sexual activity" which implies women have sex because they desire it when, in fact, we know women have sex for many reasons that don't have to do with desire. My colleague, David Buss, and I documented 237 reasons why women have sex. Most of those don't have to do with desire, for example, revenge or curiosity or adventure or duty or mate guarding, mate poaching, stress reduction, economic gain just to name a few.

Also, this wording "desire for sexual activity" was based on Masters and Johnson and Kaplan's linear model of sexual response where desire precedes arousal precedes orgasm. And as we heard from Dr. Basson, this may not describe all women's sexual response. For some women, it may be a more circular pattern where, for example, arousal may, in

fact, precede desire in some situations.

Female sexual arousal disorder was defined in the DSM-4 as persistent or recurrent inability to attain or to maintain until completion of the sexual activity an adequate lubrication swelling response of sexual excitement. The criticism here was the exclusive focus on genital lubrication which is likely a carryover from earlier DSM editions that drew analogies between the arousal lubrication response in women and the arousal erectile response in men; the criticism being that there are other extragenital changes that also occur during sexual arousal in women, for example, nipple erection or nipple sensations, muscle tension, just to name a few as well as, of course, the psychological and emotional changes that also occur.

The DSM-5 Task Force argued to eliminate the FSAD diagnosis based, in part, on their argument there is little evidence that women with FSAD have impaired genital response. They brace that on a relatively small number of older studies done in a laboratory which failed to show significant differences between

women with and without an arousal disorder using vaginal photoplethyzmography to measure genital blood flow changes.

What they failed to note, however, was that the three most recent studies done in the laboratory using vaginal photoplethyzmography that more that more carefully diagnosed specific types of genital and sexual arousal disorder actually did show significant differences on these laboratory measures. And if I could digress for a moment just to explain this further, in 2002 and 2003, an international multidisciplinary group of 13 experts specializing in female sexual dysfunction were brought together by the American Foundation of Urologic Disease to discuss the classification and diagnosis of FSD and to provide recommendations to the DSM-5. I was fortunate to be one of the members of this consensus conference where we proposed three subtypes of sexual arousal disorder: subjective sexual arousal disorder, which were the women who described a lack of ability to become psychologically turned on during sexual activity; women with genital sexual arousal disorder who failed

to experience a genital response during sexual activity -- this would include women who would meet the FSAD criteria in the DSM-4 but not limited to this. We included any type of genital sensation, not just lubrication; and then a third combined group of genital and subjective sexual arousal disorder.

So getting back to my earlier point is the three most recent studies using vaginal photoplethyzmography that used this classification system to diagnose women with arousal disorder found that women with genital sexual arousal disorder showed significantly lower levels of genital blood flow than healthy control women.

The DSM-5 Task Force also used as a reason to eliminate FSAD the desynchrony between subjective and physiological sexual arousal. Now desynchrony here refers to the relation between genital blood flow responses measured in a laboratory setting to an erotic film and this is a measurement that is taken continuously throughout the presentation of what is usually a five-minute erotic film and it's sampled 60 times a second, so you have literally thousands of

data points. It's correlated with a single Likert scale subjective rating asking the women how aroused they were to the prior erotic film. Correlations of studies done using these measures in women generally range around .3 and much is made of the fact that correlations between the erectile response and how aroused a man says he is in a laboratory setting generally range around .9.

But I disagree that this is an argument for eliminating for two reasons. One is I believe the desynchrony reported in these studies is largely a methodological artifact of the way in which the measures are taken. We published a study in my lab a few years ago showing that if you measure subjective arousal continuous throughout the presentation of the erotic film the same way you're measuring genital arousal throughout the presentation of the erotic film and you use more sophisticated statistical techniques other than a single `Pearson correlation, you actually show that the women's genital response corresponds quite nicely with how aroused she says she is to the erotic stimuli.

But secondly and more importantly, I think the notion of desynchrony is really irrelevant to classification and diagnosis. People mistakenly take this to mean in a laboratory setting, women show a genital response to an erotic film but they don't feel psychologically aroused and that's simply not the case. I've been conducting studies on desynchrony for 21 years and in every published study in a laboratory setting, a woman shows a genital response to the erotic film and she says she's aroused to the erotic film. It's simply that those two measurements do not coincide perfectly when you're using the measurement techniques I described.

Female sexual interest and arousal disorder is defined in the DSM-5 as a lack of or significantly reduced sexual interest or arousal as manifested by at least three of the following: absent/reduced interest in sexual activity; absent/reduced sexual erotic thoughts or fantasies; no or reduced initiation of sexual activity and typically unreceptive to a partner's attempts to initiate; absent/reduced sexual excitement or pleasure during sexual activity in

almost all or all sexual encounters; absent/reduced sexual interest arousal in response to any internal or external sexual erotic cues; and absent/reduced genital or non-genital sensations during sexual activity in almost all or all sexual encounters.

Justification given for combining desire and arousal disorders in the DMS-5 pertain primarily to the belief of a high overlap between desire and arousal in women, specifically that desire and arousal problems often co-exist in women, that there are high correlations between validated measures of desire an arousal and that treatments for desire often improve arousal. I agree that there have been many publications showing that there is a high co-existence of not only desire and arousal problems in women but desire, arousal, and orgasm problems in women, but it's by no means 100 percent. We find about a third of women have overlapping disorders and, in fact, the two largest studies done on women with HSDD and FSAD showed that only about a quarter of the women had overlapping desire and arousal diagnoses.

So I think it's probably, as Dr. Kweder

succinctly stated yesterday, I think perhaps the best way to view desire or arousal are as overlapping ven diagrams.

In terms of correlations, this is the table of correlations from the original female sexual function index publication. There have been many publications on this measure and the domains. I have here highlighted the correlation between desire and arousal domains. They range in the literature from .3 to .76 which I believe is the highest reported in the literature. So .76 is a moderately high correlation. To me, it suggests that there are many times where low sexual desire negatively impacts a woman's sexual arousal response or *vice versa*, or perhaps there is a third variable common factor that's negatively impacting both desire and arousal. But if we square this correlation to get a measure of shared variance or common variance between the two domains, you get 58 percent. And 58 percent by no means implies that these are identical constructs. You would need at least 90 percent for them to be considered identical.

Also, the arousal domain in the FSFI

pertains to psychological or subjective arousal, and if you look at the correlation on this table between desire and lubrication which better approximates the FSAD diagnosis, the correlation is substantially lower at .56. And if you look at the correlation between desire and orgasm, it's remarkably similar at .54. So it's not been suggested that we should combine desire an orgasm problems with this argument. I'll also note that the FSFI has been shown to significantly discriminate between women with HSDD and FSAD on all of the domains that you would expect to differ between these disorders, namely desire, arousal, lubrication, and orgasm and to not differentiate on the domains you would not expect to differ, namely satisfaction and pain.

So what are the implications for diagnosing desire problems with the DSM-5 criteria? Five of the six criteria pertain, some of them depending on how you interpret, but pertain to sexual desire. I think that some of the descriptors are better than what was in the DSM-4 which relied just on sexual fantasies. The DSM-5 covers several aspects of desire including

interest, thoughts, fantasies, initiation, and receptivity. I don't think a substantially greater or lesser number of women would meet criteria for a desire disorder using the DSM-5 versus the DSM-4 criteria from a clinical perspective.

In terms of research and drug development, however, I think this criteria is quite problematic. When we conduct research, most often we're comparing separate patient groups and if it's the case that, by chance, on patient group might meet criteria one through three which very clearly describes a desire disorder to me and the second patient group, by chance, is most likely to meet criteria four, five and six, which I would argue is more likely a genital and subjective arousal disorder, then you run the risk of having very heterogeneous patient populations which may well respond very differently to any sort of treatment intervention.

Implications for diagnosing arousal disorder with the DSM-5 criteria, if I could just remind you of the three subtypes of arousal disorder recommended by the consensus conference, first of all, genital sexual

arousal disorder or also the FSAD in the DSM-4, only one of the six criteria pertain specifically to a genital response. So we would not be able to diagnose a woman with a genital arousal disorder using this criterion unless she had co-existing low desire.

In terms of subjective sexual arousal disorder, only one of the criteria pertain to subjective arousal so like genital arousal, we would not be able to diagnose this subtype unless the woman also had coexisting low desire.

In terms of combined genital and arousal disorder, we would be able to diagnose a woman with both subjective and genital arousal with this criteria if she met criteria four, five, and six but only in situations where the problem was very severe in that she experienced problems at least three-quarters of the time.

So, overall, what are the implications for diagnosing arousal disorder? I think from a clinical perspective, it's problematic that we're unable to diagnose a genital arousal disorder. I do think this group of women exists. I don't think they always have

low desire, and they -- I think they are the group of women that would most likely benefit from a drug treatment that focused on peripheral genital vasocongestion.

I think in terms of research and drug development, these criteria would be problematic to use for the reason I described earlier. We run the risk of having different patients that we're comparing and secondly, because criteria four and criteria five are just not clear to me. The wording of "reduced sexual excitement/pleasure," I don't know what sexual excitement means and in criteria five, "absent/reduced sexual interest arousal," I don't know what arousal necessarily means. I could argue that these could either apply to psychological arousal or genital arousal and I think because of that, it adds confusion to subject selection and as I noted earlier, makes us more susceptible to having heterogeneous patient populations. Thank you for your attention.

(Applause.)

DR. CHANG: Thank you, Dr. Meston. I'll be sure to look up the 230-plus reasons for women to have

sex later.

MS. VAIDYA Christy?

DR. CHANG: Anyway --

MS. VAIDYA: Sorry, Christy, we need to quickly dial in Dr. Basson because she got disconnected --

DR. CHANG: Okay.

DR. VAIDYA: -- and then we can continue. Sorry.

DR. CHANG: Dr. Basson?

DR. BASSON: Hello.

DR. CHANG: Okay. Next up I'm going to invite Dr. Leonard DeRogatis up to the podium, and Dr. DeRogatis will talk about patient-reported outcomes.

DR. DeROGATIS: Hi. I'm Len DeRogatis and I'm going to talk a little bit this morning about patient-reported outcomes. I'm going to start off by talking a little about where did patient-reported outcomes or PROs come from. It's a little simpler than where babies come from but not a lot, and they actually come from, although, self-report measurement which is what PROs are based on goes back to the 1890s

and Sir Francis Galton and Karl Pearson.

PROs come from the FDA and as you can see, the term PRO is an acronym proposed by the FDA to represent patient-reported outcomes. It's meant to reflect any outcome based on self-report data provided by patients, and here's the key, and used in the regulatory review process. That's the pivotal statement. And there are several references here at the bottom relating to the innovation and the early thinking around PROs and the second article by Acquadro -- I'm not pronouncing it right probably -- was published in *Value in Health* in 2003 and represents the thinking of the PRO harmonization group, and they were having a two-day meeting in 2001 and this is their report.

Okay. So there are more than one form of outcome assessment and more than one outcome assessment modality. So what are the others? Well, there are laboratory-reported outcomes like free and total testosterone, clinician-reported outcomes such as clinical rating scales, diagnosis, physical examination and then patient-reported outcomes. And

I've listed a number of the foci for patient-reported outcomes in the area of female sexual dysfunction.

I want to spend a minute on psychological assessment, nature of psychological assessment and in particular, precision of measurement and that's because psychometrics is kind of an arcane field and there are, for example, I think, more undergraduates taking electives in Sanskrit than are taking electives in psychometrics. It's not a big hit on campus and so only a few of us know much about it, tentatively anyway.

So psychological variables tend to be hypothetical constructs which are operationally defined by PROs using psychometric methods and are measured on ordinal approaching interval scales. Physical variables, like physiological variables, for example, tend to reflect tangible physical entities measured on true ratio scales. I know that's a little abstract and obscure and I'll try to clarify in a minute. These scale difference is in the measurement of construct versus tangible entities result in more sophisticated and powerful measurement for physical

variables. It is often misinterpreted. It doesn't mean that psychometric measurement is soft or unscientific. It simply implies and means that it's less precise.

Now I want to share with you one of my favorite quotes on precision in scientific measurement. And this is John Tukey who is also one of my favorite statisticians. Tukey said, "It's far better to have less precise measurement of the right thing than to have precise measurement of the wrong thing since as is so often the case, the wrong thing will, in fact, be used as an indicator of the right thing." Now I can't tell you, particularly when individuals are used to the precision of a physical measurement, they're so dependent on that kind of reductionist posture and precision that they often select variables that are the wrong thing. Often, most of the time, I think, our PROs are measuring the right thing. They just don't quite measure it as precisely as physical variables.

And the next thing I want to touch on because it's so misunderstood is the notion of

validity and in particular, construct validity. Construct validity should be represented, in my mind, as an overarching comprehensive concept including all other forms of validity. And this was not always thinking -- predominant thinking before Chronbach and Meehl in a seminal paper in 1955 which is the year I graduated from high school, barely. Up to that point, there were many, many concepts of validity. However, today construct validity is composed or contributed to by discriminate validation, known group studies, predictive validation, responsiveness to treatment studies, content validation which is the construct comprehensiveness, clarity and relevance, and any other experiments, exercises, studies that suggest that the instrument measures what it purports to measure. So construct validity is an overarching concept, okay.

And two of my favorite, unfortunately now gone, psychometricians from the 20th Century had some very, I think, clarifying things to say. Jum Nunnally says the validation process is akin to an expanding network of circumstantial evidence supporting the

validity of the test. Validation, by the way, is programmatic and theoretically, it's in perpetuity so it never stops. You can always contribute to the construct validity of an instrument. Sam Messick from Penn said, "The operations involved in validating a psychological experiment equate with those required in testing a scientific theory. The theory's main hypothesis is this test validly measures this construct and all of the evidence from these other studies contributes, or doesn't, to that overarching concept.

Okay, enough of that. Let's deal with something more tangible. What I've listed out here, and these are just the reliabilities, are six sexual outcome measures, a screening measure, and a distress measure that I feel have very good validity. Do they have enough validity? Well, we'll see in a minute what that might imply. But these are the reliability coefficients. I'm not going to dwell on them because all this is available to you and I don't want to obsess.

Now the next slide takes these same

measures, and I'll name them, the ASEX; the Changes in Sexual Functioning Questionnaire, one of my favorites, the DeRogatis Interview for Sexual Functioning; the Female Sexual Function Index; the Profile of Female Sexual Functioning; the Sexual Functioning Questionnaire 28; then the DSDS Screener which you've already heard some things about; and the FSDS-R Distress Measure. And I have to say, embarrassed as I am, that I made an error on this chart and I made the error on my own FSDS-R. It does have demonstrated content validity. I was thinking of a newer version when I put "no" in that column. It's a minor point but I wanted to clarify that.

So, these are instruments that I believe are ready to use, have demonstrated construct validity to varying extents but either are close or capable of being used as outcomes measures in phase three pivotal trials. Now I want to make four quick recommendations. These issues have all been the focus of consistent debate. They represent suggestions and that's all I'm saying, and they're intended to have a primary heuristic value, that is to stimulate

discussion, debate, hopefully not argument but that's okay, too. And we should address them in a collaborative effort, okay, not in an us versus them mode.

The first one of these has to do with minimum criteria for the term validated. I keep talking about these validated tests but what are the criteria? Well, they're like a will-o-the-wisp. They move, they change. There are recommendations in the guidance but we've all sat in meetings where half the meeting though the test had met the recommendations and the other half of the meeting thought that they didn't and we've gone back and forth. So I think minimum criteria for the term "validated:" clear evidence of acceptable test/re-test and internal consistency reliabilities; clear evidence of comprehensive content validity, and I'll come back to that later, including content representation, clarity, and relevance; compelling evidence of discriminate validity such as known groups, case versus non-case; and compelling evidence of relevant predictive validity, particularly in our context here,

responsiveness. So I want to put that forward as minimum criteria to consider an instrument validated and that's something we can debate.

Now, one of my pet peeves in this field, and I've been in it a long time, is we don't use norms. We think we use norms but we don't. Norms are eschewed routinely. We say things like, "Well, there is a .3 difference on a five point Likert scale." That's not a norm. Or we use a cutoff score. That's kind of a norm but it really isn't' a norm. And I believe that a substantial amount of information about the absolute and relative efficacy of our drugs, particularly regarding clinical significance and magnitude of effect, is lost because we don't use norms.

Now this next slide is a little complicated so bear with me while I run through it, but I think it shows an excellent application for norms in defining clinical significance or helping to define clinical significance. Okay, let me run through this quickly. This is an eight-week study of a drug which is primarily an antidepressant but has found to have pro

sexual properties. It is measured week zero, week eight. The outcomes instrument is my DISF which is measured on an area t-score -- area -- I know this is technical but try to bear with me -- area t-scores give you the advantage of the actual proportions under the normal curve. Well, so what. Well, what that enables you to do is o translate them directly -- you'll see in the second -- well, you can't see that -- okay -- in the -- here translates directly into percentiles, okay. And we all understand percentiles. They're very straightforward and so we can start to talk about things like, well, what percentile of the norm is the mean response after treatment.

Okay, so this is the DISF. There are five dimension scores and a total score, and I'm not going to go over all of them. But there are two things you can see here. One is a p value and that p value tells you whether the drug-placebo comparison was significant. Okay, that's A and that's half the equation. If that's so, then the next question, and maybe the more important one, is is it clinically

significant, not just magnitude of effect -- that's -- but from a clinical perspective, from the clinician prescribing this drug, is this effect significant. Well, I maintain that a good way of learning more about that is to use the norm and for example, we see here on arousal that well, the mean has moved from below the normal range well into the normal range. Unfortunately, it's not -- it's marginally statistically significant but that's important information to know.

We jump over to desire, we can see the desire moved from the edge of the normal range right into the middle of the normal range and this is a very significant outcomes measure.

Drive and orgasm, we have statistical significance but we didn't move into the normal range.

Now, there are lots of technical details with this and as we all know, the devil is in the details and this is something we would need to work out. We have lots of folks that are really good at this and so they'll help us work it out. But I want to suggest more application of norms, okay. Now I'll

get off of that soapbox. Maybe I won't.

And I want to make my next to last suggestion on recall period. And those of us who have been in the field for a while have gone through so many tussles over recall period that just the mere phrases makes me cringe when I think of like, oh, not recall period again. Okay. The Agency's position, in general, appears to be the shorter the period, the better since distortion from forgetting can impact on the accuracy of the recall with the use of longer periods. The counterargument is that a number of the PROs on the previous list have already demonstrated high reliability, high known groups validity and treatment responsiveness with longer, such as 28-day, recall periods.

In addition, and this is so critical and I keep saying this -- nobody pays attention but I'm going to say it again -- forgetting results in unreliability and unreliability reflects increase in error of measurement. Since reliability is a necessary condition for valid measurement, if these PROs have demonstrated responsiveness, discriminative

validity, that is valid measurement. The issue of recall period should no longer be an issue of debate for that PRO in that specific population because, in my estimate, it's been validated. Okay, so, that's my suggestion.

And finally, a kind of nitty-gritty suggestion about content validity: PRO guidance from December 2009 states the items and domains of an instrument should be appropriate and comprehensive relative to its intended measurement concept, population, and use. Well, who can argue with that? I mean, of course, it should.

Now, the trick is in the details and I just mention a few here that have -- when I sit down with sponsors, they ask these questions and I don't have an answer. I say, "Well, kind of." And lately, the FDA has been saying this and so I want to make a suggestion that we be more explicit. For example, what is the minimum number of patients required for focus groups and cognitive debriefing to be judged sufficient? Not a precise number but the minimum number so if the sponsor doesn't have that minimum

number, he can say, "pack it up, go home, you just don't have even the basic necessities."

What specific criteria determine appropriateness? I mean, you know, like we were doing tests of arithmetic, we'd say, "well, we've got to have problems reflecting addition, subtraction, multiplication, and division, and some have to be easy, some have to be more difficult" but this a little trickier in our field.

How is comprehensiveness defined? Okay, not easy but it would be helpful, in my estimation, if the Agency would be a little more explicit in their recommendations. There's nothing wrong with the basic recommendation. I'd just like to see a little more detail.

And then finally, and I realize these are small points but they're where you get stuck a lot of times, if concept saturation is to be formally accepted as a criterion of sufficiency for PRO content, what is the recommended number of respondents contributing no new content to establish that saturation has been reached? And I've been asked

this; well, how many do we -- well, it's like four? I don't know, the last time they didn't like that. Well, about 6, 10? How many times do we have to see, gee, there's nothing new in what this individual had to say; we must have comprehensive content and it's covered.

And finally, PRO instruments have a very important purpose in measuring outcomes in clinical trials of FSD through assessing and quantifying those variables and constructs of which there are no physical equivalents, you can't get nanograms of depression or, you know, anything like that. They're distinguished from physical measurement not by scientific quality but rather by level of precision.

And finally, much more can be done, I believe, to make optimum use of PROs to elucidate the efficacy of our treatments. The effort needs to include the FDA, clinicians, and industry working together collaboratively. Thank you.

(Applause.)

DR. CHANG: Thank you, Dr. DeRogatis. Now I want to invite Dr. Ashley Sagle from FDA. She is

the -- I'll let her introduce herself.

MS. VAIDYA: Excuse me. We'll be handing index cards if you have any questions to ask during the clarifying question session at 9:50.

DR. SLAGLE: Good morning. My name is Ashley Slagle. I'm a social scientist analyst in the Office of New Drugs here at the FDA. I work with the Study Endpoints Team and I'm very happy to be here today to share a regulatory perspective on assessing patient-reported outcomes or PROs in clinical trials.

The first part of my presentation will focus on the types of things that we think about more generally when we're evaluating outcome assessments and then I'll share some perspectives on the challenges that we've seen in outcome assessment as it specifically relates to FSD clinical trials.

So we use outcome assessments to determine whether or not a drug has been shown to provide benefits to patients. One of the most important aspects then of drug development is how treatment benefit is measured. Ultimately, we seek to evaluate treatment benefit; that is that the drug has some

positive impact on something that is important to people with the condition so specifically, how long they live, how they feel or function in daily life. We then weigh the benefits quantified in clinical trials with known risks of the product in order to make drug approval and labeling decisions.

From the regulatory perspective, it's necessary that drug developers document substantial evidence of treatment benefit from adequate and well-controlled studies. The regulations also specifically indicate that the methods of assessment of a subject's response should be well-defined and reliable. This is important. It means that well-defined and reliable become the key criteria by which the FDA judges outcome assessments to document evidence of treatment benefit.

I wanted to note that there are other types of outcome assessments that we can use to evaluate treatment benefit but in the case of FSD, patient-reported experiences are primary to our understanding of the condition and treatment benefit so we'll focus on PRO assessments during today's discussion. So when

is a PRO well-defined and reliable and appropriate for use in adequate and well-controlled studies? Well, when we're measuring the right thing in the right way in that population and that the score that quantifies that thing that we're measuring does so accurately and reliably so that the effects that we see in an outcome assessment can be interpreted as clear treatment benefit.

We refer to the PRO guidance that describes good measurement principles that might be considered to evaluate whether measurement is well-defined and reliable. The guidance provides really an optimal approach to PRO development but we understand that flexibility and creativity are often needed in order to both meet regulatory demands as well as the practical demands of drug development.

Specifically, when we evaluate whether PRO assessment is well-defined and reliable, we evaluate the tool's measurement properties. First and foremost, we consider content validity. What are we measuring? Is that the right thing to measure in that population? Does the patient understand the items and

respond in the way intended? When we combine all of the items in an assessment into one score, what does that score represent. As regulators, we put a big emphasis on content validity because we need to ensure that when we see a score change on an assessment, we can determine what that score change means and importantly, that we can describe that score change in terms of meaningful treatment benefit in a way that is not potentially false and misleading.

After content validity is established, we do consider other measurement properties including construct validity, reliability, and ability to detect change. Another aspect to regulators is the consideration of that constitutes meaningful change on an assessment. Often, statistically significant changes alone are not fully interpretable so if we see a very small change in score that is statistically significant, we have to think about whether that amount of improvement is meaningful to that patient population and then weigh the amount of improvement or benefit against the risks.

When we think about PRO assessments, it's

important to remember that assessments reported by patients are not all adequate for use as clinical outcome assessments to evaluate treatment benefit in trials. There are assessments that while reported by patients are useful for very different purposes. These measures may be used for diagnostic purposes, prognostic purposes, used to select patients for participation in clinical trials, used for epidemiologic or population studies to better understand characteristics of the natural history of a condition, or used to assist in clinical practice decision making.

Assessments used for other purposes are often not appropriate for use as outcome assessments in clinical trials, at least not without some modifications. For example, an instrument or measure might be a, quote, validated checklist of symptoms that could be great in identifying patients who have FSIAD versus those who do not, but that same instrument might not quantify the severity of those symptoms in order to detect change in a way that is interpretable to inform a conclusion of treatment

benefit during a trial.

Another example: often diagnostic tools are very broad in order to capture all patients who have a condition. For example, a diagnostic tool for FSIAD might be based on the DSM-5 criteria and would include items related to both arousal and desire. This tool would identify women have either arousal concerns, desire concerns, or both. However, if we use this tool as an outcome assessment, there may be many items that won't move with treatment. So for example, the desire items will not improve in women who only had arousal concerns but that had normal desire. When there are many items on an assessment that don't change during treatment, it makes it harder to see an improvement on that total score. The beneficial effect on arousal that might be there will be lost or obscured by the other items that are not relevant to that woman's experience. Therefore, it's critically important that our outcome assessments be appropriate for the clinical trial population in order to provide the best chance to detect treatment benefit.

This graphic is very busy and I'm not going

to through it now. It's really just meant to identify the types of things that might be considered in order to improve our ability of outcome assessments to accurately measure treatment benefit. I really just wanted to alert you to the existence of this tool on our website and to drive home a key point. It's critical that adequate attention is given to the first two columns, that is understanding the disease or condition and conceptualizing treatment benefit before we can think about selection or developing an appropriate outcome assessment.

When understanding the condition and conceptualizing treatment benefit, we think about defining the context of use and defining what concepts are important to measure in that clinical context. And in fact, that was one of the goals of yesterday's meeting, to help shed more light on what is important to measure, to hear directly from patients in order to help identify those important concepts that could be the basis for outcome measures in clinical trials.

I've listed here some of the elements of the context abuse that could impact assessment decisions.

In the interest of time, I'm not going to go through these but I do encourage those engaged in making decisions about outcome assessments to give some consideration and to discuss these with the Agency.

Once we've selected the concepts we want to assess in our specific clinical context, we then need to think about the various elements of that concept that should factor into the score representing that concept. So to help organize this, we use conceptual frameworks and this is an example of a conceptual framework for an instrument that might be relevant for assessing sexual dysfunction. Organizing the content of an assessment this way allows us to consider whether all of the elements that are important to patients are included in the instrument score or scores.

Another note about selecting concepts: We need to consider closely-related the concepts are to the disease and treatment. This does not mean that more distal concepts are less important. It means that there are many more variables that might impact those concepts in addition to the disease and the

treatment. The farther that we move to the right on this diagram, the harder it becomes to detect a treatment difference or to interpret any treatment difference that is indentified. If more distal concepts are considered for measurement in clinical trials, we need to ensure that the variables that contribute to those concepts are also measured so that we can interpret trial results. For example, if we wish to measure health-related quality of life, we will need to make sure that we assess symptoms, adverse events and toxicities, and all impacts that contribute to health-related quality of life including general psychological functioning, physical functioning, social functioning, and so on.

So the discussion of proximal-distal concepts brings me to the next portion of my talk where I'd like to focus more specifically on some of the FSD measurement challenges and questions, things that we've been giving a lot of thought to here at the FDA. One challenge is related to the concept of satisfying sexual events or SSEs. As you know, this has typically been recommended as a key focus of

measurement in clinical trials for FSIAD. However, some questions still remain. Are SSEs truly disease-defining experiences or are these only more downstream or distal impacts of the other more proximal symptoms such as desire and arousal? What other factors contribute to a woman's definition of an SSE that might need to be incorporated into the measurement plans? Often, to assess this, women are asked for each sexual event, was it satisfying, yes or no. When we evaluate SSEs in this way using a single dichotomous item assessing satisfaction, are we truly able to understand whether the score change is meaningful? Satisfying sex is a broad multidimensional concept that likely relies on multiple factors, psychological, physiological, social, situational, relationship factors, and may not be validly and reliably measured using just a single item.

We need to think about with the specific population or subpopulation of FSIAD first, are SSEs disease-defining experiences that should be assessed as primary endpoints in clinical trials? And two, if

so, what are the elements that contribute to satisfaction that should be assessed in order to interpret score changes identified on SSEs measures?

As I've mentioned, the content or the individual items of the assessment and how that content is combined into a single score for interpretation of treatment benefit is critically important. So I'd like to describe a few additional challenges that we've seen in the past related to this with PRO assessments in clinical trials for FSIAD that make it difficult to either show treatment benefit or if an improvement in score is detected, making it difficult to interpret whether that score change really represents something meaningful. I'm sharing these with a goal to help sponsors and instrument developers understand the challenges that we face and hope that we can all work together to select or develop outcome assessments that provide the best chance of being able to detect interpretable treatment benefit in trials.

So with assessments that ask about multiple experiences in one question, something we call multi-

barreled, it's impossible for us to know what is driving any score change that is observed making it difficult to understand whether trial participants are truly experiencing benefit in some cases, particularly when the score change is small.

So suppose that one single question combines and asks women to rate all of the components in the DSM-5 criteria, rate your interest, initiation, feeling receptive and so on on one scale and during treatment a woman's score changes from, say, two to three? While all of these elements may be important, the construction of the question does not allow us to distinguish which feature of the condition is improving. It may be that a drug product only improves one of these things. For example, maybe fantasizing about sex is increased by the study drug but all of the other concerns remain unchanged, we would still see an improvement on the overall score on this question without the ability to check and see which components are improving. If we labeled this drug as a treatment of arousal and desire dysfunction, this could be considered misleading because the women

who are expecting other elements of desire and arousal to improve would not see those benefits with the drug.

So again, we encourage sponsors to talk with us early in development so that we can help identify some of these pitfalls and provide suggestions for a path forward. In cases like this, we would recommend that the assessment be modified so that each element, interest, initiation, receptivity, etcetera, is evaluated as its own question within the assessment rather than being lumped together in one question.

We've also had concerns that patients aren't consistently understanding and interpreting questions on some of the PRO assessments for post free use in clinical trials. For example, when patients are asked about their sexual activity, how does each woman define sexual activity? Does each woman have a different definition for this? Or genital sensations, this can mean different things to different women. Desire, what elements contribute to desire and how do women define this? Is being receptive to a partner's initiation enough or are there other key elements of desire that women include in their personal

definition?

In cases like this, we recommend qualitative research or interviews with patients be performed in women representative of those who will be in clinical trials to understand these questions and if needed, to potentially modify wording of the questions to improve the accuracy and consistency of interpretation across patients.

Other challenges that we've seen relate to the response options for the questions in the assessment. For example, suppose a woman is asked to rate how often she has erotic thoughts with response options ranging from never to always? It's not clear that always having erotic thoughts is a good thing. Might that be disruptive a woman's life? Well, this might show up on the assessment looking like an improvement on the score, we have to question if this is, in fact, representative of something that women want. Alternatively, if we assume that always fantasizing is a good thing, this could be a really high bar to hit for a drug product. With limited response options such as never, sometimes, and always,

it would take a very powerful drug to move a woman's response from sometimes to always on the scale and therefore smaller but still important improvements could be missed using this assessment in a clinical trial. So in cases like this, we would recommend that the response options be explored with patients and a response scale with more gradations be used that captures more subtle but meaningful changes.

Recall periods or the time period that we're asking patients to think back over in order to report their symptoms have been the focus of much attention and discussion both inside and outside of the Agency. Some instruments ask patients to think back over the last month and rate their symptom. Recall periods should, in part, be based on what symptom is being measured and how variable that symptom is over a time period. For example, with desire, is desire a steady state feeling that doesn't change at all over the course of a month so that a woman can easily report their desire state accurately over that past month?

From the patient interview transcripts that we've read and from what we heard from women

yesterday, it seems that at least for some, desire may ebb and flow over the course of a month, particularly during treatment. So asking a woman to provide one rating for a month of desire might be challenging. Does the woman try to average all of the days in the month and select her rating? Does she think about her best day, her worst days, her current state that might not really be representative of other days that month?

In the case of a medication that is used throughout the month only on an as-needed basis, how do we link the benefit identified on an assessment using a one-month recall to the effect of the drug product that was used intermittently throughout the month? Probably each woman thinks about how to make a one-month rating a little bit differently and may even do it differently herself over time.

Typically, these longer recall periods have the effect of adding unwanted variability to the assessments or making it harder to detect treatment benefit, but if these assessments are able to detect an improved score during the clinical trial, how do we interpret it? Was bias introduced that limits our

confidence in the trial results? So to avoid these concerns, we have typically recommended that symptoms like desire be assessed daily. This doesn't necessarily mean every single day during a six-month trial because we worry about patient burden too but maybe daily for a week at baseline and potentially daily for a week prior to each clinic visit or at some pre-determined weeks throughout the study.

And again, we always encourage discussions with the Agency so that we can provide some assistance in making these tough assessment and implementation decisions.

Another challenge that we have faced is how to interpret what is meaningful change on an outcome assessment of, say, desire, distress, or SSEs. We have to think very carefully when weighing risks and benefits of drugs. For example, if a scale assessing desire has a total score that ranges from zero to 10 with zero being no desire and 10 being a perfectly satisfactory level of desire and the placebo group increases by one point and the treatment increases by two points, we want to know that this is meaningful

change to women. Is going to a zero to a two on a scale or a four to a six on the scale benefit enough to outweigh the risks that have been identified during the trials? These are not unusual decisions and it's the job of FDA to incorporate regulations, science and judgment to weight quantified risks and benefits to make approval decisions. However, this is where we need input from patients to help us understand what is a meaningful amount of change on various assessments and how do patients weigh these risks and benefits.

So we would like, to the extent that we can, to share our learnings with drug developers and help ensure the highest likelihood of being able to detect treatment benefit in trials. We have two pathways that we can provide advice on outcome assessments in clinical trials: first, within the context of an individual drug development program; and again, we encourage sponsors to begin these discussions earlier, as early as the pre-I&D stage, if possible, so that if there is work that needs to be done on an outcome assessment, there is time within what we know are very tight development timelines. The second pathway is

outside of any individual drug development program. This is through our drug development tool qualification process. In this program, we can work with outcome assessment developers to develop and qualify assessments for use across multiple drug development programs. We work collaboratively with many different stakeholders in this program including various consortia, patient groups, individual academic investigators, and drug developers.

We do have a guidance that describes the DDT qualification process and I want to note here that there has been some confusion about this process. Outcome assessments used in clinical trials are not required to be qualified through this formal process but we believe that when assessments are developed in collaboration with CDER and then ultimately qualified, this will help to encourage drug companies to pursue drug development in these areas since they can feel confident that FDA agrees with the content of the measure and the measurement properties thus lowering their risk.

This is a high-level view of another diagram

on our website for anyone who's interested in qualification or PRO development more broadly. I'm not going to walk through this but I do encourage you to take a look at the website. We often hear that developing or documenting the selection of an outcome assessment is very hard work. So why do it? Why go to all of this effort? Of course, we have the regulatory standards that we have to meet but I think also critically important in the case of a failed clinical trial, we don't want to be left wondering was it the drug that failed or did we just use a bad outcome measure that wasn't capable of detecting interpretable treatment benefit.

And lastly, for those interested, here is the link to our website. Again, I do encourage you to take a look at it. And with that, I thank you and I look forward to continued discussions.

(Applause.)

MS. VAIDYA: Excuse me. If you have any questions, could you just send those sheets to the ends of the rows and we'll pick them up. Thank you.

DR. CHANG: Thank you to all the presenters.

So now we're going to open up to the Q and A session relating to the five presentations. And I know that Dr. Basson has joined us as well so she should be able to respond to any questions that are directed to her presentation. So again, I'm going to ask all the -- I'm going to let the panel weigh in first, the expert panel as well as the FDA panel. And right now our staff members are collecting the index cards for questions from the audience so we can group them for later. So anybody want to start?

When the expert panel asks a question, I'm going to ask you to state your name for our the transcription purposes and as well as to whom your question is addressed. Any takers now?

(No response.)

DR. CHANG: So no questions from the panel for any of the presentations?

(No response.)

DR. CHANG: Okay. Now why don't we go to the audience questions? Dr. Gassman, do you have…

DR. GASSMAN: Okay. We have our first question for Dr. Basson who, I gather, is -- can hear?

DR. BASSON: Yes, hello.

DR. GASSMAN: Yes. This is from Dr. Portman from Columbus Center for Women's Health Research. He has three questions. The first question is that you stated women with zero satisfying sexual events have not been studied. It said we have many of these patients enrolled in clinical trials. What are you basing your comment on?

DR. BASSON: Well, for the RCTs, we're going to have to, as far as I understand, have a number of events per month in order to be able to put something in the diary that can be rated. So if that situation is such that no events are satisfying, they may well be having less than one sexual engagement per month because the fallout living with a difficulty like that, on both partners --

DR. CHANG: Okay. Oh, sorry. Gone.

DR. BASSON: -- because what are you going to study? It brings me to another point which perhaps we could discuss at another time today but that is that my own feeling is that couples need other kinds of help to get to a baseline of perhaps some healing

of a disturbance that happened to both of them over many months or years before you put them on a drug that might well help. I don't see a drug having too much chance of helping given the fallout for those partners. So that's going back to why a woman who never had a satisfying time is probably not able to be recruited to the study.

And as you know, on average, looking at the testosterone patch studies and the Flibanserin studies, women were often having two or three satisfying events a month. (Inaudible) might argue is perhaps not pathology

DR. GASSMAN: Thank you. The second question is you state HSDD has been discredited. What validation of FSIAD is there? How can we discredit women who self-identify as distressing, low, or absent desire?

DR. BASSON: In terms of -- excuse me -- the discrediting, I was really referring to (inaudible) factor three (inaudible) sexual behavior in 2010 but (inaudible) --

DR. CHANG: Excuse me, Dr. Basson, could we

ask you to turn your volume up so we can hear you better. This is Christy.

DR. BASSON: Okay. I was going to mute so I'm mute?

DR. CHANG: No. Would you speak a little louder into your mic?

DR. BASSON: Can you hear me now?

DR. CHANG: It's a little bit better --

DR. GASSMAN: Yes.

DR. CHANG: -- but could you be a little louder still?

DR. BASSON: I'm going to just do something. Let me know is this better now? I clicked something that says "unmute my speaker." Is that better?

DR. GASSMAN: Yes.

DR. BASSON: Is this better now or not?

DR. GASSMAN: Yeah. No?

DR. BASSON: No? Okay. I'll go back to the way it was. Tell me if you can't hear and I'll just speak with a bigger voice. The discrediting on the criteria had to do (inaudible) that evidence (inaudible) that fact that women tend to feel that

they're on track or is (inaudible) engaged with a partner rather than being a marker of their inherent sexual working, that is showing that women who are perfectly satisfied with their sexual life (inaudible) this one study -- it was about 3,000 women -- it lacked women -- a large majority, some 80 percent saying their life's were perfectly sexually -- satisfactory sexually.

UNIDENTIFIED FEMALE: Christy, stop. We can't --

DR. BASSON: But yet they said rarely or never did they actually sense desire, so the discrediting of this idea of kind of anticipatory desire (inaudible) as (inaudible) itself pathology. That was what I meant, not to say that we don't all have many, many women who are saying I have too little sexual desire or interest or motivation, whatever words they're using. Is that more clear?

DR. GASSMAN: I believe so. No?

DR. BASSON: (Inaudible).

UNIDENTIFIED FEMALE: No. It's not really clear because she's (inaudible) --

DR. GASSMAN: All right. Well, we'll keep going. We'll have a -- we will do some transcripts of that. Can you justify labeling women as nearly all having a depression or anxiety disorder?

DR. BASSON: I did send a reference list with some of the references for closely linked complaints of low interest, arousal, desire. I mean even if we -- you can look at the list or anybody can. I think it will be available to everyone but if you want to be very recent, a the large -- that self-study coming out of Britain just the end of last year clearly linking mood disorder, depression with these type of sexual concerns. And then if you look at other papers, other studies (inaudible) excluded when they were (inaudible) I'm thinking of some of our European colleagues' (inaudible) menopause (inaudible) showing the exclusion of a clinical depression.

Nevertheless, the other women recruited to this, the studies of low desire (inaudible) had more (inaudible) anxious thought, low self image even though these weren't amounting to a clinical diagnosis. So it's very rare to come across actually

an epidemiological study that doesn't link depression (inaudible) study that I mentioned in the (inaudible) recruit 125 women were low desire, it took almost five years to recruit from a clinic because 90 percent -- in fact, over 90 percent were either on an antidepressant or screened with likely depression on the (inaudible).

DR. CHANG: Dr. Basson, Dr. Kingsberg would like to make a comment.

DR. KINGSBERG: Hello. It's not only is the sound a little bad but it's a shame you weren't here yesterday because, unfortunately, I think most of what you've described in terms of depression leading to desire problems flies in the face of almost every woman who described their situation yesterday. They did not say that depression was the cause of their low desire but, in fact, might be the result of low desire. And in fact, in most of the clinical trials that I've been involved with, desire is -- excuse me -- depression is a rule out. We certainly screen out for depression and we've really had very little trouble recruiting for clinical trials for hypoactive

sexual desire disorder.

DR. BASSON: Well, thank you, Sheryl. (Inaudible) this experience in Canada. We must be doing something quite different or having different kinds of women who were actually seeking help, which is interesting because one would think with depression there would be less motivation to do anything including going through the hoops to get into (inaudible) clinic (inaudible) You have to go through a nightmare, at least one and often two other physicians before a referral is made. So that's a very interesting comment that you do not find women being excluded on the basis of either depression screener and antidepressants. I suppose if you (inaudible) for a trial (inaudible) making it clear that (inaudible) antidepressant is an exclusion factor and you've done your work ahead of time.

DR. KOHN: Well, certainly, on the phone, we try to screen that out but once they're in the clinic, we certainly rule that out. They're not included in the trial but we still don't have trouble recruiting. We do have many women who are depressed. We have

similar weather in Cleveland as you do in Vancouver that may be part of that but we, unfortunately, have to exclude them and we still recruit very nicely.

DR. CHANG: Rosemary, if you could pick up your handset and speak into the phone, I'm wondering if -- I've been told that that might be a possible remedy.

DR. BASSON: Okay. Is that better?

UNIDENTIFIED FEMALE: Yes.

DR. BASSON: I've got the handset now.

DR. CHANG: Yes, that's much better. Thank you.

DR. BASSON: Okay.

DR. GASSMAN: Okay. We have one last question for Dr. Basson. It said in current -- it's from Karen Hicks at Lehigh University -- in current clinical trials, why are there so many exclusion criteria, such stringent criteria for inclusion which might leave the wrong subjects who may need the most help? Could you just briefly comment on the inclusion and exclusion criteria for these trials?

DR. BASSON: I would completely agree with

the -- I'm sorry, I didn't catch your name -- the questioner's name clearly but I would agree that we're not -- that the drug trials don't actually include the, quote, real women. That was my comment about, you know, how difficult it was. Our study was not a drug trial. The study I was referring to, we were trying to look at the hypothalamic pituitary (inaudible). Sorry.

DR. CHANG: You're still on.

DR. BASSON: I'm sorry, should I carry on? I heard something in the background.

DR. CHANG: Yes.

DR. BASSON: Okay. The study I was referring to was not a drug trial. It was to do with testing the hypothalamic-pituitary-adrenal (inaudible) in women with and without desire concerns. But I would agree with the questioner that drug trials have not really included the women in real life. The women we see every day in our practice have far too many of those exclusion criteria. I actually agree.

DR. CHANG: Actually, that particular question will be one of our discussion questions come

this afternoon so, hopefully, we'll hear a lot more about that from every panelist. And Dr. Guess has a question.

DR. GUESS: So, Dr. Basson, I really liked your model where you distinguished psychological and physiological or physical sexual arousal differences and how you have to distinguish between the two. My question is how is it you then distinguish the psychological arousal from desire and what specific symptoms would you use to qualify desire versus psychological or subjective arousal? And then I look at our criteria in the DSM-5 where number one is absent and reduced interest in sexual activity, and number five is absent and reduced interest. The only difference between five and one seem to be that for five, its' triggered and for one, it's inclusive, both triggered and non-triggered; and is that your interpretation or what is your interpretation between the differences and what symptoms would you use to differentiate those two diagnoses?

DR. BASSON: Lots of questions in one. Thank you. The -- I do think, as perhaps -- I hope it

was clear on the various circles you saw that I do think, for most women, desire and arousal are very, very difficult to distinguish and that many times we begin the sexual experience for all sorts of reasons that don't necessarily have much in the way, shall we say, sexual urging at that initial point but where attention to stimulation and being able to focus, and providing we're enjoying the effects of that stimulation on our mind and our body, we sense this, if you want to, use the word "psychological arousal" which triggers a sense of wanting more of that, we might have began for some other reason or many other reasons. But at this point now, once we have the psychological excitement and enjoyment and feeling of wanting to really, really focus on this such that there's a sense of timelessness occurring and wanting to be close to the other person in a more sexual way, that's kind of competing with desire. And that kind of feeling, that kind of urging may well not have been there initially but is accessed or triggered, if you like, and the two are really very, very difficult to separate.

Now in the new DSM-5, I think the idea was to separate that kind of convergent statement or state from a more, if you will, academic interest in the idea of being sexually with a partner, or alone for that matter, hence the word "interest." I mean personally, if I'd had any say in this, I would have liked to use the word sexual motivation there but it's not. It's interest. I don't know if that helps at all. Does that clarify how I see it? I wouldn't really have an objective to differentiate desire and proper arousal. I would separate a motivation slash interest from a combined state of desire/arousal.

DR. CHANG: Thank you. Any other questions from the panelists?

(No questions posed.)

DR. CHANG: None, okay. Dr. Whitaker has the next question from the audience.

DR. WHITAKER: Yes, several questions for Dr. Meston. The first one is from Thea Cacchioni and she asks, "You said that the DSM-4 and 5 would capture the same number of people but then went on to say that the DSM-5 would miss many women. Can you clarify?"

DR. MESTON: What I meant, in terms of a physician diagnosing a woman for, let's call it, HSDD using the DSM-5 criteria, I think that most of those women would be captured with the DSM-5 criteria because five out of 6 of the criteria pertain to desire, particularly one through three. So my point was that I think there are better descriptors for desire for diagnosing a patient with desire than the DSM-4 which just focused on sexual fantasies. My point was, however, that it would be problematic to try to use this criteria if you weren't just diagnosing a single patient but rather were trying to do a drug trial desire disorder or arousal disorder using this criteria because you may well run the risk of having very different subject groups. If the patient meets criteria one to three, I would call that a sexual desire disorder. If she met criteria four to six, I would call that an arousal disorder.

DR. CHANG: I have a follow-up to that question, Dr. Meston. So are you, in effect, suggesting that we separate these women into different trials?

DR. MESTON: Well, I mean it depends on what the drug is being developed for. If you're developing a drug for desire, I don't think you should use this as screening criteria. I think that would be problematic. I don't think it's problematic if you develop a drug for desire and use this as an indication because most of the women using this criteria will have a desire disorder. They will have to have a desire disorder to meet the criteria. So in terms of what will the drug be indicated for, if it's a drug for desire, yes. If it's a drug for arousal, then I think it's a problem.

DR. CHANG: Thank you. Next question?

DR. WHITAKER: All right. This somewhat goes along with what was just mentioned. This is from Dr. Anita Clayton from the University of Virginia. She says, "Given the many problems with FSIAD diagnosis, the critique by Dr. Meston, the lack of validation of the diagnosis, the epidemiological data and field trials, the confoundment of the exclusion of women with FSAD only, the continued separate diagnosis of HSDD and arousal disorder, ED in men, the continued

diagnosis codes in ICD-10 and upcoming versions, and the personal experiences reported by many of the women yesterday with HSDD or FSAD only, and given the need for measurements that accurately measure change and the construct under study, shouldn't the HSDD and the FSAD diagnoses be the diagnoses under study allowing for more data to be collected on the FSIAD diagnosis, in parallel, to see if it is ready for prime time?

(Laughter.)

DR. MESTON: Okay. I'm not -- I don't know if I've grasped the question. Well, I -- is the question do we need to validate the DSM-5 criteria? is that what the question is?

DR. WHITAKER: Yes. It was my understanding. Why shouldn't we continue to use HSDD and FSAD --

DR. MESTON: Oh, I see.

DR. WHITAKER: -- while collecting data in parallel for the FSIAD?

DR. MESTON: Yes, I think we should. For studies, drug development trials, I think we should differentiate HSDD and FSAD for the reasons I

outlined, yes.

And I will add that I think it would be really problematic to even try to validate this measure. I mean we hear a lot of people saying a lot of time how complicated women's sexuality is and I think that it's really not that complicated, that we can make it complicated if we try to parse apart exactly what each of these six measurements mean and how we're going to measure them and how frequently it's going to take to, you know, meet each of these criteria.

I think most women -- and I'll speak mainly of low desire -- I think women with low desire, if you ask them do you have low desire, they know what you're talking about and they can that very simply whether they do and when the last time they experienced desire and how intense it was. I don't think you need to try to validate this questionnaire in order to get a good discreet group of women with a desire disorder.

DR. SEGRAVES: Actually, we did a study with hypoactive sexual desire and as an add on did the diagnosis of FSIAD. And much to my surprise, there's

100 percent concordance. These were premenopausal women come in with a complaint of low desire and they matched all of the FSIAD criteria. Now probably in postmenopausal women, I think it would probably be a different situation.

So I think there is a lot of furor around being asked to change how we conceptualize things. I think there's always discomfort and we're always trying to put our old systems and make them fit the new system and it doesn't always work that easily. You have to think with the new system and the new system doesn't really combine desire and arousal. It combines desire and subjective arousal or it combines spontaneous and responsive desire or arousal, and it really doesn't have anything to do with genital arousal and that's no longer part of the official psychiatric diagnostic system. I can be written in as not specified. There's a lot of confusion is all I'm saying.

DR. CHANG: Okay. Dr. Goldstein has a question.

DR. GOLDSTEIN: So I want to re-emphasize

something that Cindy said. My name is Irwin Goldstein. I'm a sex medicine physician in San Diego. I've been in sex medicine for 35 years. I've seen thousands of male and female patients who have bother and distress from their sexual problems. We have on board in our facility a sex therapist, a physical therapist, and myself as a biologist and we are into the multi-factorial world of evaluating and treating sexual medicine.

I just want to emphasize what Cindy said and what Sheryl said. There are women who are bothered by low sexual interest. Four of my patients actually were here yesterday and I'm honored that they flew 3,000 miles with me to share all this with you. They have low interest; they have reduced responsively; they have low thoughts; they're bothered. We have used the decreased sexual desire screener to diagnose them. In our clinic, we sort of take bits and pieces of their desire problem to try and help them, the psychology, the biology. As you found yesterday, there are people who have hormone problems. There are people who have other issues, like SSRI issues that

change their brain chemistry to change their interest. We have drugs, all off label because we don't have drugs yet approved. Buproprion can increase sexual interest. We have off label data on that and others.

The point is they have symptoms and the indication is HSDD. We have to recall that treatments are designed to the indication. There is going to be confusion of diagnosis. There's going to be confusion of pathophysiology. This Agency approves drugs for LUTS. I'm a urologist. I go to the American Urological Association. The diagnosis of Lutz is very controversial. The pathophysiology of Lutz is very controversial but the indication is based on the symptoms and the bother and we have many drugs approved for Lutz; by the way, with 30-day recall, to throw that in.

I just want to emphasize that this isn't -- I'm bent-kneed and we need to get treatments. And I agree with Cindy, it is not that complicated. As it is complicated in women, it's complicated in men and men have treatments and they get better and women should get treatment and women should get better.

DR. CHANG: Can I follow-up on that? Dr. Goldstein, do we have drugs approved for men, in fact, for desire?

DR. GOLDSTEIN: So --

UNIDENTIFIED SPEAKERS: No, we don't.

DR. GOLDSTEIN: -- okay, hang on. We have drugs approved for hypogonadism. We have countless of them and if you look at the package insert, the major bothersome symptom of hypogonadism -- just look at the package insert, you don't have to believe me, just go look at it yourself -- is low sexual interest, erectile dysfunction, and a slew of others. So if you read the package insert, you do have drugs for low desire.

DR. GASSMAN: But those are not the only --

DR. CHANG: Those are not FDA-approved indications. We just have to make that clarification for testosterone products. And in fact, I refer everybody to the transcripts for last month's advisory committee on testosterone products.

(Applause.)

DR. CHANG: Actually, Dr. Guess has another question.

DR. KINGSBERG: Can I finish on what Dr. Meston was saying about sex is not -- or desire is not that complicated. It concerned me that Dr. Slagle was talking about the multi-barreled approach to have to differentiate all of those components of treatment success. As Dr. Meston said, women understand the components of desire and while each woman might have her own individual wording, she gets it, what desire is, and to have to tease out each and every component of desire being fantasy, interest, motivation, I think is looking at the forest for the trees, is not necessary, and certainly shouldn't be what is required for treatment success.

DR. CHANG: Dr. Guess.

DR. GUESS: So I just want to go back to Dr. Basson's concept that psychological arousal and physical arousal are distinctly different but they are very intimately related to desire but we don't really know how they're related. So what do you think about the role of including DSM-5 for criteria for inclusion

but then separating them out so that we can then understand those relationships, because right now you're saying we're developing a drug for desire? We don't know if that drug is effecting the physiological arousal and therefore improving their desire or if it's affecting the CNS and directly affecting desire because we have no clue. Although we're saying it's simplistic, we don't know the underpinnings of the inter-relationships of all of these things. And so if we collect that data, perhaps we can go back and see what's its affecting and why their desire is improving or why their arousal is improving.

DR. GOLDSTEIN: Christina?

DR. CHANG: Yes, Dr. Goldstein?

DR. GOLDSTEIN: You brought up an issue about libido which I did not bring up about men, so I'm going to bring it back to you, okay. Does the FDA approve TV advertising? Does it -- is that a yes or a no statement, because the answer --

DR. CHANG: We --

DR. GOLDSTEIN: -- is yes. And the answer is that TV advertising speaks of low libido for

testosterone. I don't want to get into this because this is not part of -- male -- we're not here to discuss male. But there are FDA-approved treatments for libido for men because it's in the advertising. That's what men see on TV.

But let's get back to women. Women have low interest. It's an unmet need and we need treatment and we need to resolve this issue. That's why my patients flew here. That's why other patients flew here. We need to work on getting this done.

DR. GUESS: But how do you introduce a treatment when you don't know what you're treating? So I think the point of understanding the disorder is very, very important here.

DR. GOLDSTEIN: It's extremely understandable. It's -- women will walk into my office and your office, I'm sure, that say they are not interested. In the past, did you have good and satisfying interest? You should say "yes" if it's acquired. Has there been a decrease in your level of interest? And you should say "yes" to that. Does it bother you and do you want treatment? There are four

yeses. You can exclude on this DSDS screener a myriad of issues which you can also exclude in the DSM-5. They have exclusion criteria. You can diagnose it and you can -- the indication is HSDD. It's not -- the path of physiology, we can get complicated. I'm going to share with you most diseases are complicated pathophysiology but the indication is straightforward and we need treatment for them.

DR. CHANG: I think we, at this point in the morning, we all need a break so I'm going to stop there. But I really do want to bring the focus back to women but before I do that, there is one point that I just have to address is that we do not approve TV advertising. We provide comments to sponsors and we take enforcement actions when they go out of line. So that is one thing that I absolutely have to clarify. From this point forward, I hope to be focusing on problems for women's sexual health.

And so we're going to come back in 20 minutes. So we will reconvene at 10:42. Thank you.

(Whereupon, off the record at 19:19 a.m., and back on the record at 10:42 a.m.)

DR. CHANG: So at this point in the meeting, we're going to move on to the Panel Discussion Topic 1 which we already delved into quite a bit already, and that's Diagnostic Challenges. And I am going to -- the questions are reflected -- already projected on the slide here for the session, and I'm just going to call on each panelist to respond in turn and we'll start one from end and go to the other.

So in terms of diagnosing either FSIAD or HSDD or FSAD, particularly for FSIAD, question number one from FDA is "What do you view as the strengths and the weaknesses of these diagnostic criteria when used in clinical practice?" And if we could get Dr. Connell to start.

DR. CONNELL: I think the strengths are that it's inclusive and it's important to get patients' input in terms of what's bothering them. I think the weakness is, though, that you are including both -- although it's subjective arousal as we discussed before, I think there are probably many different ways that women lead to having sexual problems. And I think it's very important to collect data and to

really understand is it secondary sexual dysfunction from stress and depression, or is it primary sexual dysfunction where they're having that and that's causing depression and stress. So I think that's one of the major weaknesses.

I think we need to quantify so that we can use what's called a minimally important difference meaning that when you make a change, it means it's important to the patient. It's not just statistically significant, like a p value and some statistician came up with that. It has to be what's important to the patient. If they're already having 20-something sexual pleasures a month and you bring them up to 22, that could be statistically significant but not make a big difference. It might be very important though for someone who's having two sexual pleasures a month and who goes to five. So I think that's -- one of our weaknesses is that we need to be more quantitative.

DR. CHANG: Thank you. Dr. DeRogatis.

DR. DeROGATIS: This is just the clinical practice question?

DR. CHANG: Yes.

DR. DeROGATIS: Okay. Well, I have to say initially that I don't believe in FSIAD first of all. I don't believe -- and I won't bore you at the moment, I'll bore you later with all the reasons I don't believe in FSIAD as a viable diagnostic category. But they are multiple --

UNIDENTIFIED FEMALE: Can you speak a little louder, please?

DR. DeROGATIS: Can you hear me now?

(Chorus of yeses.)

DR. DeROGATIS: Okay, I apologize. So, I would focus on the components and I would focus on a desire disorder, whatever you want to call it, HSDD, low sexual desire, and I would focus on arousal disorder and in part, and some of us -- and this is not a unique only to me -- some of us were discussing this last night and Dr. Rosen was one of the people who pointed this out -- we develop drugs, and that the context in which I'm responding to it, in terms of indications and not diagnoses.

So indications would be low sexual desire, low sexual arousal, and so I would focus on trying to

characterize and describe and understand the nature of those component disorders which I think are valid for diagnostic purposes.

DR. CHANG: Dr. Gass.

DR. GASS: I rarely get complaints of low arousal. In the office, it's almost all low sexual desire. And I think another point that needs to be raised here is when we're talking about, say, low arousal, we need to be sure that we're talking into account menopausal changes as well because that could be a confounding factor in terms of arousal and lubrication. So those are two pieces that I think we need to tend to.

DR. CHANG: Thanks. Dr. Gelenberg.

DR. GELENBERG: Well, first of all, I have no clinical experience or expertise in this area but when I have been involved in academic discussions that result in establishing diagnostic criteria or treatment guidelines, which I've been more involved in, the distinction between all of the parsing such as what we are experiencing at today's meeting and what actually goes on in real life is huge. One of the

difficulties is that we've got an issue, human sexuality, that runs along a spectrum and is influenced by a number of confounding variables that have been mentioned today. And then we have to, for regulatory purposes and commercial benefits, we have to dichotomize it into categories of pathology/no pathology. So get -- for a man to get a prescription paid for by insurance for Sildenafil, Viagra, the problem has to be labeled as erectile dysfunction. So we need to make that category.

In reality, the primary care physician who will see most of these patients of women with putative sexual dysfunction who fit into a category, they are not going to make these carefully parsed and nuanced diagnoses. And in fact, in most clinical trials, the staff is motivated and incentivized to get patients into trials, so they're not -- also, they're not going to be carefully making the careful diagnoses.

So we can spend a great deal of time and effort in looking at the various elements and fussing about DSM-5 which has become a favorite academic focus in the last year. And we're still going to be put

into a category of making decisions for regulatory purposes which have huge commercial implications and then turning these products loose for use where physicians have got 10 minutes to deal with six organ systems are going to be pushing a prescription across the desk once an agent has FDA's labeling.

DR. CHANG: Dr. Goldstein?

DR. GOLDSTEIN: So I have, in difference, lots of clinical experience and I see lots of women with low sexual interest, as a few others on the panel have just said. I also, as did Len DeRogatis, say he doesn't believe in FSIAD, I see HSDD and FSAD as items that I understand and I see patients with those and we see therapies that help these women. So I think that the HSDD part of FSIAD and the arousal part of FSIAD are what we should focus on. If you do that, then the DSM-5 version adds a little bit more in symptoms and adds a little bit more in exclusions than the DSM-4, so those are the issues.

DR. GUESS: So I honestly think that the --

DR. CHANG: Microphone.

DR. GUESS: -- I think that the DSM-5 were

written to correlate with diagnostic criteria for inclusion criteria and they're not clinical diagnoses. I think that if a patient has absent, low or reduced problems with arousal or desire, they have a problem and they should be able to qualified as someone with these problems. I also think that if in 50 percent, 30 percent, or 20 percent of the time, I am not having arousal or desire and its' bothering me or affecting my relationship, then I have a clinical diagnosis.

UNIDENTIFIED MALE: Thank you.

DR. GUESS: I think we need to separate clinical diagnoses from inclusion and exclusion criteria and diagnoses for trials and that has not been done in this DSM-5 diagnoses criteria.

DR. CHANG: D. Heiman.

DR. HEIMAN: Julian Heiman, Indiana University and the Kinsey Institute. I think that really the main the issue with DSM-5 is the confluence, which are the issues they tried to solve with the DSM-4 of the two disorders. It just doesn't happen. Let me give you an opposite example. When in -- around 1998 when Viagra was so exciting, and that's

not a clinical statement --

(Laughter.)

DR. HEIMAN: -- the discussion that was going around when it was coming to women and then selecting people for those studies, this is -- I'm getting off on the research but I do think it's applicable -- so we started to look for women who had low -- I was in one of those clinical trials -- we looked for women who just had low sexual arousal. Well, we couldn't find any.

Now clinically, when I couldn't -- I don't see very many people with low sexual arousal, I always thought they more would likely go into an MD setting first rather than a PhD setting, which is my background. Well, when we -- I -- we -- literally, our team screened over 700 people, women. Now there were other exclusionary criteria, of course, than just the arousal versus a desire but we couldn't find people with sexual desire disorder of the strict qualifications, and that was DSM-4.

And so it's, to me, fascinating that the outcome of that is now at this point a mixture of

arousal and desire. So I will be on the team of allowing just pure desire problems to come in with three or four of these. I'm not sure how many. After Cindy's talk, I realized I'm more confused about these, some of these that I think actually could go in the other direction, separating out arousal and separating out desire. And if they go together, fine, but don't make them go together. That would be my vote.

DR. CHANG: Dr. Kingsberg.

DR. KINGSBERG: Well, to answer question number one specifically, as a strength, since I need to give you a strength, it will get the clinician to a diagnosis of HSDD or FSIAD if it's a desire issue. It might get to subjective arousal, okay, so it will get the clinician there.

As a weakness, though, it might-might get to subjective arousal but it certainly will not get to genital arousal problems and there's no validation. And while that's not really a clinical practice issue, I worry about clinicians being able to sort of make sense of what might be confusing desire and arousal.

But going back to a strength -- let's end on a positive note -- it will get the clinician to HSDD or FSIAD.

DR. CHANG: Dr. Meston.

DR. MESTON: Well, I think I have expressed my opinion so I'll be brief, but a strength is I do like the addition of the other descriptors for sexual interest being more than just sexual fantasies in the DMS-4. I agree with Sheryl that it will, in terms of clinical diagnoses, it will get us, or a clinician, to be able to diagnose HSDD.

But I view there are many weaknesses in combining the desire and arousal. It adds a lot of confusion in terms of implications for treatment but also just in terms of trying to diagnose who these women are.

DR. CHANG: Dr. Mirkin.

DR. MIRKIN: So I'm an OB/GYN --

DR. CHANG: Could you put a mic on.

DR. MIRKIN: Yeah. But more importantly, I'm a drug developer so I don't want to get directly to question number two which is the area of my

expertise but I want to lay it out that I have, you know, serious concerns using the DSM-5 definition directly into clinical trial without the proper validation.

Regarding question number one, it seems to me -- and again, I'm not a clinical practicing physician -- but it seems to me that it's a highly subjective definition in which having six different ways of characterizing populations making it into this condition, I mean we may run into a situation in which we have different types of patients within the same condition.

DR. CHANG: Dr. Segraves.

DR. SEGRAVES: Okay. I first have a disclosure. I'm one of the evil people who is responsible for FSIAD and I was on that committee and chaired the sexual dysfunction subcommittee, so I'm evil in that way.

I also have a disclosure. I'm an advisor and a stockholder of S1Biopharm. I think I forgot to mention that earlier.

In terms of the strengths, of course, I'm

biased. I see a lot of strengths in the new system. I think a number of the things are that we tried to exclude things that clearly we didn't think should be considered, a psychiatric diagnosis. In other words, is the problem has a medical etiology, it doesn't merit the DSM-5 diagnosis. If it's depression, anxiety, it doesn’t meet a diagnosis for a sexual problem. If it's interpersonal conflicts of your interpersonal conflict, it's not a sexual problem. We're trying to delineate who should be appropriate for treatment.

We also tried to eliminate false positives and there was a six-month duration, the higher thresholds for the diagnosis. We didn't want to classify women who were normal as having an illness, and that was part of the whole thrust of the committee.

I think the disadvantage of that, obviously, is there are some people might like to get treatment who would not meet criteria. That was a thing we tossed back and forth.

I think clinically, we find that it's often

very hard in premenopausal to find women who have arousal problems who don't also have desire problems. And we think they overlap considerable.

I think one way of going forward would be if we did a study would be to have all of the criteria to enter a study be listed and then follow. One you could follow: do they all cluster together the way I think they do? And then the other thing would be then to follow each one over time and see if an intervention affects some differentially from others. I think that might be one way to go forth. I'd be willing to bet a hundred bucks it'll hit all of them, an effective drug will hit all six dimensions. Anybody -- Irwin, you'll take me up?

DR. GOLDSTEIN: No.

DR. SEGRAVES: Okay. That's the end of my comments.

DR. CHANG: Dr. Wierman.

DR. WIERMAN: I'm Maggie Wierman from the University of Colorado. I'm the Vice President, Clinical Scientist for the Endocrine Society. I chaired the guidelines on the role of androgens,

testosterone and DHEA in women recently published in *JCNM*.

I think many of the comments have already been raised that I was going to make concerning question one. I think the comment that was just raised was that this DSM criteria were raised for psychiatric disease and, for example, when a man has erectile dysfunction, it's not a psychiatric disease. And when women have sexual dysfunction, it's not always a psychiatric disease.

And so I think we have to realize that these criteria were made for psychiatric disease with the 75 percent, etcetera, etiology. And I think that as clinicians in the clinic, if somebody has 25 percent episodes of dysfunction and it's distressing to them, upsetting to them, we do a lot of other things in clinical medicine where we treat for that delta of a change. And so I think designing studies for clinical benefit or for drug indications is very different than making a psychiatric diagnosis in our clinical practice.

(Applause.)

DR. CHANG: Thank you. I want to go to the phone for Dr. Basson.

DR. BASSON: Yes, hello. I think one of the strengths is that --

DR. CHANG: Dr. Basson, can you have your -- the handset to the phone?

DR. BASSON: Yes, I have.

DR. CHANG: Okay.

DR. BASSON: I have. I think one of the strengths is there is now a focus on arousability, in other words responding to sexual cues, either internal or external which have been absent before. So the idea of, if you like, triggered a responsive desire and arousal is there so that's, I think, a strength.

I think one of the weaknesses is perhaps item three, low initiation and typically unreceptive to a partner's attempt. This doesn't necessarily denote pathology in a woman because there's so many possibilities of partner factors, for instance, lack of skills from the partner or even the partner's own sexual dysfunction that would be reason enough not to initiate or to be unreceptive. So I have problems

with that one.

I also have problems with, you know, the situational option because if in some circumstances response is fine and other circumstances it isn't, that doesn't really sound like the pathology within the woman's own sex response system. It would give clues of the difficulties with the context and the environment or inadequate stimulation.

And I think there's an intent there to include the genital arousal disorder that Cindy had mentioned that we try to have an adjunct diagnostic entity in 2002-2003 except that it's kind of a little bit mixed up because it said non-genital sensations as well. So I think agreeing with many previous speakers that there is this separate entity in our experience 2:41:48, it's typically around menopause when women are not deficient in estrogen, that's being supplemented as necessary, but there is what is often described as a genital deadness.

And I agree with other speaker that they may or may not have lost their sexual interest. It depends when you see then. If it's just happened,

they may well have interest or because they're still aroused from non-physical stimuli. But if you see them a few years later, motivation/interest has gone down, understandably, because experiences have been so unrewarding. So there's an attempt at keeping that and then I would think it would be fine to keep it as a subgroup or make it a separate entity.

So basically, a plus is that there's this arousability factor and then the main minus for me is that the idea of responding to a partner and initiating with that partner, I don't think that necessarily notes pathology within the woman, so I'm not really happy with that criteria.

DR. CHANG: Thank you. Since we have Dr. Basson on the line, I was going to go straight to question two and ask her to respond. So question two for this topic is "What do you view as the strengths and the weaknesses of these diagnostic criteria when used for defining inclusion and exclusion criteria for clinical trials that will test drug products?"

DR. BASSON: I think it kind of overlaps with what I've just been saying. I think they're the

same points really. I would want it not to be -- to do with context and -- which would include the relationship and I don't mean only the non-sexual relationship. I mean actually what's occurring in the sexual relationship. So I think they would have to be pruned, if you like, or some of the criteria removed.

I think, as I have said earlier on this morning, that one would need to address the fallout option, living with the dysfunction before thinking that adding the medication for arousal or increasing arousability to sexual cues has a chance of working. It may be that when the fallout, which would include not particularly expecting a good outcome, not putting any effort into making the context optimal, not really being able to focus on any sexual stimuli or asking the partner just to, quote, hurry up because it's now become a chore, there's no real intent or motivation to really focus and see if some arousal can occur because it's been so disappointing. So if none of that is addressed and then a drug is given, it's either got to be immensely powerful, and I can't imagine it would be legal, or it won't work. So I

really -- I guess my main theme is I think psychological, or if you want to call it sex therapy type of approach, is needed first and then there's a possibility of seeing do we still need a medication and if so, compare it with a placebo and at least there would be a chance of seeing perhaps some effect.

DR. CHANG: Thank you. So we'll go to the panel here in the room. So Dr. Connell.

DR. CONNELL: So I agree with Dr. Segraves and Dr. Kingsberg in that these new criteria are good about getting people into a diagnosis and into a study, which I think is great. And let's face it, we have zero science on female sexual dysfunction so I think it's very clear to know what is the drug supposed to be doing; what is it supposed to be targeting. It shouldn't just be this 1800's cart going around with an elixir saying this going to fix everything. We should know the exact indications and know what are the outcomes that we're supposed to be seeing from this drug. Now we may see arousal if we're able to target desire and they are linked. I mean even in the slides, they said they always said it

was desire and then arousal occurs but sometimes you can have arousal and then desire is then occurring and feeding into the arousal. So there is clearly a physiologic feedback loop.

So I think it's very important to know -- and that's why I think collecting all these -- I think you can't be inclusive enough in terms of what are you outcome measures. I think these are great to include people but we need to break it down. They need to be so inclusive from their personal history, psychiatric history, medical history, all their meds so that, like Dr. Segraves mentioned before, it may work for a certain subset of patients but maybe not for everybody and that may be important in the end. We could say, you know what, this drug is great for Mrs. Jones but it's not going to work for Mrs. Smith and that's going to be really important to Mrs. Smith, because if it doesn't work for her, she's going to feel like a failure and that's, I think, important to really understand the biology.

That being said, this is going to take a lot of money. We need to have powered studies. There's

very little money for women's health when you break it down. At the NIH, we have NIDDK -- I mean Dr. Goldstein mentioned lower urinary tract, the LUTS; that's lower urinary tract symptoms. NIDDK has millions of dollars and there are tons of labs that are well-funded across the country in urology looking at these things. For example, for urogynecology, all of the prolapse and women's health goes to the National Institute for Child Health and Human Development. Not even in the title is there the word "women's health." So that being said, the amount that goes to women's health is very small because you're competing with other, you know, diseases and pediatrics and neonatology.

So I think we need to really not only partner with all of the drugs coming out and do very well-powered and well-designed trials, we need to get some basic science and really look at animal models and just look at what does aging do to the brain and what does again to the genital sensation and function. So I think right now we're sort of shot gunning and that bothers me, but we need a solution today and we

probably have some really promising things. We just need to be really careful how we look at them.

So going back, I think it's good to be all inclusive but we need to be very detailed and systematic in how we collect our data.

DR. CHANG: Dr. DeRogatis.

DR. DeROGATIS: Let me begin by what I feel is a strength because that won't take me long. In terms of research criteria, the explicit six-month duration of symptoms is excellent and a definite advance over the DSM-4 non criterion. Having said that, I think, you know, I have problems with FSIAD on so many levels but the one -- or I think it could be the most damaging -- is an expansion of what Dr. Meston said earlier. This is lumping at its worst and if, in fact, you lump two so-called disorders together and there's really only one, then there's no real damage done. But if there are two distinct disorders with two distinct etiologies, pathophysiologies, prognoses, etcetera, and you call them both the same thing and then you're developing a drug, okay, two pivotal trials for phase three drugs, and you recruit

people with FSIAD, first trial goes great and, you know, you knock it out of the park, significance, clinical significance, etcetera. Second trial bombs, just no clinical -- no, none, nothing, nothing significant.

You say, how can this be? I mean it was -- the drug was so effective in the first trial. Well -- and there's no way of you knowing this -- if the first trial had 80 percent HSDD patients in it and the second trial had 40 percent HSDD patients in it, both called the same thing, FSIAD, okay, and your drug is selective for HSDD, then you're going to have a big problem getting two pivotal trials to have it come out the same way because you have a prevalence of two conditions masquerading as one and no awareness of what that prevalence number is.

So basically, for me, FSIAD is a chimera. It's a non-diagnostic entity that just got slapped together and I think we'll be struggling with it for a while.

DR. CHANG: Dr. Gass.

DR. GASS: I would agree with the preceding

comments. I think it is fine for a clinical office diagnosis to put them together but if you really want to know what a drug product is using, I think you need to make those specific endpoints for that particular product, so I would go with that. Inclusion criteria, yes, but I think careful attention is needed as the exclusion criteria because I think we've all experienced situations where when somebody tells us about their home environment, we say we wouldn't have any interest either in sex. So those issues I do need to be teased out because we can't expect drugs to override interpersonal problems and other situations the patient is going through.

DR. CHANG: Dr. Gelenberg.

DR. GELENBERG: Yeah. I strongly agree with the last comments because my biggest concern is that once the drug is on the market, it's going to be used in ways that are not part of everything in the discussion today. The other point I have about whatever the strengths and weaknesses in the inclusion and exclusion criteria decided for a pharmacologic trial, it behooves FDA to make sure that they're

actually applied. When you get into these proprietary testing sites, very often the criteria that we might agree and scientific panels are optimal, are given lip service but aren't actually applied.

And there are technologies that can allow that just as in psychotherapy research we can actually video and have audits of the interviews or use the patient-reported outcomes or use electronic capture or various techniques that are used in psychiatric research to try to at least assure ourselves that regardless of the criteria, they're actually being adhered to faithfully.

DR. CHANG: Dr. Goldstein.

DR. GOLDSTEIN: So I flew 3,000 miles here to come and spend two days of my life and I want to get back to the basics. I have patients today in the audience and I have patients who have come here. They have sexual dysfunction based on low interest. We have unmet needs here. We need treatments. I'm not going to bash DSM-5 because that's not going to get us anywhere. When diagnostic systems went outside of the American Psychiatric Society and went into a

multidisciplinary society that's -- Cindy talked about the American Foundation of Urologic Diseases -- their conclusion of the classification was desire is separate from arousal separate from orgasm separate from pain. But that's not even the point. The point is women have symptoms, symptoms have indications, and treatments are directed towards indications.

We can have confusions over diagnostic systems. That's not the issue we need to address at this meeting. We need to get a treatment with an indication. The indication is HSDD. We have great systems to diagnose HSDD that were worked with the Agency. The decreased sexual desire screener is a screener that's validated that was worked with your Agency that will give us the symptoms and an indication and then we can develop drugs for that. Thank you.

DR. CHANG: Dr. Guess?

DR. GUESS: So sticking to the question that's being proposed, the strengths and weaknesses, I think that the strengths, to me, are it does include most people who have either arousal and/or desire

dysfunction. So the components are there and I don't mind using it for exclusion and inclusion criteria. I think it goes back to -- and I'm sorry, I don't remember the gentleman towards the end's last name but -- the idea that you can group them all when recruiting patients but then we need to stratify them to try to figure out what these drugs or proposed drugs are actually treating because we don't know so that if you are going to use these are the inclusion criteria, you need to make sure you have enough people that present with each of these diagnoses to be able to then sub-analyze to determine does the drug affect their interest; does it affect their physiological arousal; does it affect their psychological arousal; or does it affect all three. And I think that if we do that and not just focus on the fact that these are inclusion and exclusion criteria, we could probably derive the conclusions that we're looking for in trying to evaluate these treatments.

DR. CHANG: Dr. Heiman.

DR. HEIMAN: So I won't go over the comments that have been made already rather well. I'll just

maybe say one of the things that I think is useful are the modifiers which have to do with clinically significant distress but also relationship distress and other significant stressors and psychiatric conditions plus lifelong and acquired, generalized, situational, mild, moderate, and severe. So what will be interesting is how those get parsed in terms of making selection. For example, lifelong and severe indeed what drug separate from other issues could really be expected to address that and what else might this person need that would be useful in clinically valuable.

The other thing I just want to -- we will come back to this in some way but just kind of separate out the partner issue -- not the partner issue but the fact of partners. So some of the criteria seem to imply a partner is necessary to have this condition. And as we all, a number of women come in and they're between partners or getting rid of one partner and so indeed the current relationship is either out the window, but they're still interested in doing something about their condition. And so what

will a drug trial do with those folks? Will it insist that everybody have a partner or not? So it's a question but it's implied by these other criteria.

DR. CHANG: Dr. Kingsberg.

DR. KINGSBERG: Yes. In terms of the specific question, the strengths are the specifiers, that it's six months, that it rules out other medical conditions and drugs and severe relationship problems. It does include HSDD and has, as Dr. Meston mentioned, better descriptors.

But the weaknesses, to Dr. DeRogatis' point, is that it's a lumper and that it confuses HSDD and FSAD. And my concern is that we not rely or the Agency does not rely so much on the need to validate the DSM-5 and FSIAD to hold back drug development, that HSDD still works as an indication, as Dr. Goldstein said, that we just need the indication. The diagnosis is not as critical and that HSDD and FSAD are clear indications.

DR. CHANG: Can I -- I'm sorry, before we go to Dr. Meston, can I ask a question of the panel -- and I don't have an answer -- is whether the ICD code

includes -- is going to include DSM-5, the FSIAD, because if it's not included in the ICD code, insurance reimbursement may not happen. And even if we approve a drug, our patients may not be able to get it with their health insurance access. So, you know, that's a question to consider.

DR. SEGRAVES: I have contact with the ICD-11 committee and it looks like the FSIAD will be in that diagnostic system, although I think we're still in ICD-9 in this country for billing, aren't we? So this might be two decades out before it will affect anything.

DR. GOLDSTEIN: Just -- and to follow-up, where it might be two decades, FSIAD currently and the next one is HSDD, it's low interest.

DR. CHANG: Dr. Meston, sorry to interrupt.

DR. MESTON: In terms of strength, I will agree with others. I like the fact that it needs to be minimum duration of six months. It needs to cause significant distress and I also appreciate the attempt to rule out the disorder if there is severe relationship distress, although I don't know how we

would really quantify that. That's another question.

In terms of the weaknesses, as I mentioned earlier and what Len described so clearly, is just the -- by having all these criteria which, to me, differentiate a desire from an arousal disorder, lumping them all together, we run the risk of having very heterogeneous patient populations in terms of clinical trials. And as I mentioned in my talk, another problem to me is the working of criterion four and criterion five, I could interpret different ways. Sexual excitement, I don't know what that means. Is it mental excitement; you know, psychological turn-on; is it genital excitement? We use the word "excitement" to describe lubrication in the DSM-4,

And then criterion five, absent/reduced sexual interest slash arousal; again, are we talking psychological or genital arousal? And in response to any internal or external sexual erotic cues, that's a very wide definition. I don't know how we would begin to ask all that. In my lab, we documented 125 distinct cues that trigger sexual desire in women. I'm sure there are many more of those. And then if we

get to internal cues as well, it would be hard to cover them all.

DR. CHANG: Dr. Mirkin.

DR. MIRKIN: So I fully agree with Dr. Goldstein. I don't think anybody could argue that this is an imminent need on this condition and you call this what you want to, right, so I don't want event to argue that. So since there's an imminent need, I really -- I want to applaud the efforts that FDA has putting together this panel to discuss this very important topic.

I think that we need to understand there is nothing more important for those, like me, that develop drugs to have clear protocols, because clear protocols only will allow to have a clear experiment and only that will allow to know exactly whether a drug will be useful for a target population.

So I want to lay down like three important concepts around drug development that are very simple but I want you to think about when you try to understand the whole topic that we're discussing today. Number one, we need to think about what is the

indication that we are discussing. And it seems to me there is not a clear understanding within the panel what is this indication we are talking about.

Secondly, the more clear the inclusion-exclusion criteria are, the easier the product will be to be executed. And I don't see the DMS-5 as an easy tool to be lumped all together in a clinical protocol to assess any drug in a phase three clinical setting. It will be tough to use.

And the third important concept is that the more homogeneous your population is, the easier it will be to interpret your data. And here we're also debating whether arousal and interest are the same, so my gut feeling, right, without being an expert in the field will be not to pull, not to combine these two, quote, unquote, symptoms together in a phase three clinical trial.

DR. CHANG: Dr. Segraves.

DR. SEGRAVES: This was -- these criteria were set up to be clinical descriptive criteria. They were not set up to be criteria for pharmaceutical studies. And I think for pharmaceutical studies, they

have obvious disadvantages. I think to have people screened to fit in these trials, you're going to need people who are quite expert in this area to do the screening, to really do meaningful screening. Otherwise, and they can either do videoconferencing or video checking and things like that Dr. Gelenberg mentioned. So those are real disadvantages. Whether we're lumping -- I think was heard -- or putting a heterogeneous group together or not, I think is still unknown. I think if you used all of the criteria and you mark them separately, then you could find out very quickly on the first studies.

DR. CHANG: Dr. Wierman.

DR. WIERMAN: I'm struck by the discussion and the panel how complex this and I was trying in my mind to sort of compare it to where we were when we understood erectile dysfunction. And we understood the biology. We discovered nitric oxide. We discovered the pathway and then drugs were targeted to it and patients were recruited who weren't excluded who had depression or diabetes or were on other medications. And we found how the drug worked in

different populations because we understood the science and we understood the biology.

What I'm struck with is we don't understand the whole biology of female sexual function or dysfunction and, therefore we're either going to go out and recruit a broad range of women with disordered sexual function and then go back and power it to find out how the drug works in different subpopulations because we don't understand the biology, which is difficult for a drug developer and for indications.

Or we're going to create such a narrow -- several people have commented that they like the five on the fact that it excludes all other medical problems or anybody who's depressed, but we heard Dr. Basson say that most of the literature suggests that cognitive or psychological aspects are, at least by the time the patient comes to our clinic, part of the process. So it worries me that we're going to create such a narrow indication if you're going to exclude everybody that it won't be clinically relevant and that's the yin and the yang.

DR. CHANG: Thank you for your responses for

the second question. We'll move on to the third question. Before we get going, I just wanted to remind everybody about the time. So in the interest of time, if you feel like you agree mostly with previous comments, it's okay to say so and be brief because we do want to have time allowed for public questions.

So number three, "How would you precisely define and quantify each of the six indicators of absent or reduced interest/arousal. For example, a, "How would you define and quantify reduced frequency and how much reduction in frequency is needed to meet the criteria for FSIAD?" Or b, "How would you define other terminologies?" And I'll just leave these on the slides. So if we can get started with Dr. Connell?

DR. CONNELL: I think we would almost have to take a step back. I mean, for example, the at least 75 percent of encounters I think is great in terms of selecting patients for a drug trial, like Dr. Wierman mentioned, but could exclude the person who's 66 percent of the time not satisfied and upset.

So I think we almost have to take a step back and just talk to patients. I meant they're here today. They're willing to give their time and their money. I think we really need to figure out what is it. I mean Dr. Meston was mentioning women get it if you say, you know, decreased desire but what does that mean to each person individually. And I think it is a moving target and so vague, so I think that's probably one of the hardest parts of studying this and targeting patients.

DR. CHANG: DR. DeRogatis.

DR. DeROGATIS: I think the first one is the easiest one in the sense that I think frequency has to be defined in a relative way rather than an absolute. I mean absolute makes no sense at all, so relative to some prior period when you were functional or relative to some prior period in a trial design.

The others, I think, are problematic because well, sexual activity would be defined operationally, you would simply list out those sexual events and activities very much like we do now in clinical trial protocols and essentially say operationally, these are

sexual activities. Are there others? Of course. They're endless. But I mean for purposes of the trial and for purposes of definition, I think you have to operationalize them. Now you can do that with sexual activity but as you get to these others, they become very difficult to define. You know, it's a set of words and you wind up looking for another set of words that explains that set of words and suddenly, you're very quickly into an infinite regress. So I'm going to chicken out and not go any further as a suggestion in that regard.

DR. CHANG: Dr. Guess.

DR. GASS: I agree that it's relational and in my practice, I ask people "When was sex good for you, and what was your frequency then, and how is it now?" And so you get some kind of a percentage decrease for what it has been when they thought it was good and that could be any kind of sexual activity as was just said.

DR. CHANG: Dr. Gelenberg.

DR. GELENBERG: I agree with the comments.

DR. CHANG: Dr. Goldstein.

DR. GOLDSTEIN: I use the DSDS. That's what we use in clinical practice when we want to identify women with low interest. In the past, was your level of sex desire interest good and satisfying to you? They say yes. If they had an acquired version, "Has it been a decrease in your level of sexual desire and interest?" They say "yes." Are you bothered by it? They say "yes." Would you like something done about it?" If they say "yes," we then work with them. The other classification systems are missing the symptom indication importance that we talked about before.

DR. CHANG: Dr. Guess.

DR. GUESS: So I agree with the others on frequency but I also think that when we ask that question, we need to have them quantify for us so that we can look back on what the individuals have put as far as a range is concerned, so that we can gain an understanding of what that range of abnormality is for our group.

As far as defining these other terminologies, I think specific questions should be asked. "Do you experience a decrease in vaginal

lubrication?" Do you experience breast tenderness, nipple erection" because again, I don't think we understand enough about the physiology of the disorder to just assume that using these terms will get us to a better understanding of these issues.

DR. CHANG: Dr. Heiman.

DR. HEIMAN: I basically agree with the other comments. It's almost as if that would be a separate study to address points, particularly point b, in order to find that out. And still, if you did a separate study and got some agreement on that, on all of those terms, with a new sample of people and a new generation of people, they would shift. So I think the main reference point I would use is whatever the patient or participant in the study would come in with and then decide what our cutoffs were.

DR. CHANG: Dr. Kingsberg.

DR. KINGSBERG: For point a, I would say what Dr. DeRogatis said, that it's a relative decline. For point b, I'm guessing I will agree with what Dr. Meston will say, that it's very difficult -- and I think the question actually is "how would you define

other terminologies to whom, to this group or to patients or to clinical trial participants" because that may be different. As a clinician, I can easily help them define the words and give examples in the infinite regress, as Dr. DeRogatis said, and I can give operationally-defined definitions in the clinical trial. But I think the reality is for what purpose.

DR. CHANG: Dr. Meston.

DR. MESTON: I agree with everything that has been said. I'll just add as Dr. Segraves said, the DSM-5 was developed for use for clinicians and so presumably a clinician would know the question would know the questions to ask and to be able to make a diagnosis using this criteria.

To use it for clinical trials and to try to define each of these six criterion I think would be an enormous task. I think that you could run focus groups for the next 10 years and collect data and then try to crunch it down and then to try to find some arbitrary number of how many of the criteria you need to meet to really meet the criterion, and none of us would agree and it would only still in the end cover

some of the women's experience of low desire because it is very individual. And I think to try to attempt to do that would just be a big waste of time and money when we already have, as Dr. DeRogatis pointed out, a number of very well validated studies that have shown the test of time and discriminating between patient populations and showing treatment effectiveness and keeps it very simply. And as I said earlier, women who have low desire know what desire is. We don't have to define it in such an intricate way.

DR. CHANG: Dr. Mirkin.

DR. MIRKIN: I don't think that we do spend too much time trying to define what this reduced frequency -- I think as far as someone has clinically significant distress, I don't care whether it's 70 less or 80 less. It's -- I think it's important enough as a physician to offer to these subjects a pharmacological intervention if a safe pharmacological intervention exists.

So I don't think that, you know, quantifying with percentages will help here. I think it would be important to try to determine what is the best tool

that we have to define what is the clinical significant distress and that's the way I will try to propose to start, you know, focusing on this particular condition.

I don't have comments on item number b.

DR. CHANG: Dr. Segraves.

DR. SEGRAVES: I think some of these are fairly easy, like absent interest in sexual activity is zero. I mean that's -- the absence -- every one of these things is zero. That's a simple number. And reduced, I think all of us agree that 25 percent is probably a significant reduction. I mean I think there are ways we could proceed logically as long as we clearly specify what we're doing.

DR. CHANG: Dr. Wierman.

DR. WIERMAN: I don't have any other comments.

DR. CHANG: Can we go to the phone for Dr. Basson for her response to question three?

DR. BASSON: Question three, you know, I'm not able to see your screen anymore. Could you give me the question.

DR. CHANG: Question three states "How would you precisely define and quantify each of the six indicators of absent/reduced interest/arousal?" And then we have two examples.

DR. BASSON: Okay. The question you've all been discussing right now?

DR. CHANG: Yes.

DR. BASSON: Okay. You're not moving us on. All right. Certainly, I'm agreeing with others as in it is straightforward and reduced frequency is relative. The question is, of course, the one with the lifelong concerns who, you know, is not able to compare with anything in the past, saying I never have but again, that would be just really taken care of with the first one, i.e., the absent.

I agree also with others that were saying that trying to understand what these terms mean implies that the person doing the assessment needs to be very experienced in this field so that they can. Will the individual really hear what she means by interest or arousal and try to define what interviewer means the same thing. So I don't think this --

because it's so nuanced and there's cultural and perhaps English second language issues, etcetera, etcetera, I don't think this can be spelled out in a manual for somebody that was not very experienced in this field.

I think -- I had another point but I've lost it. Maybe you can come back to me on it.

DR. CHANG: Okay. Dr. Goldstein actually has a point.

DR. GOLDSTEIN: I have a point that's based on some comments that have been filtering through that I just want to clarify. And since I was intimately, intimately involved in Viagra and its development, the thought that we knew that nitric oxide relaxed muscle in the penis and we dedicated drugs like PDE5 inhibitors to that is completely false. This was an accident. We had drugs for -- nitrates chest pain and the only thing that happened was a side effect. They got erections in the middle of the night that allowed us to convert the development of the drug from the nitrate use to the erectile dysfunction. My point being, and I'll be short, is that you don't need the

science to predict the drug. Quinine was involved in malaria before we even knew the mosquito was causing the malaria. If you see action with the drug, it's okay to use it for its indication. LUTS, there's huge disagreement of what cause LUTS. We have drugs that improve the treatment, overactive bladder and over and again. Thank you.

DR. GASSMAN Dr. Guess has a response.

DR. GUESS: I just -- I don't disagree. I think you got we're grouping whether or not you should approve a drug based on this versus whether or not we should collect the data. The point is simply that we should still collect this information so that we can look back, as scientists, and try to figure out if someone doesn't respond, could it be that they're not responding because they don't have these specific criteria, whereas the ones that responded do have these criteria. So collecting data and approving a drug should be distinguished. We should still collect this information and understand the frequency of these things and have specific numbers for this. It doesn't necessarily dictate whether or not we approve a drug

that is working for a patient.

DR. CHANG: Okay. We really do have to move on to question four. "How would you define or quantify significant distress?" Dr. Connell.

DR. CONNELL: I'm not a psychiatrist so I'll be brief. I think it would be anything that impacts a person's daily life where they're spending time worrying about that problem. I'm sure there is validated things and I'm sure my colleagues here can describe them more.

DR. CHANG: Dr. DeRogatis.

DR. DeROGATIS: I would do it operationally. I would do it the way we've done it already by taking a distribution of patients who indicate they have distress, sexually-related personal distress, taking a distribution of individuals who indicate they have no sexually-related personal distress, take the optimum cut point that minimizes false positives and false errors, and that score and greater would define significant distress. It's totally operationally, totally empirically based.

DR. CHANG: Dr. Gass.

DR. GASS: Yes. I usually take that at face value. However, once in a while there is a person who comes in and the message seems to be "I just wonder if all those people are having more fun on TV than I am and maybe I'm abnormal" but didn't really have much distress to start with. But otherwise, I would just take it face value. They came in because they were distressed.

DR. CHANG: Dr. Gelenberg.

DR. GELENBERG: I agree with the TV qualification. For the most part, patients don't get to clinical encounters and don't get to clinical trials unless they're having distress, so I wouldn't set a very high bar for that.

DR. CHANG: Dr. Goldstein.

DR. GOLDSTEIN: I agree. In my experience, being in the office with this horribly personal problem is usual. The operational measurement of the distress scale is what we use in our practice right now.

DR. CHANG: Dr. Guess.

DR. GUESS: I agree with the comments.

DR. CHANG: Dr. Heiman.

DR. HEIMAN: I agree with Len on this. The only -- Dr. DeRogatis -- sorry -- the only issue would be that I think it's a little different clinically than it might be in a drug trial and clinically, sort of any level of distress deserves attention. But in a drug trial, I would think, as in another research trial, a cutoff would be important depending on the distribution.

One other thing I wanted to just possibly raise, though it's not -- it is indirectly relevant, and that is given that the population has changed a lot, I don't know how well the DeRogatis Distress Scale has been normalized on broader samples that would include people of different ethnicities and so on. So maybe that' a separate kind of issue but it would be terribly important now.

DR. DeROGATIS: The distress scale has been validated on multiple samples of women, both premenopausal and postmenopausal as discriminate validity, responsiveness, content validity. It's in a newer incarnation. We just presented at the American

Psychiatric meetings in May on validation again. So it's widely validated and as bad as it sounds in terms of tooting my own horn, I've never seen -- and there were many of us that put that together by the way -- it hasn't ever failed in a major drug program in terms of discriminating successful individuals from non-responders. So it's a pretty good little scale.

DR. HEIMAN: I love the scale. That's not the point. I just raised the question of ethnicity and etcetera. I haven't looked at that on the scale.

DR. DeROGATIS: Yeah. We haven't broadly general -- I mean validation programs can go on, as I said earlier, infinitely and you can always find a new population to broaden the generalizability of the validity. But for women with female sexual dysfunction, both premenopausal and postmenopausal, we have had a very consistent experience with the FSD series now.

DR. CHANG: Okay. Dr. Kingsberg.

DR. KINGSBERG: The question is -- how I would define it is based on a clinical population. If they come into my office -- particularly if you've

ever had to park to come to my office, you know that there is significant distress, but the quantification would be for a clinical trial and I think Dr. DeRogatis stated that very well.

DR. CHANG: Dr. Meston.

DR. MESTON: I agree with Dr. DeRogatis and the rest of my colleagues here.

DR. CHANG: Dr. Mirkin.

DR. MIRKIN: Yeah, I agree as well. For a clinical trial, you need to use the available tools. If the tool is well-validated and been tested in all the populations that, you know, we are making the experiment, I don't have a problem using the current tools. Now, if we believe that this tool needs to be updated or go through further validation, I'm hoping we can start this work as soon as possible.

DR. CHANG: Dr. Segraves.

DR. SEGRAVES: Minor issue. Actually, the DSM-5, it's clinically significant distress in the individual is the specific wording. It's trivial but we fought over that for years so I just want to make sure that we got that straight.

I think any of the common instruments, particularly Len's instrument, would pick up exactly that no problem.

DR. CHANG: Dr. Wierman.

DR. WIERMAN: No additional comments.

DR. CHANG: And Dr. Basson?

DR. BASSON: The only additional one is the context is very interesting although I don't think this has been scientifically studied, how the distress severity can change when -- from the very first measurement before any detailed assessment or formulation is given. Once the formulation is given and the patient can understand why it is the way it is, often before there's any, quote, therapy of any form, oh, I'm so -- I feel so much better; you know, it's logical. Somebody else in my situation would be feeling this way, having little interest and slow or no arousal, whatever the concern is. So that's something that I think needs some thought about when do you measure this distress and how often, particularly in a drug trial, is the formulation ever made and said that to the patient.

DR. CHANG: Okay. Let's move on to question five. "How would define or quantify severe relationship stress in patients who are not experiencing partner violence?" Dr. Connell.

DR. CONNELL: Again, I'm not a psychiatrist so I'm going to leave most of that to my colleagues here but I would say it's important not just to think about violence. I'm a urogynecologist and a lot of the patients that I see actually have had their husbands leave or going through a divorce, so I think that's really an important thing to look at.

DR. CHANG: Dr. DeRogatis

DR. DeROGATIS: I would try to establish, to my satisfaction as a clinician, that these individuals were in conflict, a; unhappy, b; and since we're calling it "severe," at the end of their rope, so to speak, without any discernible options beyond divorce or something akin to that, and if they met all three criteria, then I would say this is significant relationship distress. Now you can soften them. You can add more specific criteria, but I think it's important that you don't say, "Well, as a clinician,

I've seen a lot of distressed people and this person fits the bill," although we do that, I mean, because that's -- we're clinicians. But I mean I think in your mind, you have to have explicit criteria for why you've come to this conclusion about the patient's status.

DR. CHANG: Dr. Gass.

DR. GASS: I do think that has to be given some thought. I think it's a little too severe to say "severe distress" because I think a lot, perhaps even moderate stress in a relationship often kills sexual desire for women so I'll let the psychologists determine that.

DR. CHANG: Dr. Gelenberg.

DR. GELENBERG: Thanks. As Dr. Segraves said earlier, the category was created for clinical use and I don't think that's a -- in general psychiatric clinical practice, that's a kind of a give me. You just can make a subjective assessment. I would be very fearful of using this in a clinical trial. I would set some kind of strict criterion on the collaborating centers as to what's involved and

rule those patients out. But based on experiences that we had in Arizona validating the ASEX scale, even relationship variability much below severe relationship stress is apt to have important influence in female sexual functions in all the domains, and so even if these patients come into the study, it would be worthwhile for the investigators to capture indices of comings and goings and improvement and worsening in relationships because that may have greater leverage on the final outcome of the important dependent variables than any pharmacologic intervention. That's largely been our experience in antidepressant trials.

So I would define characteristics for excluding severe relationship distress and then I would capture something about the relationship to load into statistical analyses later.

DR. CHANG: Dr. Goldstein.

DR. GOLDSTEIN: Thank you. In clinical trials, we have an interview and during the interview, we ask questions and we seem to weed out those who are in love, have a stable relationship and those who are not, but -- that's how we currently do it.

DR. CHANG: Dr. Guess.

DR. GUESS: I don't think that being in love and having a stable relationship qualifies you for having good sex. So I have patients who have violent relationships who are about to get divorced but have great sex with their partners. So to me, the question is, "Is this someone you expect to achieve or want to achieve a satisfactual sexual experience with?" And if it's not, then you shouldn't be in the trial. If it is and you still can't have these experiences, then you qualify for participation.

DR. CHANG: Dr. Heiman.

DR. HEIMAN: Thank you. So I think that severe is too limiting, I would agree, for a trial. Now while I don't know if I recommend it, I would feel fine in my own research which is maybe different than a clinical trial, using a scale to measure relationship distress and kind of decide what looks like it will be out of the range. I mean one would need to think about it for a study like this.

The other thing is just coming back to what we were getting at before with regard to the partner

and we'll come to in a minute, and that is is this drug only going to test, which I presume it will, whatever drug is around is only going to test partner sex? So we're all assuming that. If we assume that, then in my opinion, not only does the patient's relationship stress need to be measured but, frankly, I think the partner's does too.

DR. CHANG: Dr. Kingsberg.

DR. KINGSBERG: Well, I think severe is similar to significant in that it's the patients' determination. But really, the point, I think, is that this is a chicken or egg phenomenon, that if somebody walks in and has severe relationship distress because they've had sexual dysfunction, then they qualify for a trial. If on the other hand they have a terrible relationship or a significant relationship problem and that impacts their interest in wanting to be sexual, then they are excluded from the trial, and it is really an order issue as opposed to a severity issue.

DR. CHANG: Dr. Meston.

DR. MESTON: I was going to say the exact

same thing as Dr. Kingsberg so just ditto what she said.

DR. CHANG: Dr. Mirkin.

DR. MIRKIN: Again, purely from the clinical perspective, trying to decide whether a patient will make it to a trial or not, right -- I don't want to debate the other aspect of this -- I think that we need a clear tool assessing these, evaluate the tool and therefore that's a way to define and quantify what the severe relationship distress will be for someone to make it or not into a given clinical trial.

DR. CHANG: Dr. Segraves.

DR. SEGRAVES: When we were in the DSM deliberations, there was a lot of argument about -- disagreement about how to modify relationship stress. And our goal was to not diagnose a sexual dysfunction if the problem was clearly related to interpersonal problems and we couldn't figure out how to do that and that's the reason we put the severe. Our concern was if we made it less dramatic, some clinicians would say everything is related to interpersonal stress and other clinicians would say nothing so that was the

problem.

I think for clinical trials, you could probably use one of the standard marital adjustment scales and sometimes there's a couple deviations all throughout the study, simple.

DR. CHANG: Dr. Wierman.

DR. WIERMAN: I guess my only comment would be -- again, I keep comparing to males. I mean men were recruited into studies of erectile dysfunction with bad relationship stress and a certain drug target might be independent of any kind of relationship stress on female sexual dysfunction depending on the drug target. And so I would be a little concerned about having this as an absolute exclusion criteria.

DR. CHANG: Dr. Basson.

DR. BASSON: Yes, agree with many previous speakers, especially just now with Dr. Wierman. However, the drug is looking at desire/arousal/interest.

Then I would agree with others previously because the "severe" is too severe, too strict because if we look at all the studies, what comes up

repeatedly as it is, you know, emotional closeness to the partner is so linked with desire and arousability with the partner. So depending on what the target is, I think if it's desire, then there needs to be much scrutiny and assessment of that relationship.

And if it's been damaged, whether it's chicken or egg is another -- as has been said, it doesn't -- in the end, it doesn't actually matter. This still needs to be address first because again, the point I've said before is that to see effect of a drug where there is clear disharmony and resentment about that disharmony, to see benefit is not going to be particularly likely.

DR. CHANG: Thank you. I wanted to move on to our last question for the morning discussion session which is, "Is the input from a partner needed or useful?" And I think we've already heard some of it already. Dr. Connell.

DR. CONNELL: As a urogynecologist, I see lots of women with pelvic organ prolapse, urinary incontinence, fecal incontinence, and sexual dysfunction so obviously very sensitive topics. And I

have to say I do not think sexual partner information is necessary but it can be useful. And I say that in context because a lot of couples, when they come in together, the husband is very caring but I get a very different story when the husband is sitting in the room and I'm taking a history. Or if I'm seeing them after surgery, everything is hunky dory; and when the husband steps out while we do the exam, then the wife will tell me, "well, this isn't exactly going so great" or "actually, he has erectile dysfunction." So I think if partners are going to be involved, I think it is very helpful but that needs to be separate and de-identified and yes, maybe linked to the couples but they should be able to see each other's answers.

DR. CHANG: Dr. DeRogatis

DR. DeROGATIS: I can only relate to my experience in trials that I've done. Now as a clinician, I think partner input is very useful and whenever I can get both members of a couple in the office together, I always learn a lot more about what's going on than if just one of them is there and often it's a very distinct picture from one and the

other.

In clinical trials, and this is just the trials that I've done over the years, I haven't found input from the partner particularly useful. And from a methodologic point of view, you now have two sets of errors of measurement, and so which one is the correct one. And it's complicated and I'm still waiting to see a great trial where the partner's input really added something to it and I haven't so far so that's all I can say.

DR. CHANG: Dr. Gass.

DR. GASS: Well, for a clinical trial, I would say no.

DR. CHANG: Dr. Gelenberg.

DR. GELENBERG: I like partner input in many kinds of areas, in behavioral difficulties and in psychiatric research and I would opt for no on this one.

DR. CHANG: Dr. Goldstein.

DR. GOLDSTEIN: I agree.

DR. CHANG: Dr. Guess.

DR. GUESS: I agree.

DR. HEIMAN: I don't agree but I don't agree to the extent that partners should be involved in everything. I think some degree of assessment at the beginning would be wise. Suppose the partner, as those of us who've seen people and couples, is actually planning to leave the relationship, so the patient may have a very different idea of what's happening. So that would be one place. I don't think the partner should be used for corroboration data. I don't think that makes any sense and I don't -- that would be silly, especially in a -- well, particularly in a clinical trial.

But I do -- I think we're missing something. This is a social activity. This is not just like depression, although there are some things one could say about that, too in terms of partners. This is activity that directly involves the partner. Should or shouldn't he know -- so I'm just going to pose this as a question perhaps -- that she's taking a drug? Well, it's her body, she can do what she wants but if she's going to be taking a drug and he knows it, what are the pressures on her? I think there are several

things to discuss around this but this may not be the moment and the place but I just have a slightly different view on this.

DR. KINGSBERG: I think in clinical practice, it is useful. I think in a clinical trial, it is not necessary and I do think it adds too much error.

DR. MESTON: I would agree with that. In a clinical trial, I think it would be kind of confusing how you should use it. In clinical practice, definitely. I mean if the partner is available to collect information on, it can be certainly informative in research. But for clinical trials, I don't think it's necessary at all.

DR. CHANG: Dr. Mirkin.

DR. MIRKIN: Yeah, I agree. I don't think it's relevant information to be measuring this in a clinical trial.

DR. CHANG: Dr. Segraves.

DR. SEGRAVES: I think on the first visit, you would like a partner present just to see the partner's involved enough to come in. I think that's

a big thing. After that -- I remember one trial where we had patients listing how frequently they had had intercourse. And one women's frequency just shot sky high and in this trial, the partner had to initial. And we looked at the initials, the initial handwriting had changed when her sexual activity spiked. So I think there is some need to have some sort of partner check or something there. I'm not sure how to do it and how to make it easy to do methodologically with a clinical trial.

DR. WIERMAN: No other comments.

DR. CHANG: All right. Thank you to all the panelists for the lively discussion. And now we are going to move to audience questions. Or perhaps we can --

UNIDENTIFIED FEMALE: (Inaudible).

DR. CHANG: -- oh, I'm sorry. Dr. Basson hasn't provided a response.

DR. BASSON: Just to say as a clinician, I have always -- or we always see both partners but individually, so we would see usually the couple on the first visit and then depending on time, separate

them and begin to see one alone and the second visit continue, see the other one alone. In nearly all circumstances, more information has added, more understanding has added. Now that's clinical practice.

And I'm trying to think would that be of value in a clinical trial and I would think but yes, because there's more true understanding of the difficulty in almost every situation. It would -- I would not want it to mean that single women could not be recruited but not seeing the partner, I think, is going to potentially annul this diagnosis. So I would definitely (inaudible).

DR. GASSMAN: Okay. So what we're going to do is we have one question from the audience, of someone who needs to leave. And then what we'll do is we'll break for lunch but we will make time after lunch for everyone so that we can take questions on this. So I'm not -- we're just -- I want to make sure that everybody gets a chance to have lunch.

The question is for Dr. DeRogatis and it's from Karen Hicks at Lehigh. She asks "How inclusive

are the present scales on the diversity of women by ethnicity, income, sexual orientation, and non-partnered activity?"

DR. DeROGATIS: My generic answer is not very. The -- building a norm for any one of those partitions or demarcations takes a fair amount of time, energy, money, effort, and it's just not easy to get the resources along any of those domains to accomplish that.

But that's where the notion that I mentioned earlier of validation of scales is in perpetuity. So if you have a particular group of interest, an ethnic group, a gender group, etcetera, then I would recommend petitioning the authors or whoever controlled the scale to see if they will collaborate with you to build such a norm, because it's just very, very difficult to do all this work across that spectrum of characteristics. It just -- the resources aren't there.

DR. CHANG: So thank. This concludes our morning session and we're going to break for lunch. I'm going to ask everybody to return to this room at

one p.m.

(Whereupon, off the record at 12:06 p.m., and back on the record at 1:04 p.m.)

DR. JOFFE: My name's Hylton Joffe. I'm the Director of the Division of Bone, Reproductive and Urologic Products here at FDA. What we're going to do is we're going to move into Panel Discussion Topic Number 2. I'm going to do my very best to stay on time or end that one a little early and then we'll take questions for Topic 1 and Topic 2 together after that.

Also, we're going to change things. We're going to let folks who have questions just come up to the microphone and ask the questions directly rather than playing telephone here.

I realize the panelists didn't get to introduce themselves at the beginning. In the interest of time, I'll just say that online, we have a full roster with everybody's names and qualifications, and we made sure that we put folks on our panel who would have wise advice for us and for other folks doing research in this area.

So let's turn now to Panel Discussion Topic Number 2, and what I'm going to do is I'm going to combine questions one and two together. So this is now talking about endpoints for clinical trials. And what the questions is that for female sexual desire disorders, we've recommended in the past that drug companies show improvement compared to placebo in two co-primary efficacy endpoints, one is satisfying sexual events and the other is improvement in sexual desire. And we've also had one key secondary efficacy endpoint, which is distress because of low sexual desire.

So what we wanted to hear from the panel is what you all would recommend as the key efficacy endpoints for assessing drugs that are used to treat either FSIAD or aspects of FSIAD such as the arousal or the desire components. We've listed several here but by all means, if you have other ones that you think are better, feel free to propose them.

So one is improvement in satisfying sexual events, and I'd particularly like to hear the panelists' views on this because we've been using this

in clinical trials. So companies say well, that's not really part of the diagnosis so why are we including that. So I'd like to hear what folks think about that, and then improvement in sexual desire, improvement in sexual arousal and then a reduction in distress. So those are all the endpoints and then as I said, others.

And then the second question asks what are the strengths and weaknesses of each of the efficacy endpoints above as well as any others you're recommending. So as you go, if you could please hit question and question two together. And why don't we start with Dr. Wierman for this question.

DR. WIERMAN: As I see these two questions, I guess the advantage of staying with the prior criteria, the two co-primary efficacy endpoints, satisfying sexual events and sexual desire, with the secondary endpoint of distress is that you match what has previously been done in prior trials and you have a comparator, i.e, is the new agent better, the same, or less strong. And these are the important aspects that most women would consider significant.

I guess the other issue is do you need two primary events and if they come to you because they have altered sexual desire, is one primary event and two secondary endpoints just as good for the majority of the patients clinically who present in the clinic. And again, I think one of the problems is because we don't understand the process of these different factors that influence these outcomes, that's where the prioritization becomes an issue. So if you always do events as the primary end, it's much more complicated. The number of patients needed to be enrolled in the study or the power may limit the drugs that are coming down the pipeline. Those were the comments I would have.

DR. JOFFE: Dr. Segraves and Dr. Meston, just to catch you up to speed, we're answering question one and two on this round, and it's asking about what you think should be the key efficacy measures for FSIAD or components of FSIAD and what do you think are the strengths and weaknesses of those efficacy endpoints, particularly hearing about satisfying sexual events and then others are

improvement in sexual desire, arousal, distress.

DR. SEGRAVES: I think, obviously, improving sexual desire should be one of the primary endpoints. In terms of satisfying sexual events, I think we probably ought to keep that measure because that way we'll have some continuity with previous research. I think there are a lot of problems with that measure though in terms of what is a satisfying sexual event. It may have to do with more of a relationship than it has to do with any biological increase in desire.

DR. MESTON: I would argue that the key endpoints, if it's a desire disorder, improvement in desire; if it's more arousal disorder, improvement in arousal and for both, a reduction in distress. I am personally not crazy about satisfying sexual events as a marker. I think it's unclear what that really means. I think it means very different things to different women. Yesterday we heard one woman describe a sexually satisfying event as one where she successfully faked her husband into believing that she enjoyed the event. So it's quite -- it can mean very different things I think.

And also, we conducted a study in my lab. It was a treatment outcome study on -- it was a drug company sponsored study but it looked at a drug versus sex therapy versus combination, and it was an eight-week trial and we looked to see what best predicted treatment success, treatment outcome as defined as clinician kind of gold standard interviews. And we compared -- these were for women with FSAD and we compared satisfying sexual events with the FFSI, with vaginal photoplethyzmograph measures, and the only predictor of treatment efficacy was the FFSI. Satisfying sexual events were not at all significantly predictive, so I'm not a big fan of them.

DR. MIRKIN: So I would agree. I mean I think it would need o be very literal, right, if you're trying to develop a drug to improve female sexual desire, certainly the key primary endpoint should be improvement in sexual desire and there should be a clear tool on how to measure that.

I do believe that the distress component is important so I would have distress because of the low desire as a key secondary endpoint. I do believe

that's important. That's part of the definition; therefore, it should be part of the clinical trial.

I also concur and agree that the satisfying sexual events do not seem to be correlated what is the indication in which we're trying to develop the drug. Therefore, although it may be informative, I wouldn't consider this to be a primary or secondary endpoint in a clinical trial.

DR. KINGSBERG: So I think that improvement in sexual desire as measured by the FFSI desire domain has been validated. It has been shown in many trials and in many studies to be very effective and, you know, to Dr. DeRogatis' point, it's an ever infinite way to validate and validate and validate but this is the gold standard. So I think we have a wonderful tool and it should be the primary endpoint if we're looking at improving hypoactive sexual desire.

Satisfying sexual events, I've said on many occasions, is not the best endpoint. It is, at best, a downstream even of desire and as Dr. Meston has pointed out and Dr. Basson as well, there are many reasons why women will choose to have sexual events.

Many of them may end satisfyingly but desire is not necessarily the key to that, and women will come into our trials having satisfying sexual events.

And certainly, reduction in distress should be a key secondary. I think if we're looking at an HSDD trial looking at improvement in arousal is not a necessary endpoint. It's interesting but it is not necessarily a key endpoint. But if we're looking FSIAD or really FSAD, then obviously my position changes and we're looking at c as the important endpoint of arousal.

DR. HEIMAN: Okay. To keep this going quickly, I would agree that diagnosis for an endpoint, the diagnosis is what it is. So desire for desire and sexual arousal for sexual arousal is the primary endpoint.

The issue of distress, indeed that needs to go down so I don't quite know what to do about that.

Satisfying sexual events, that -- it's never been a great measure. If it's anything -- if it needs to be in because of some sort of consistency over time, then certainly secondary. Sure would be great

to know really what it means.

DR. GUESS: So I agree with both the desire and the distress being on there or arousal and distress. I also think though it may be perhaps unpowered though again asking for arousal even in a study that's looking at desire and asking about desire and a study that's looking for arousal because again, I don't think we understand these drugs and mechanisms well enough to just exclude them completely. And you don't have to power for it but that way, we can look back and find out if those things were affected.

I also agree with the satisfying being problematic but I do think potentially some word like "enjoyment" of sexual events because all these other things, to me, are very distress, they're very sort of esoteric terms that we use as clinicians. But what we really want to know is is this person able to enjoy their activities. And so I think perhaps using something that captures that enjoyment might be useful.

DR. GOLDSTEIN: So I would like to emphasize that in the last bunches of questions, this panel has

had more agreement in things, I think which is very important, that the concept of satisfying sexual events which has been a primary variable that you have to achieve to get a drug is way too distal to achieve. Do you have the satisfying sexual event because your desire goes up because that's what the drug is doing or other reasons? The -- all the studies that have used the appropriate PROs have shown sensitivity to the desire, to the arousal, and to the distress issues but not to the SSE. It should never be a primary outcome. It's too distal. I think in the lecture given by the expert from the FDA, I think she also agrees with that. Thank you.

DR. GELENBERG: I wouldn't make it too hard to see a signal if there were a drug where there is a signal. I would consider an arithmetic sum or something. I would make a very reasonable bar, so if you could create a sum of several of these items and can have an active drug beat placebo, I would be modest in the expectation.

DR. GASS: If FDA is going to leave together the desire and the arousal, I would suggest that the

trial determine up front the most bothersome symptom, whether that is arousal or desire. And then the measures would then be an improvement in desire or arousal and a decrease in both of those, whichever pathway you're going for

I think it would be good to consider another item which would be sexual thoughts, an increase in sexual thoughts, fantasies, and dreams. Some women are distressed that they never even think about it anymore.

And then for the satisfying sexual events, I think that needs to be more generalized, maybe even think about going to satisfying physical contact because people may not interpret hugs and kisses as a sexual event, but that might improve if their desire and interest improves.

DR. DeROGATIS: I want to agree with everyone else that I would use sexual desire as a primary or sexual arousal depending on the focus of the study.

I would elevate distress to a co-primary because it's a stated aspect of the diagnosis of any

version of HSDD or FSIAD and without it, you can't make the diagnosis.

And satisfying sexual events, I would demote to a secondary, again, for all the reasons that everyone has pointed out, that it's a downstream variable. It's often decided much more by the patient's partner than by the patient. It's, from a measurement perspective which I know is boring but nonetheless, it's a very coarse measurement compared to the PRO measurement. It's certainly relevant and it adds to our assessment but I would make it a secondary or key secondary.

DR. CONNELL: I agree like everyone here on the panel. The main thing I would just add to is just what people have been saying. If it's a drug for desire, that should be a primary aim with the distress, like Dr. DeRogatis said, because that's part of the diagnosis. And as a secondary aim, as a secondary hypothesis, I would say if it's made for desire, we secondarily hypothesize it will affect arousal and/or vice versa. So I think whatever your primary target is should be in your primary aim and

since we don't understand the pathophysiology fully, the other disorders should be in your secondary aim.

DR. JOFFE: Thanks, everyone. Dr. Basson, if you're still on the phone, any thoughts from you?

DR. BASSON: Yes, thank you. So definitely I would agree to make distress a primary, especially if we're thinking in terms of perhaps comparative pharmacological versus psychological treatment.

Regarding sexual satisfaction or satisfying events, you know, we do have qualitative data clarifying that women don't equate satisfaction with absence of dysfunction, so it does make it rather complicated to make that an endpoint.

My third point is that with the DSM-5 definition, there's the fifth criterion of absent arousal or interest that's responsive to the sexual cues, and so we don't have an endpoint capturing that but I guess is under "others" in question one. Would there be other endpoints? Thank you.

DR. JOFFE: Okay. Thanks, everyone. Why don't we go to the next question, three, and actually we're going to lump three and four together because

they're related, and this gets to the sticky issue of recall periods and what should be the appropriate recall period in a clinical trial for satisfying sexual events, sexual desire, sexual arousal, distress, and any of the other endpoints that came up in the first question.

And then question four, which is related, asks whether the recall period should be the same for all these efficacy endpoints or if they should differ depending on the efficacy endpoint.

And maybe one other nuance to throw in here, yesterday at the patient workshop, we heard from some women how they feel their symptoms are very constant from day-to-day, others seem to say there was more of a fluctuation in symptoms and trying to gauge whether that impacts what the recall period should be.

And basically, here we're trying to get a sense of what would be reasonable recall that would ensure patients can accurately recall their feelings of desire or arousal but also something that's not overly burdensome in a clinical trial that leads to burnout or other issues. So maybe Dr. Basson, we're

start with you on this one.

DR. BASSON: Thank you. I think recall is different for more than a week and yet a week is not going to be -- quite likely won't be representative. My suggestion would be that the participants would be required to, at the end of a week, make note, make -- provide a table of how their desire -- how the criterion, the desire was that past week and it should be done on a weekly basis and then, you know, I think the four weeks could be combined so you'd end up with a four-week recall but it would not be done at that one endpoint at four weeks. It will be done on a weekly basis to make it more accurate.

DR. JOFFE: Okay. Why don't we go ahead, Dr. Connell. We'll go from this side.

DR. CONNELL: I agree with Dr. Basson. I think, you know, the more accurate the better and I do think it's hard, especially if people are distressed about this or, you know, everyone's busy and they have busy lives. So I think a week is very reasonable in terms of asking patients to do that and in getting accurate data.

DR. DeROGATIS: First, let me answer the second question. The recall period should not be the same for all these variables. These are very different variables and the notion -- one of the important notions in clinical measurement is that you're measurement period be relevant for the phenomena you're assessing. And so, at least in my mind, and I don't know anyone else's, they're different enough that you wouldn't want the same recall period.

And then in terms of the specific recalls, I think that SSEs -- I think the shortest period I would do SSEs -- I know this, for the FDA, this is heresy but I would do it three days. That's the shortest. I wouldn't burden people with daily SSE. If you can't remember sexual events for the past three days, you've got another medical problem on your hands and it's not sexual.

(Laughter.)

DR. DeROGATIS: So then the longest period that I would do is seven. I've done trials way back when and we asked people to do seven days. There

didn't seem to be a lot of error or measurement. It's a week. You can kind of remember what went on this week. So I would do three and either -- shortest, three; longest, seven.

For desire and distress, I would do 28 days and I won't burden you with, again, all the details. There is just a ton of validation and reliability data showing that these instruments are sufficiently error free to be sensitive to drug effects over and over and over again, both the distress scale and more often -- more relevant -- I'm sorry -- the FFSI. So I would do 28 day measurement for these PROs anyway.

And an anecdote which I'll share with you which I think is relevant is I have had increasing interactions with physical therapy lately. I don't know why that is but it seems like I go to the dentist and the physical therapist. There's something, there's a signal there or something, my body is deteriorating at a rapid rate. And so when you go to physical therapy, with like a protractor-like device, they do range of motion for your joints and then they do applications to you and you scream and then at the

end of the session, they do measurement again. So there's a daily measurement at each physical therapy session. But then for the month, and this is not an elegant measurement and I've kept my mouth shut because I don't want to antagonize my therapist, they give you a 10-point scale and you rate, self-report your flexibility.

Okay. So the overarching construct, the PRO, as it were, is physical flexibility. And I think that works great. I mean, you know, you get the detailed measurement with the daily sessions and then you get the overall measurement with the PRO-type construct. And I don't -- you know, I couldn't tell you what my flexibility is on a daily basis but I say, oh, this month was pretty good. I'll give it a seven, something like that. So that's my thought on it and I won't bore you with tons validation data that I've got in a secret little stash down here.

DR. GASS: I think I would go with a weekly assessment. I think getting much more frequent than that just kind of rubs in it that they may not be very successful, so I'd go with a week.

DR. GELENBERG: I would do daily. I would do a very quick assessment in realtime on a Smartphone that would take less than a minute and would capture the ecological momentary assessment in realtime, you know, where the patient is and it can -- it gets around the problem of different women interpreting different monthly my worst day, my worst experience, best one averaged and so forth. That's the way most clinical trials of symptomatic variables are going.

DR. GOLDSTEIN: Yesterday when I listened to the patients talk, I was very impressed by what I see clinically because they're my patients and they're clinical, that this is really a persistent and insistent dysfunction, it's a state of being in the dysfunction. And I agree with Len from the perspective of desire and from the perspective of distress, a 28-day recall is absolutely important. When a woman comes into the office, I don't ask her "How was your desire yesterday?" I don't ask her how her desire was the day before. We talk about her desire over her period of time that she's complaining. It's a more constant construct. We do have day-to-day

and minute-to-minute fluctuations. Our sugar changes but our hemoglobin A1C is what we're actually more interested in.

I think it's demeaning to women to ask them to measure desire differently than we ask men to measure their LUTS measurements and their overactive bladder measurements and their erectile dysfunction measurements which are 28-day recalls. However, the satisfying sexual event, which I think shouldn't be a primary, it should be a secondary, may be asked more frequently but I really feel strongly based on what happened yesterday.

And I think what the FDA is missing, if I may, that they believe they're in the state of dysfunction, it's not change, if they get a treatment like a pellet which lasts for a period of time and falls, that's where you're getting the fluctuation. If the treatment was constant, they would be able to assess their function over that 28-day recall.

DR. GUESS: So I agree with the Smartphone concept. I think to understand things like minimally important difference and more -- the value of numbers,

we need to know absolute events, so I'd say daily they can upload into a phone just whether or not they had this and how many times they had it on that given day. But then perhaps a monthly sort of qualitative assessment of has it improved, has it stayed the same, has it gotten worse so that you can get their perception of their symptoms but also have a quantitative understanding of what's going on.

DR. HEIMAN: For satisfying sexual events, again, presuming that will be a secondary endpoint, usually events are at the event and therefore I'd do it as often as those events happen and Smartphone or some other easy method that's very short to respond. It tends to work well in other kinds of studies that are reporting on personal behaviors. And so that's the nature of that reporting mechanism. Whereas sexual desire, sexual arousal, and distress, I completely agree monthly would be the appropriate way to go and is the validated way to go.

DR. KINGSBERG: So I do think that they are different measures and different concepts and satisfying sexual events is okay to use on a shorter

recall hoping that they are now secondary and not primary and it's okay within about three days, I agree with Len, that women can remember and it's not particularly satisfying if they can't remember within three days, and it allows for it to be less burdensome to the patient to have to pull out her Smartphone at the end of every sexual event. That loses some of its impact.

In terms of desire though, two things. One is to have a measurement that's shorter and then a 28-day recall I think allows for a nice correlation. So instead of having every measure be the same time, I think it's useful to have the two together, a shorter recall and a longer.

In terms of understanding desire, I think it's important to recognize that desire really is a state and the best way for women to understand it is like gestalt, and it is almost sort of like hunger versus appetite. Women understand desire as their overall appetite and to ask them to report on their appetite on a daily basis is like zooming in -- let me give you two mixed messages -- but it's like asking a

woman about her hunger on a daily basis. Appetite is their understanding and they get it what their overall appetite is and their hunger might be different based on different things happening in their monthly life. So I think it's an inappropriate measure to ask them to report every day.

Similarly, I think it's burdensome. It's like zooming in a microscope too close. It distorts the experience and women, asking them do you have desire, do you have desire today, we've seen that a daily measure of that does not work well. Women don't relate to that and it's better to have a 28-day recall as the state of desire being appetite.

DR. MESTON: I would agree with that. If I had to measure satisfying sexual events, I would do it on a weekly basis. We heard from a woman yesterday who said if she had a sexually satisfying event in the past month, that she would definitely remember it. So I certainly think a week is a good recall. I think daily or event wise you run the risk of, like a different patient said yesterday, that it just gets depressing to be recording this every day.

For desire, arousal, and distress, I would use the 28 days. There's been a ton of validation studies, as Dr. DeRogatis pointed out, that point that this is an effective recall period.

DR. MIRKIN: So in drug development, we use PRO tools to measure subjective efficacy endpoints and these tools should be fully validated before we start doing an experiment in a phase two or phase three clinical setting. So the validation of the tool includes a recall period and the physical instrument. So we have a tool in which the validation is for 28 days, then the tool can now be used with a recall of a week. So I want to, you know, some concerns about trying to change the current tools and trying to change the recall period.

Another point of that is a tool validated using paper diaries or paper instrument may not be the same when we use an electronic device so I want also to raise some concern about that.

In terms of how frequently this needs to be measured, what is the right recall period, I don't know. But I want to challenge the concept that more

frequent is more accurate and I think that someone here had already one example about that. So I don't have (inaudible) to that but I don't want anybody to believe that if you ask every single day that that will be more precise than if you ask only weekly or on a monthly basis.

DR. SEGRAVES: I think I'm in agreement pretty much with what's been said. Obviously, for a satisfying sexual event, you would want to have a time period close to that event, presumably that's happening infrequently in this population. The other thing, I actually want less patient burden in reporting so like weekly, monthly or, you know, the least possible to get accurate data.

DR. WIERMAN: I would agree. I think that the information that people got when studying hot flashes if you -- you do a huge selection bias for people staying in studies if you go too frequent monitoring because it's a full-time job to be in the study and you really select then for a very disparate edge of your patient population, so I like the weekly and monthly and using the data you already have.

DR. JOFFE: So let me just follow this up with a question. Suppose you're on a treatment that improves your desire, I can understand maybe if someone can make an argument if someone's not anything, they're nice and stable, they have their state of mind or have a sense over the past month where they've been, but say in that past month or whenever you started a treatment and now things are changing because you're on that treatment, would having a 28-day recall be able to pick that up reliably?

I see some people shaking heads. One person, maybe not. Maybe if folks could expand on that angle? We don't have to do everybody. We could just take if anybody has any comments on that. Okay, Dr. Goldstein.

DR. GOLDSTEIN: I based it on clinical experience and clinical trial development involvement, the 28-day recall will pick up the change in desire if that's the metric, and it'll change -- it'll pick up the distress if that's the metric. They're very sensitive to changes, those two.

The satisfying sexual event, I think, has to be at a shorter interval and you can record that. But that shouldn't be your primary endpoint measurement because it's not desire that you're picking up. Did I say that or not? Yes.

DR. JOFFE: Let's hear few more (inaudible) here I think.

DR. GASS: Most of the patients I see with low desire can tell you exactly when they last had intercourse. It might have been three or six months ago. They don't need to be asked every three days. If you remember the Proctor and Gamble studies with the testosterone patch, there was one more Satisfying event per month and I'm sure they remember that event very clearly. So that was my rationale for recommending less frequent, at least a week apart.

UNIDENTIFIED MALE: (Inaudible).

DR. JOFFE: Anyone else?

DR. HEIMAN: Just a comment on events. So event is usually like within 24 hours you record it. It's not going to be every day so that's really what I was thinking in thinking of doing frequent sampling of

events.

DR. GASS: So you were saying something like you have the phone there and you just want them to record as it happens; is that what you were saying?

DR. HEIMAN: Well, not while it's happening but --

(Laughter.)

DR. HEIMAN: -- although that could be another study, but within 24 hours, they report on that event, not…

DR. GOLDSTEIN: But just to be clear from the panel, most people, I think, are in agreement that the constructive desire and distress, even on treatment, does not need to be recalled weekly, daily, hourly, minutely but by the month.

UNIDENTIFIED FEMALE: Yes.

DR. GOLDSTEIN: Okay, that's the consensus here unless you have a different point.

DR. GUESS: No, but I think her concept -- the capturing each event --

DR. GOLDSTEIN: The event.

DR. GUESS: -- is still important.

DR. GOLDSTEIN: Yeah, okay, so we separate those two.

DR. JOFFE: Any other comments on this? Okay.

DR. MIRKIN: (Inaudible) my position is the tool needs to be used as it was developed, right. We are discussing here a tool in which the recall period is four weeks and that's the way to do it.

DR. GOLDSTEIN: Yes, for FFSI, the recall is that but for distress, there is no recall period built in unless I'm incorrect.

UNIDENTIFIED FEMALE: Yes, there is.

DR. GOLDSTEIN: There is? It's over the month. Okay.

DR. JOFFE: Right, so --

DR. GOLDSTEIN: So then it's designed to --

DR. MIRKIN: -- usually a month.

DR. GOLDSTEIN: Okay, thank you.

DR. JOFFE: Yes.

DR. SEGRAVES: I agree. I think it's highly unlikely we have a clinically significant effect that we're going to miss it only getting monthly data. I

mean if it's a trivial thing, maybe it'll -- we wouldn't pick it up. It's clinically significant, we'll pick it up in monthly reports.

DR. CONNELL: But I think in going back to what Marsha said, there's a difference in how sometimes people interpret what's going on and actually what's going. And at the end of the day, you might just use satisfaction scores and if it's helping people's lives, then that's going to be a drug they still use. But if they've only had one event versus 10 events, it gives you a sense of physiologically is it doing something where they feel desire, you know, twice a week versus only once in the month and they're really happy.

DR. KINGSBERG: I'm going to argue again that desire is a state and that it's best understood over a greater period of time. And it's not just 28 days ago. It's day 27, day 26, day 25 until you get all the way down to 1, and it gives a fuller perspective which has less variability of what might be going on in the week. And if these are, for example, premenopausal women, they have their period

for a week or maybe their partner's out of town or something. A month is a much better time period and once again, it is what the FFSI is validated on.

DR. CONNELL: That I understand but if we don't fully understand the physiology and what -- is this drug going to help arousal, is it going to help desire, if you have recorded events, they may say their desire is better and that's fine and then you can still give it for that indication, like symptoms like Dr. Goldstein was saying. But physiologically, it could be affecting their arousal and not necessarily their desire but then, you know -- so I think it's a feedback loop. So I think its two different things. I understand what you're saying, that it's been validated but if we really don't know, we're still shot gunning if we don't understand what physiologically is happening.

DR. KINGSBERG: But you have the measure of the satisfying sexual events which is a shorter recall period and so now you've got both together.

DR. GUESS: But if you group it as events versus did you have desire on this day and arousal on

this day, we don't know the answer. We don't know if they correlate so why not capture the information just to figure out if it does correlate but use their overall, you know, assessment of how -- whether or not they've improved over that 28 days as your outcome?

DR. KINGSBERG: Because I think that it distorts the data to ask women to report on their desire on a daily basis. That is not how the women yesterday described it. It is more of a state and it distorts that data to ask them to report on a daily basis. Maybe arousal if they're paying attention to, asking them some objective measure but for desire, it is not a useful measurement and it is a burden and it distorts.

DR. GUESS: I'm sorry, I didn't mean on a daily basis, more like the events capturing, like capturing desire. When they have, they click a button, "I had desire today."

DR. CONNELL: Right, because there are going to b some subgroups of women. We still don't know the physiology so there's going to be different people with different pathophysiologies with the same

symptoms, like what Dr. Goldstein -- we treat the symptoms so if you have one something -- something a wrong with you and something b but you both have decreased arousal or decreased desire, we don't understand who's who and what this drug -- so the drug may affect some people in one way and, unfortunately, another group are not -- and even if the drug only works for 10 percent, then we know that's the indication for this 10 percent and we have to go back to the drawing board for the 90 other percent that it did not work for. I mean we're talking about as if we're assuming it's going to work. We don't even know if it's going to work, and I think that's important data, to know who it does work for or doesn't work.

DR. KINGSBERG: So remember you are basic scientists. Feel free to do that basic science research to get to the pathophysiology. This is a drug development clinical trial you're talking about and what we're looking at is treatment effect. And the best treatment effect for desire that gets picked up clinically will be on a monthly basis of desire. You can do the other research but I think that's an

unreasonable burden for a clinical trial to also try to pick up the etiology. We don't do that in other drug trials…

DR. CONNELL: Well, it was also very unreasonable for people to put transvaginal mesh on the market and here we are today, that's about 30 percent of my business. So we do have to look at these things while we're in realtime because if there is secondary downstream like side effects that happen, we need to know who it's going to be good for and who it's not going to be good for. So I'm thinking prospectively as opposed to retrospectively 10 years from now.

(Applause.)

DR. KINGSBERG: So you're saying that measuring the vaginal mesh every day would have given you a different effect than measuring it on a monthly basis. I think you're looking at two different things. That's a safety issue and we have -- you know, there are certain other things we look at for safety.

DR. CONNELL: Right, but isn't that what

we're here for today? We're here to make sure every -- we all want a drug for women. I'm not barring women against drugs. I mean I think we need it here and now and today, but we also have to make sure it's safe.

DR. JOFFE: In the interest of time, I think I saw Dr. DeRogatis, Dr. Goldstein and then Dr. Basson. And then after that, Ashley, I'm going to look at you and see if there is anything you want to ask the panel about recall periods because I know this has been a contentious issue, so if there's anything you want to hear about that or there's something that wasn't clear, feel free to come to the mic after that. So --

DR. DeROGATIS: I just wanted to say, as I listened to the back and forth there, it seems to me that there are at least two things being addressed here. Randomized clinical trial and the normal phasing of one, two, three, at least up to three, is a vehicle to establish certain kinds of results. So you're trying to establish safety first of all in a global sense. You're trying to establish efficacy.

You're trying to establish clinical significance. You're not doing a trivial change even though it's statistically significant.

And what, if I hear you right, you're describing is -- I mean these are studies that have to have a hypothesis. The notion that we don't understand the pathophysiology of some of these conditions, if we stop to do that, you know we'd back in the 8th century with -- I mean we treat lots of conditions for which we don't know the pathophysiology.

Now what I would like to suggest, just my thought, is if you have a hypothesis or hypotheses about there's a differential pathophysiology between this group and that group, then test it out in a phase four or some subsequent trial where you're taking -- you're designing a trial explicitly to focus on that issue. You're not asking -- you know, it's like not asking an 18-wheel truck to deliver bakery products to mom and pop stores. I mean, you know, controlled clinical trial is a big, you know, systematic device to answer certain questions. What you're saying --

your questions are, I think, extremely valid. I just think a different vehicle might be the better way to address it. I don't know.

DR. CONNELL: But we're talking about human lives here. I mean it's not -- if we're not going to spend the time and do the basic science in laboratories and we are going to give this to women who are sexually active and some are of reproductive age, and nobody's talking about birth control here, so we do have to be careful. I think we do need to get as much -- I mean we only have one shot here and it's kind of frustrating because a lot of times in women's health, things are just sort of thrown out there. And then like, "Oh, we should have thought of that."

So why not be as careful as we can while still going forward. I'm not saying don't do these trials but just collect as much data as you can. And I understand the validation point but I'm saying if we don't know -- like here we are, we're still -- the diagnosis -- like people can't even decide on what the diagnosis is and are they one process, are they two. It's still a lot of checking.

DR. DeROGATIS: They're different questions and the fact that you seem to be implying that if you collect it more often, it's more detailed and more sensitive and better; that seemed to be the implication. But in fact, it could be worse because if you're taking measurements of desire, a day is an artificial period to ask someone about her desire. And so you may be getting -- and I would think there's evidence, good evidence that you will be getting increased error of measurement by virtue of your methodology. And then when you look at that, you're apt to get a different answer. So as I've argued with many of you in this room over and over again, daily measurement has its virtues but it's not above and beyond all other forms of measurement.

DR. CONNELL: But I think just going back, I think we're talking about things like daily versus events, like how many times did they have desire where they initiated --

DR. JOFFE: In the interest of time, both points are noted. Over there, Dr. Goldstein, is there anything -- you got covered over there by -- okay.

How about Dr. Basson on the phone?

DR. BASSON: Thank you. Yes, just listening. Also to the bad controls, the 28-day recall of desire as the only measure of desire won't capture desire triggered along with arousal during an event or perhaps even during exposure to sexual environment and there was no activity or event, in quotes. So I think something over and beyond the 28-day measure of desire is needed. Then it would be addressing the criterion five and the DSM-5 definition. And so it could be perhaps hooked into this question of a satisfying event, what is meant by satisfying. Does it -- is -- was it to do with more arousal and desire or was it something quite different, you know, more to do with mutuality or feeling lost in the experience of whatever. So I think that could be captured in that way.

But definitely to agree with those who have said, we need something over and beyond the 28-day recall of the appetite, to keep that for sure but we need something else as well perhaps tied into the degree of satisfaction to qualify that in more detail

with events. And I'm not quite sure what to do with being exposed to a sexual environment but not having an event because I think that's important as well but maybe that's perhaps too complicated. Thank you.

DR. JOFFE: Thank you. Ashley, anything you wanted to ask?

DR. SLAGLE: So I appreciate all the comments about recall period. And so the question that I'm going to ask, I don't' want it to imply that I'm not taking in what everyone's saying. I just have a question about the FFSI, the way the desire question is worded, it asks about how often you feel desire. So the question itself implies that desire is not a steady state but that it sort of changes over the month. And so I'm curious how, if we're asking women to report over the month, it's a steady state when the very question itself is implying that it's changing over the month because the recall options are how often do you feel sexual desire: almost, always, most times, sometimes, a few times, so it's just -- maybe this is too detailed for this discussion but I think it plays into the recall question. It's just an

outstanding question that I have that -- if someone could…

DR. KINGSBERG: I think it gets to the fact that an over -- women will respond over the month "how often do you feel desire". To ask them every day gives you too granular an approach. That does not give you an accurate sense of their overall desire. That wording allows for a gestalt of "how often do you feel desire over the last month" and that will give you a much more accurate sense of their desire.

DR. JOFFE: Any other -- Dr. Goldstein.

DR. GOLDSTEIN: Just to -- Ashley, just the point -- it's not often in the construct of one, two, three, four. It's how often you are feeling it and you have the never, always, or -- so I think what -- I support what Sheryl said.

DR. GASS: I'm just wondering, in order to get away from this episodic approach, if it has been considered to use more of a Likert scale and say where do you rank your level of desire on a 1 to 10 and then as she repeats that on and on, you can see whether she moves her own point.

DR. KINGSBERG: I think we have a validated measure already. I don't think we need to create a new one.

DR. GASS: Okay. But you're talking about the categorizing how often she had desire.

DR. KINGSBERG: I think women -- the -- you know, there are other people here who have actually developed the scale that might want to jump in, but I think it's well-validated and women respond pretty accurately.

DR. JOFFE: Let's, in the interest of time, move to the last question and then we'll open up the mic on the floor. And this is for drugs that are intended for use on an as-needed basis. Now yesterday we heard from some of the women that they didn't really understand why they would use a drug like this as opposed to something that's taken chronically.

So -- but there may be companies out there who are interested in something like this, developing something on an as-needed basis and how does that impact the decision on the recall, if at all. If you're having a drug that you might take that day of

the event of shortly before the event that might boost your desire or distress over the next couple of hours and would the same type of recall periods make sense? So maybe we'll start with Dr. Wierman this time and we'll work our way through.

DR. WHITAKER: I guess the problem is you don't have an outcome measure that's been validated for this kind of an acute response of desire to intervention, so you don't have a tool that's been developed yet to have validity in that kind of an issue. So I think you have use the same outcome and hope that three times a month will give you the same overall gestalt as something that you took every day because you don't have that outcome measure yet.

DR. SEGRAVES: I guess I would vote for daily and I would note that in premature ejaculation studies in Europe, they use stop watches daily to measure the effect on ejaculatory latency. So why should it be any different for women?

DR. MIRKIN: I'm going to go basic overall development, right. We don't have the tool yet so it's kind of, you know, esoteric to start talking

about recall periods in this type of condition. But now if the tool has been evaluated to use on a daily basis, I will agree on that. If then on a weekly basis, I will agree on that.

Dr. Emami I agree. We don't have a tool so it's kind of hard to debate. I agree with what you said.

DR. KINGSBERG: Well, this is an interesting concept because an on as-needed basis, depending if the goal is to improve desire and the drug is intermittent, it still can give you a gestalt of overall desire even through in the episode, again, difference between hunger and appetite, there is also a feedback loop so that if you improve hunger in that event, can it then create an experience of satisfaction that then spreads like a ripple -- I'm mixing my metaphors -- throughout the month. So I still think that you would have the event-based recall for the satisfying sexual event that you take the medication and you also still use the validated tool for overall desire to see if that impacted desire.

DR. HEIMAN: I agree that that makes the

most sense.

DR. GUESS: I semi-agree with the caveat that I think that the episodic event should be more clarified as to desire and arousal and not just satisfying event, and that way you can look back and see if that treatment affected desire, arousal or both.

DR. GOLDSTEIN: I've had experience in clinical trial development with chronic daily use and with prn use of drugs for HSDD and for arousal. And we have found the same sensitivity of the measurements for the prn as for the chronic dosing for the desire, arousal and distress, and I would use some closer event for the satisfying sexual event. So in summary, I don't within there's a difference, actually, between the prn or the chronic use for the already sensitive, already validated measure of desire or arousal, depending on the outcome that you're searching and the stress. And the satisfying sexual event, I would take either at the time or some relatively near time.

DR. GELENBERG: If you have a robust treatment effect, it's not going to matter. It will

shine through daily or monthly or in virtually any instrument. We're looking for more subtle effects and I would still favor some instruments that capture the integrated month report for some domains and the daily Smartphone less than 60-second capture of what's going on within the course of the month for both the prn or the daily use.

DR. GASS: I can see it argued either way in this case.

DR. DeROGATIS: It turns out that both the FSFI and the FSTS have been validated for shorter periods and both of them have crossover studies, 28 day versus 7-day and then crossing back over, and both of them show equivalents, the 7-day and 28-day measurement of the constructs they represent. So we do have some experience with shorter intervals, periods and my preference would be to do both. I mean rather than say well, we're going to do it this way or we're going to do it that way, do monthly and do weekly. I mean -- and they're already validated for these periods. Find out if there's a difference. We're already seen that they're highly correlated in

certain studies and so that's how I would approach it.

DR. CONNELL: That sounds like a reasonable approach to me.

DR. JOFFE: Dr. Basson, anything from you?

DR. BASSON: No, I don't think that I have anymore to add. Thank you.

DR. JOFFE: Okay. I think we're at two o'clock. We're right on time. Good. Why don't we open the floor to questions and folks come up to the microphone if you have questions either for the first panel discussion or the second one. Please introduce yourself, if you have any potential conflicts of interest. And these are questions to the panel. FDA is in listening mode today and please focus them specifically on the female sexual dysfunction because we're trying to not get derailed here.

DR. PORTMAN: David Portman, Columbus Ohio. I'm the Director of the Columbus Center for Women's Health Research, a private gynecologist and doing clinical research in this area for close to 18 years so I do have a host of relationships with companies. In this space, I would include Trimel, Sprout,

Palatin, as well as Shionogi and other companies for a vulva vaginal atrophy, Actavis, Pfizer, Endoceutics, so I don't have any one particular horse in this race.

My question is either Dr. Kingsberg or perhaps Dr. DeRogatis, anybody who can tell us a little bit about diary fatigue. Especially in this particular therapeutic area, it's been found that daily desire scores do not correlate very well at all, in fact. The placebo response with daily diary scores seems to contaminate the results so much that it seems as though that may not be the direction to go. The SSEs, obviously, can be captured in a shorter period of time, but can somebody elaborate on why they think maybe daily desire goes so wrong when we use it as a marker?

DR. DeROGATIS: The answer -- and this is just a guess because I don't know, but I'm perfectly willing to guess. I think daily desire score is like asking somebody to report daily liberalism score or daily conservativisms. I mean it's an alien time period for something like sexual desire. Sexual desire is one of those constructs, you know, that it's

a gestalt really. It's not something that's experienced on a momentary basis but rather it’s a gestalt, an accumulation of experience that says "wow, I really feel kind of horny (inaudible)" so that I think it imposes an artificial time constraint or recall period on a construct that just doesn't fit. That's m guess.

DR. KINGSBERG: And the fatigue component is that it reduced compliance, that women were annoyed by it and that has its own impact and it really is distorting the fact. Like I said, it's the microscope zooming in too close and that doesn’t give women an accurate perspective on what overall desire feels like.

DR. DeROGATIS: Also, I just wanted to add one criterion of a good measure is variance, and these daily diary day measures have much higher variance than equivalent measures of the same construct given in different time periods. So it suggests that there is a lot of random error in the measure. And why? Because I think it's artificially imposed.

DR. MESTON: If I could just add based on

some of the patient comments yesterday, I think recording daily you run the risk of negatively impacting mood which is going to have a negative impact on desire.

DR. JOFFE: Other questions?

MS. GREENBERG: Well, I hope I heard you correctly in saying we're also talking about some of the issues that were raised this morning during the FDA discussion. I'm glad FDA is in listening mode, but I didn't really feel like what I was hearing from FDA folks this morning was listening mode because there was a lot of really impassioned discussions from patients yesterday. And I just felt like there was no kind of connection with the patient perspective and I found that somewhat distressing, since we're talking about distress.

So -- yeah, I'm Sally Greenberg -- apologize -- Sally Greenberg. I'm with the National Consumers League and nobody paid me to be here.

The -- some of the discussions that patients talked about yesterday, Barbara and her daughter Vicky (ph) talked about the fact that they have no libido,

that they're distressed about it, that they have loving relationships and that they're not depressed and that this is a real condition. And I feel like we got to listen to that and we got to listen to the clinicians who have come forward who treat patients all the time and are here because they care about these patients and feel like the FDA sometimes isn't listening.

I wanted to pick up on one point and that is the issue that was raised about the safety question. Is it a vaginal mesh that you raised? I think it would be interesting for the -- since we weren't really talking about safety but all of a sudden this curveball came in, safety's obviously very important to those of us who advocate on behalf of patients, critically important.

And since we had this issue raised in this discussion, I think it would be helpful for those clinicians and others who have studied some of the drugs in the pipeline to talk a little about that, because the last thing we want is to introduce a drug into the marketplace that has, you know, serious

safety concerns but one of our panelists raised that issue and it really, you know, wasn't part of the specific question. So let's get it out there and maybe panelists can talk about the safety question. I think it's critical for all of us who advocate on behalf of patients.

DR. JOFFE: All right. I would like to start off by saying we are listening at FDA. We're still processing what we heard yesterday. We are waiting for transcripts. We want to go back and read that. What you're hearing today is our thinking leading up to this two-day workshop based on advice we've given. And what we find challenging is dealing with a company one-on-one or one expert one-on-one and so we really wanted to bring everyone here and as a group hear perspectives and give experts in the room the opportunity to question each other and bring up viewpoints on things.

With regard to safety, we could have folks comment if you'd like. You know, all drugs have a standard approach towards evaluating safety. There's a battery of non-clinical animal studies that have to

be done, chemistry findings to find impurities, clinical pharmacology issues to see if there's interactions with other drugs and the drug you're taking that may raise levels to an unsafe range or other interactions with comorbid conditions. And then there are standard safety assessments in all these clinical trials. And then depending on the pharmacology of the drug, the members in the class, there are what we call adverse events of interest which may be specific safety things that we're looking at because of the known pharmacologic activity of the drug or it's centrally acting and there might be other issues to be raised.

So we have a standard framework for working through safety. The important thing is to make sure that trials are designed up front to pick up these things because if you're not looking properly, you won't see it, making sure you have enough patients in your program to be able to detect what you're trying to detect, and then there is this issue of not possibly knowing everything about a drug at the time of approval. The time of approval, we have to decide

that the benefit of the drug outweighs the risks. But you can't know everything about a drug that's been tested in whatever, a few thousand patients that then goes and gets used in a broad -- much more patients and side effects you didn't see in these trials may pop up as well. So they're complex issues.

FDA is working on benefit-risk, some of you may know, with PDUFA V. That's one of the things we're doing. It's not specific to this drug. It's in general how we approach benefit-risk, putting the context of the diseased in perspective, trying to figure out whether the efficacies, not just the statistical improvement but really something that's clinically meaningful to patients and then balancing that with risk. Yes, Dr. Kingsberg.

DR. KINGSBERG: Well, I think that it's an important question because, to channel Dr. Goldstein, if you look at how some of the male drugs have gotten approved in the past six months for Viagra with I don't know how many patients but, for example, in one of the drugs looking for approval, Flibanserin, that's been studied in 11,000 women. So to try to look at

this as a safety issue of recall period, I think really threw this in the wrong direction. I think that this is more of a risk-benefit with maybe the misperception that female sexual desire or hypoactive sexual desire disorder is not worth any risk. And I happen to think that that's part of the problem, that there has been such a disconnect, which is why yesterday was so important, with the impact of HSDD on women's lives and the fact that it is a true medical unmet need. Maybe that message is now getting clear so that risk-benefit allows for minimal side effects or modest side effects, no serious adverse events to allow for drug development and drug approval.

(Applause.)

DR. GOLDSTEIN: So in the space that I work in, the sexual medicine world, there was a drug recently approved that you actually inject an enzyme into the wall of the tissue of the penis with one of the risks being that if you make that wall too thin, the penis will fracture and there's recognized operative requirements for that. Yet in that period that that drug was assessed, it was approved for male

sexual dysfunction indications.

So I just wanted to point out that as you bring out in general the drugs that we've studied for women including the Flibanserin and the Bremelanotide, Librido and Libridos and the Femprox, they tend to be very safe. At least we have in 11,000 people, which is probably five or six times more than the Viagra people, we haven't had any serious adverse events. So it's interesting that in one gender, we can have fracture and surgery yet it's getting approved and the other one, we still are waiting for the unmet need to be filled.

DR. JOFFE: And again, we're not using this as a format to pick on specific drugs or anything like this, so I really don't want to get derailed into that. I know it's come up a few times already today and yesterday and the past. So other questions?

MS. PEARSON: Yes, thank you. I'm Cindy Pearson from National Women's Health Network based here in Washington, DC. We don't take any kind of financial contribution from industry or anyone involved in health insurance or any medical treatment.

So my question is about -- to the panel, listening to your discussion of the endpoints, there was definitely a variety of opinions but I would say as I listened, the most common opinion expressed was to drop satisfying sexual events out of its current stature as a primary endpoint. And as a feminist and as someone who is respectful of women's ability to accurately describe their own experiences, I really get that using women's description of my desire used to be bad, now it's better; my arousal used to be bad, now it's better and believing that and not needed numerical counts of something that happens, that's a respectful position for the FDA and the medical industry to be in. So that's interesting but it's also interesting to me, and I'd really love to hear your opinions on if the FDA were to take your advice and to issue revised guidelines that took satisfying sexual events and moved it down to secondary endpoint -- maybe some of you thought reduced distress should be a co-primary endpoint but that the main primary endpoint is either more arousal or more desire -- I'm just curious, do you all think that

sponsors will be better served in getting a really bang, knockout big success and women will then be better served with a drug that passes through the FDA approval process with flying colors and resounding votes for approval if the sponsors narrow in on either one or the other, desire or arousal?

The earlier discussion, as you pointed out, some of you, left room for a lot of heterogeneity in the potential enrollment criteria for a clinical trial because the definition that would then eventually be used for reimbursement, for a code that approved reimbursement for the product is broad.

So it's just really, you know, a curiosity question of if you think a woman's report of change in her arousal or desire could be a standalone endpoint? Do you think companies would be doing themselves and women a favor if they sort of narrowed in on and made their clinical trials just the one or the other?

DR. GOLDSTEIN: I'll try and answer. Oh, you go first, please.

DR. GUESS: I guess my only comment is that again, we don't really know why they're working. So

if we're going to spend that money even collecting as a secondary aim and obtaining that information so if it doesn't work, if I throw it back at you, so we show that it doesn't work, are we throwing something off the market that could have been on the market for the other outcome because it actually did improve that other outcome. And if we're going to invest all this money and time into that trial, shouldn't we at least try to capture some of that information would be my question.

MS. PEARSON: But then, as you pointed out, power becomes the issue because you would need to power it well enough to know.

DR. GUESS: Right, but --

DR. GOLDSTEIN: The only thing I would add to that is I wouldn't do arousal or desire alone as a primary. I'd -- you would have to show that it lowered distress significantly and meaningfully.

MS. PEARSON: Right.

DR. GOLDSTEIN: So I would put those two as your co-primaries. Those make logical sense. They're part of the definitions. The measurements we have a

very sensitive for those and, to me, that would serve everybody.

MS. PEARSON: But what about the enrollment?

DR. GOLDSTEIN: Well, the enrollment will be based on meeting the indication of HSDD and/or arousal and that would be based on their symptoms.

DR. MESTON: Well, I'll just add to that. In terms of primary endpoints, Dr. DeRogatis provided a number of validated questionnaires and one of those is the FSFI. For the purpose of full disclosure, I was a co-author on that instrument but I think I can be objective in saying that with the FSFI, there are six different domains and they include desire and subjective arousal, and lubrication, and orgasm, pain, satisfaction. And what we find, there have been now 200 validation studies using that instrument and over 500 publications, and it's been validated both in women with female sexual arousal disorder and a separate validation in women with hypoactive sexual desire disorder and every type of validity, and reliability has been tested over and over again.

And so getting to your question, if that

were used as a primary endpoint, we find that the full scale measure has predictive validity in showing treatment outcomes, success. It shows discriminative validity between women with and without an arousal disorder or a desire disorder. And then we also have a cutoff point for hypoactive sexual desire disorder and a clinical cutoff point for the full-scale score. So even if you use the full-scale score, you would be able to look subcomponents of desire and arousal that have been equally well-validated in and of themselves.

DR. DeROGATIS: I would just like to add that one of the risks in drug development, and it's a major risk although we don't hear a lot about it, is that you'll have a drug that's effective and not be able to demonstrate it. And so hundred, thousands of individuals, women in this case, will go untreated by that effective drug because your design isn't sufficiently powerful, to use a statistical term, to demonstrate it. And I don't speak for my colleagues but I will briefly -- and they can beat me up later -- one of the reasons that some of us are excited about changing the hierarchy of outcomes measures around,

perhaps so that we have -- let's just take desire as an example, as a primary -- and instead of satisfying sexual events as a second primary, we elevate distress to a second primary and make satisfying sexual events a key secondary. Well, all of these still get measured except in our opinions, at least in my opinion, the two most sensitive outcomes measures are the primaries, and so you stand a better chance, a significantly better chance of demonstrating efficacy if it's there. And if it's not there, you still stand a significantly better chance of demonstrating that it's not efficacious because you're doing the best measurement you can from fairly esoteric principles but nonetheless they're real.

And then there's the conceptual or logical aspect of it that satisfying sexual events are a course measure, they're counting; counting and measurements circles is not considered elegant. They are much more determined by the partner than the women often. How often I don't know. And they're not related to any of the diagnostic definitions, you know, as distress and lower desire are. So I think

what we're trying to do, or I'm trying to day anyway, is to get the best outcomes measurement possible to be able to demonstrate an effective compound if it's there. And that's my answer to your question.

MS. PEARSON: Thanks.

DR. CACCHIONI: Hi. Thea Cacchioni from the University of Warwick -- or sorry -- University of Victoria. I've moved. I've been studying the sexual pharmaceuticals and the industry around them for 15 years. And I guess similar question but maybe more back to basics. I noted that in the panel, on the whole, it seems as though most of you were in disagreement with Rosemary Basson's notion of this typically blurry line between desire and arousal, and you had problems with the interest/arousal disorder diagnosis. And a lot of you have come back to your clinical observations and your patient voices. And we heard from patients yesterday.

What I heard yesterday and what I've heard from you today is that patients know what desire is and yesterday many of these patients talked about desire but many of them talked about it as something

they want 24/7; you know, 7 days a week one woman said, on demand, and that seems quite out of step with research on norms of desire.

So I just wonder if you take your patients' sort of understandings of desire as objective and not mediated by kind of social norms, how you disentangle that.

DR. GOLDSTEIN: I'm not sure I'm going to address your question but thank you for the question. I think that in several clinical trials, an improvement in sexual function that was two or three episodes more or one or two episodes a month more was fabulously meaningful to the patient. So I don't know about the daily thing and I don't know about the social norm thing, but when a woman is missing this want to want and it's plaguing her because she wasn't like that, the switch turned off and she wants some semblance of it back, some semblance of it back is fabulously important to that woman. That's my experience.

DR. CACCHIONI: Right. And then there has been such a high placebo effect in every clinical

trial so far, so it says to me there is something socially happening that when you give a woman license to take sex seriously, to prioritize it in everyday life, to reflect on it, to be given kind of professional go ahead to make this, you know, an important thing, what is behind this placebo effect?

DR. GOLDSTEIN: I'll answer but I would love other people to answer. The measurement that the FDA required, the drug companies to measure was the insensitive satisfying sexual event measurement --

DR. CACCHIONI: Yeah.

DR. GOLDSTEIN: -- which we have dissed and have placed in, really, its correct position. It's too distal. So you're seeing placebo response when you're asked to measure desire daily, which was the original request by the FDA followed by SSE. We seem to have gotten rid of both of those and come back to the very sensitive measure for which the placebo responses aren't there. There is great discrimination. It's the most sensitive and, obviously, you know more about this than I do but --

DR. CACCHIONI: And that sensitive measure

is?

DR. GOLDSTEIN: -- the placebo responses were, in large part, based on the sort of sad measurements that we had to do.

DR. CACCHIONI: Sorry, what was that measurement that you were saying would not create the placebo? It is?

DR. GOLDSTEIN: The PROs, the monthly recall PROs. So there are many of them but the one that -- for which -- listen, I'm Editor in Chief of the Journal of Sex in Medicine.

DR. CACCHIONI: Yeah.

DR. GOLDSTEIN: Over the 11 years I've been there, we've had over 200 publications. It's actually translated into almost every language in the world now. It's used universally.

DR. CACCHIONI: Um-hmm.

DR. GOLDSTEIN: That is a robust measure, not SSE and not daily desire scores.

DR. MESTON: I think whatever measure we use, there is going to be a substantial placebo effect. And just answering how and why that placebo

effect occurs, I think the biggest explanation is taking a drug changes expectations and the expectation is that I'm going to feel better, I'm going to have my desire back. And along with that expectation, in some women, there will be behavioral change. In some women, it radically will change communication with a partner because all of a sudden, they have an external attribution. There wasn't something wrong with me, there was something minimal that got fixed and now I'm better and isn't this great and suddenly they're talking about sex again that they haven't talked about, you know, sometimes for years or they've avoided not just sexual intimacy but even holding hands. As some of the patients yesterday described, they didn't want to give cues of being interested in sex because they weren't interested in sex, so they'd stop holding hands and their partners stopped approaching them.

And so the placebo effect will occur regardless of what measure we're going to use, but -- and I think that's inevitable -- but we'll still be able to see a drug effect that's a real drug effect

beyond the expectation effect.

DR. CACCHIONI: Thank you. I'll give it over but I think that's my point, is that whatever's happening in the placebo effect, which you just described so well, I think does happen in other therapies of which there has been scores of peer-reviewed research also validating the efficacy of those therapies.

DR. HEIMAN: So don't go away because I think your question is a really good one.

DR. CACCHIONI: Okay.

DR. HEIMAN: And we can't answer it thoroughly up here but there are probably many components going into it. When, in the past, I've done just clinical outcome studies, not using drugs but using couple's sex therapy, and when people were on a waiting list control for three months, their sexuality increased, some of them significantly in both the male and the female. So there is also this, if you will, effort with people when they make an effort to solve a problem even when they're discouraged that also -- and an acting active role I

think is important.

DR. CACCHIONI: Yeah.

DR. HEIMAN: But other cultural things and expectations about women's sexuality, I don't want to dismiss that because it's just not something we've looked at it but it's probably all important to understand placebo effect. If we could bottle that placebo effect, that would be handy.

DR. CACCHIONI: Exactly. So I think there is something to be excited and optimistic about in that sense.

DR. KINGSBERG: But I think we also need to make the point that with that large placebo effect, if you still show a drug treatment above and beyond that placebo effect, that nice big placebo effect, then you have some data that you have an efficacious drug treatment. So we don't want to forget that and I think that was true in male Viagra or PD5 inhibitor trials, too. There was a significant, about a 25 percent, placebo effect.

DR. GOLDSTEIN: Thirty-three percent.

DR. KINGSBERG: Okay. So it's not just

women who respond to placebo and it's not just sexual dysfunction trials. These are common placebo responses.

DR. CACCHIONI: Yeah. And there's --

DR. JOFFE: Yeah. I think symptomatic conditions often have large placebo effects. We see it across many different conditions. Why don't we take one last question and then we'll go for a break.

DR. CLAYTON: So I'm Anita Clayton. I'm the David C. Wilson Professor and the Interim Chair of Psychiatry and Neurobehavioral Sciences and also a Professor of Clinical Obstetrics and Gynecology at the University of Virginia.

I could name a whole list of companies with whom I have research grants related to treatment of depression and specifically antidepressant-associated sexual dysfunction. But with regard to the subject today, I have research grants and consulting to Palatin, S1Biopharma, Sprout, and Trimel.

And I want to thank the FDA for sponsoring this meeting, the panelists for being here and providing their opinions.

I wanted to go back to this morning and I don't intend to give a lecture here so sorry if my questions are long -- or my comments, but I wanted to go to the issue of criterion c for the diagnoses which has been true for HSDD and FSAD. There has always been a criterion c that said if you have distressing low sexual desire, it can't be due to a psychiatric or medical condition and/or due to drugs causing this problem and that is carried over into the FIASD criteria as well.

But when you all were talking about the issues of severe relationship distress or other significant stressors and the issue of a co-morbid psychiatric condition like depression, it seemed as if you were not talking about the bidirectional effect of those two things. Atlantis and Sullivan have studied this and found that if you have depression, you have a 30 to 70 percent increased chance of having sexual dysfunction associated with it. But if you have sexual dysfunction, you have 170 to 210 percent chance -- risk of having depression. So it's a lot worse to have sexual dysfunction in that it's more

likely to cause depression than the other way around.

The conversation that was going on this morning and what Rosemary Basson appeared to be speaking to also is that women who have sexual dysfunction who have it for long enough and severely enough develop depression and that's who she's seeing in her clinic. But many of the women we heard yesterday, and certainly it's true in clinical practice and we've been able to exclude women with depression from these trials and not had a problem enrolling them, is that most of the women who have HSDD do not have comorbid depression.

This was also evaluated in a very large population-based study, the Preside study that was sponsored by Boehringer Ingelheim a long time ago, but it's a standard panel that's used for a lot of other clinical issues and they used screening tools for depression that used the PHQ, the having previously had a diagnosis of depression or having been taking an antidepressant at the time they completed the survey. And what was found was that of the 10 percent of women who had the first two criteria for HSDD, 40 percent o

them met one of those criteria for depression, either they currently had symptoms of depression, they were being treated for it, or they'd had it before and now were well.

Still, that means 60 percent of the people in this population-based survey had HSDD without any signs of depression whatsoever. And so I think in your discussion about criterion c, I think it's very important to look at the temporal relationship, should problems in relationships exist, should depression exist, which one came first.

What the women reported yesterday was that they had great relationships with their partner, they'd previously had great sexual relationships with their partner but what happened was they developed HSDD and as a result, they were worried about their relationship, they felt their relationship had suffered. That's not the same thing as being in a bad relationship and it makes you not want to have sex with your partner. And the same thing is true with depression. If you have depression, then you might have a diminished libido. I mean it is a symptom.

You have a decreased interest in everything when you have depression. But more often than not, if women have HSDD, they don't have depression.

And so I think -- I'd like to hear your comments about this, talking about this in this temporal relationship order as opposed to -- it almost sounded like it was a result, more of the discussion was as a result of having HSDD that people had bad relation -- you were talking about the severe relationship distress, etcetera. Those are to screen out and exclude people from meeting the criteria for HSDD, right Taylor -- of FSIAD?

DR. JOFFE: Any comments? We're going to kind of touch a little bit on this in the next panel session where we talk about coexisting conditions, generalizability, so I don't know, maybe what we could do if anybody has a comment or two, we could share it now. Otherwise, we can dive into that more in the next panel.

DR. SEGRAVES: There's an excellent old study of Raul Schiavi which I'm sure you know of where he took women presenting with a complaint of low

sexual dysfunction, a very mythological and sophisticated study, and he had absolutely no signs of depression at that time but they had a higher past incidence of depression. And he questioned whether there may be a genetic vulnerability both to depression and low desire and maybe we're talking about variations of the same thing which I think is a very, very interesting hypothesis. I don't know if that directly answers what you were asking. I don't think so.

DR. CLAYTON: I think there are other data. Murray's data suggests that there is a genetic (inaudible) published recently suggests -- also, they looked at two genetic factors and found that one of those factors was related to desire, arousal, lubrication, and orgasm. The other had absolutely no relationship to desire, so it separated desire from arousal, lubrication, and orgasmic function, and so that was also sort of predictive of genetic information. And then there's a lot more data looking at antidepressant associated sexual dysfunction which is a serotonergic-driven phenomena in most people

which is inhibitory in terms of sexual function, that the networks that go to the frontal areas, they appear to be similarly affected in women with HSDD in that they're negatively impacted upon as well. So you're talking about network systems that involve the same neurotransmitters, dopamine, norepinephrine and serotonin, that impact on sexual functioning as well as impacting on mood.

DR. JOFFE: Maybe we can pull into -- I think in our next panel discussion -- why don't we have a break, a 15-minute break because we're 5 minutes over already, come back 2:50. And then in one of our questions, we'll touch on this issue of how to handle depression and other comorbidities.

(Whereupon, off the record at 2:32 p.m., and back on the record at 2:44 p.m.

DR. JOFFE: We're on the home stretch. Okay. Let's go ahead and turn to our third set of panel topics. We've got about an hour or 55 minutes to spend on this and then some questions and open public comment period, closing remarks, and then we're done.

So question -- let's start with the first question in this set and we've heard a little bit about some of these instruments already. This first question I would like to hear a little bit more about what folks view as the strengths and weaknesses of instruments that have been used for key efficacy endpoints in trials that have tested, for example, low sexual desire, the FSFI which you've heard a little bit about already to assess both desire and arousal, and then also the female sexual distress scale revised, the FSDS-R to assist distress. I would like to hear what folks see as the strengths and weaknesses. And also, if you think there is another instrument that we should be using instead, so we're open to hearing about other instruments also.

And with that, why don't we start with Dr. Connell, please.

DR. CONNELL: I think both the FSFI and the FSDS-Revised are really excellent tools and I think there is no need for additional instruments because the FSFI is really good at teasing out, as Dr. Meston mentioned, both arousal and desire, and then you have

the bother scores with the distress scales.

DR. DeROGATIS: Well, obviously, I have a vested interest so I can't be unbiased in my evaluation. But be that as it may, I think they're good scales and are very effective and productive because they meet all the requirements that I outlined earlier in terms of the various reliabilities, forms of validity, overall construct validity. They've been validated repeatedly and particularly the FSFI but also the FSDS-R. There's just a lot of data, all of it communicating that this is a valid measure of the construct.

So could you develop better scales? Of course, you could. It's going to take you a while because these scales take a while to develop and then they take a lot longer to validate. Are there other constructs that could be useful? Yes, there are and I'm sure we will discover them along the way. But awful lot of data saying that these are effective, sensitive measures and besides, I developed one so I would recommend them.

DR. GASS: I would agree with what he has

said. To me, the only question is whether or not any additional measures are indicated and if we were interested in the patient-reported outcomes. We were talking at the end about whether -- earlier about whether meaningful improvement translated to the patient and so I think a question that would address that issue might be good as well.

DR. GELENBERG: I agree with the comments.

DR. GOLDSTEIN: I completely agree with the comments but I had a question at the -- or a comment at the end that Taylor stimulated my brain and then we went on break but I re-stimulated my brain. You mentioned the name Schiavi and fabulous researchers, Schiavi, Lief, Kaplan -- this is back in the 70's -- described HSDD. We're talking about a condition and an indication that's 37 years old now. We have described classification systems with Basson, classification system DSM, the AFUD classification system. They're just classification systems. This condition which we saw the patients and their bother and their unmet needs in treatment has been existing 37 years. I think it's time we have treatments and we

have fabulous scales. I mean we could -- as Dr. DeRogatis said, you could spend another 10 years making scales but that just means we're not going to have drugs for another 10 years. We have to end -- we have drugs for men. We need drugs for women. Thank you.

DR. GUESS: I think that these are more than acceptable scales and they really do the job in answering the questions.

DR. HEIMAN: I agree as well and I'm particularly pleased in reading some of the materials to hear about question 13 on the distress scale which is nice to know that one question carries a lot of weight. But that's not appropriate for this particular summary, so both scales are good.

DR. KINGSBERG: I agree. I think both scales are excellent and very useful.

DR. MESTON: I'll agree both scales are very well-validated and useful. I've already talked about some of the validation. I'll just add that the FSFI as well has been translated into at least 30 different languages. I know that that's different than

ethnicity but it does touch on the questions raised earlier this morning whether these scales have been validated in different cultures.

DR. MIRKIN: So I will agree with the rest of the panel. I think these two tools are solid, well-validated and they have enough sensitivity to be used in clinical trials. I think that we need to put some effort trying to tease out what is the minimal clinical meaningful effect or the minimal clinical significant treatment effect in a way to determine what we are seeing in our clinical trials is really clinically meaningful. And I don't know how much of experience the rest of the panel has on that concept.

DR. SEGRAVES: Both instruments are excellent. Both instruments are well-validated, been used extensively and are done by very skilled psychometricians.

DR. KWEDER: I have no other comments.

DR. JOFFE: Dr. Basson?

DR. BASSON: Thank you. Yes, no concerns from me on the FSDS-Revised. As, I'm sure, predictable, I do have troubles with the FSFI that

pose two questions mainly because I still am very, very uncertain that not having a sense of desire is necessarily pathological from the data that I already mentioned this morning and is in the reference list and having discussed -- we've just been speaking about Kaplan -- Dr. (Inaudible) was mentioning Helen Kaplan but she stated there was a sense of innate desire may be present but those are also responsive desire and not having a sense of innate desire particularly later in life, I cannot convince myself is pathological.

So I do have trouble with question one and two but I meant the problem with question one is just the wording "over the past four weeks, how often did you feel sexual desire, almost always." What does that mean, every waking moment? I never quite understood how that could possibly be that almost always would ever be checked off. Or did it mean actually do women actually interpret it as actual desire when I'm sexual or not? So I have a lesser severe worry about the wording but a much more severe worry that I really cannot convince myself that this is pathology. Thank you.

DR. MESTON: If I could just a comment. Question one and two are the two questions that comprise the desire composite and we've published showing that these two items discriminate between women with HSDD and controls. And as I mentioned earlier, the FSFI has been validated separately on a group of women with HSDD showing that it discriminates between healthy controls and HSDD and also between HSDD and FSAD. So I'm not concerned about the wording of those two questions.

DR. BASSON: May I respond again?

DR. JOFFE: Yes, go ahead.

DR. BASSON: Thanks. My concern is much deeper than that. I'm not sure that HSDD is the pathological entity based on fantasies, thought, desire and not allowing the possibility that despite these absences, there is some responsive desire. So I totally understand. So it's just FSFI will discriminate against HSDD and controls. My point is much more basic than that. I do not conclude from looking at the epidemiological studies of HSDD there's pathology. There's a difference but I there's a

spectrum of innate desire across women and that the one end where this is not a conscious state but it has to be triggered is pathology.

DR. KINGSBERG: Can I jump in? I have to say once again it's really a shame that you weren't here yesterday to hear the women talk about their experience of HSDD. And I think the FDA started these first two days acknowledging that this is an unmet medical need, and it is a true clinical condition, and it accepts the fact that some women have responsive desire. It isn't to say that you have to have the spontaneous drive, that you can have responsive desire and that would exclude you from the diagnosis but it doesn't mean that some of these women who were so compelling yesterday talking about the fact that even with all of those triggers did not have responsive desire and they were truly distressed and it impacted their life greatly. And I have to disagree that -- HSDD is truly an unmet medical need and deserves treatment.

DR. BASSON: But as you describe it, Dr. Kingsberg -- I wasn't able to watch yesterday because

of the time change -- but that -- those women who you're describing were saying nothing works, I can't trigger desire. I would agree with you that's, you know, a very -- potentially extremely distressing dysfunction but that's not what HSDD defines. There's no mention of having the responsive desire.

DR. GOLDSTEIN: It's painful to hear that HSDD is not pathology because I see this every day in my practice. But Ed Lowman did a fabulous study and took HSDD and measured metrics for quality of life: emotional satisfaction, happiness and another metric, and HSDD had very high ratings for significantly diminished quality of life. It is pathology.

DR. JOFFE: Okay. Let's go to question number two. This is interested in hearing the panelists' thoughts on whether there is any role for sex or couple's therapy, behavioral therapy as an adjunctive treatment to drug therapy. So should women -- say there's a drug approved, should women just be given this drug and use just by itself or should it be in combination with some kind of behavioral or sex therapy? Why don't we start on this end and work our

way around. I guess we started with you last time, Dr. Connell, so we don't do Dr. Wierman this time.

DR. WIERMAN: Well, I think that we've heard in many women with altered sexual function, either as a primary cause, there's associated depression, or a secondary cause, there's associated depression and/or relationship issues. So it's -- I think the issue in my mind is what are the data concerning, the effectiveness or sex or behavioral therapy alone or in combination with drug therapy. And I haven't heard data presented on that so we don't know.

DR. SEGRAVES: Yeah. My reading of the literature is the data supporting the efficacy of behavioral sex therapy for hypoactive sexual desire is pretty meager. And I think if you try to add that in a clinical trial, you're just going to add more error variance. It's going to confuse the finding of -- I agree there are certainly psychosocial issues but I don't think we have a proven method to address them.

DR. MIRKIN: Yeah, I agree with that and I wouldn't add it into a clinical trial because you're going to be biased in the results.

DR. MESTON: I think it's a very interesting question and an important question that we should study but not in a clinical trial. We first need to know if there is drug efficacy and then down the road look to see whether adding an adjunctive behavioral or cognitive therapy is going to enhance that or make it more sustainable.

DR. KINGSBERG: Yes. Actually, I think the question is not clear. If the question is "do you see a role for evaluating sex or behavior therapy as an adjunctive treatment to drug therapy in clinical trials to evaluate drug therapy," no, that would be like combining desire and arousal. It would be too confusing and you wouldn't get good data.

If you're asking "is there a role for sex or behavior therapy," I sure hope so or I'm out of a job. And just like with the drug therapy for depression, I certainly treat a lot of women and couple -- well, women with clinical depression and with wonderful drug therapies, there is still a role for me in cognitive behavior therapy and I do think that there will be a role for sex therapy.

I think one of the questions has been "should sex therapy be tried first" and I think good screeners make it fairly simple for even the average clinician to be able to tease out who would be a better candidate for a drug therapy and who would be a better candidate for psychotherapy or sex therapy, just like we looked at -- you know, if a woman comes in and says, you know, I am depressed and have a downstream effect on my sexual dysfunction, we would treat her depression. If there's a clear drive issue, then she would sort of be geared towards a drug therapy.

I think the DSDS, decreased sexual desire screener, for example, helps clarify what are the components that would help a clinician go to one versus the other.

But back to the first question, I don't think it's appropriate in a drug trial.

DR. HEIMAN: So it doesn’t' really fit in a drug trial but boy, this is something that I'd like to see developed. But from where will it be developed? it also costs money to develop a validated treatment,

especially a brief one for desire. And so it is meager indeed, as Dr. Segraves said, and that's how it could best work. So if we look to the depression example, one of the very cool things about depression treatment outcome is that, not for everybody, but typically what they found is that therapies, different kinds of therapies did as well in the long run as drug treatment. That isn't for every single patient but overall, that's good, and with similar although slightly different brain changes. So -- and then if you combine the two, the efficacy is greater and lasts longer.

So that would be a nice future but we're not there and to combine it with a drug trial, it wouldn't fit I'm afraid but I hope it's part of the future.

DR. GUESS: So agree with Dr. Meston's step right approach. Let's first get the drugs out of the starting gate and once we have determined what works, we can always go back and look adjuvant treatments.

DR. GOLDSTEIN: So in men, we have a drug out of the starting gate, many for erectile dysfunction, and we have studied that when you take a

PD5 inhibitor alone, you get a certain success rate and when you add sex and behavioral therapy to it, an agreed upon strategy, you actually improve the IIEF, the 30-day recall measure for men but I think it has to follow that pattern. You need a drug, get it approved, and then we can do this stuff for women.

DR. GELENBERG: We talked about the placebo effect earlier and as a patient, I really like the placebo effect. As an investigator, I really hate it and so people have mentioned, several of the panelists earlier, that it adds noise to your signal detection. If you add this as an adjunct for all patients, it'll make it harder to see a drug placebo difference.

On the other hand, I like the idea of a lead in which would rule out patients who are responsive to psychosocial treatment. It will add to the cost of the study because it would prolong it and take out some potential subjects. On the other hand, it could increase your signal detection ability because presumably, you'd be lowering your placebo response rate.

So as a clinician, I really like the idea of

patients having access to behavioral and sex therapies and I can see a role for the adjunct along with a medication, if one is found that's efficacious and safe. But I would consider, in terms of clinical trial design, a lead in model.

DR. GASS: I agree with the majority here. I do not think psychotherapy should be included in the clinical trial here with the FDA. And to my knowledge in testing antidepressants, I don't think that psychotherapy was included in the drug trials. Is that correct?

UNIDENTIFIED MALE: No.

DR. JOFFE: It's a different division. I'm not sure.

DR. GASS: So I think it should be a pure drug trial to see what the effects are there and certainly in clinical practice, it's good to have both options.

DR. DeROGATIS: I think it's a phase four issue where once the drug, as someone just said earlier, once the drug is established and approved, if you're attempting to find out what kind of an

increment of total therapeutic effect you can develop by adding some form of psychotherapy, behavior therapy, etcetera, then it's very interesting to do. It's complicated and expensive to do and when we did them years ago for depression and for anxiety disorders, what we found was that the combined treatment, no matter w hat it was, did better than either the drug or the psychotherapy alone and that's -- you know, which kind of makes because you have two treatments instead of only one. But we didn't find that one had a superior, you know, contribution to the other.

DR. CONNELL: I agree. I think it's a great idea but probably not for the initial study.

DR. JOFFE: Dr. Basson.

DR. BASSON: Yes. As a clinician, you know, ultimately I think clinicians would optimally choose to use both. However, I think just going back a step, leaving aside actually any formal sex therapy or CBT, couple therapy, actually just remembering that if there is a detailed assessment and especially if both partners are interviewed, that can be therapeutic;

whereas if it's, you know, like a screener questionnaire, although perhaps there's a mild element of therapeutic nature there, there's not just concerns are validated, someone's listening, someone's interested, but when there's a full assessment, I think probably most would agree that could be quite therapeutic, especially when there's some feedback of what's underlying the problem, what the formulation is.

So it might happen that there is an adjunctive treatment, even if it's not intended or was not the study of 1:56:12 and the patients are aware of the logic of their situation and the various factors that are involved etiologically.

DR. JOFFE: Okay, thank you. Let's go to question number three and this touches on Dr. Clayton's question from earlier today so maybe we can tackle that. It's kind of inter-related to what this question is about and this is interest on FDA's part of encouraging companies to include patients in their trials who are representative of the patient population who would use the drug once it's approved.

And if there are too many exclusions, comorbid conditions, coexisting medications that might interact with the drug product, you then wonder how generalizable the results are either for efficacy or safety when this product is used in a broader population.

So we heard about the definition kind of excluding these comorbid conditions and relationship distress due to other reasons, severe relationship distress.

So the question here is whether there is an basis or any reason or any thoughts on including some of these comorbid conditions in patients who are enrolled in the trials to see how they interact with the treatment or if that's going to make the trial too difficult to interpret. And maybe we can hit, you know, this issue of the chicken or the egg in terms of depression and relationship distress, whether that is what led reduced desire or whether someone had reduced desire and then we think developed depression because of that or relationship distress. So why don't we start with -- I think we're on this side now -- Dr.

Connell.

DR. CONNELL: Yeah. I think it is very hard because it can be chicken or the egg. I think if you can power it to include everybody, then that would make it generalizable. And I think you just have to really think about what are your indications going be. Is it going to be for patients with just sexual dysfunction and nothing else but you're probably only going to be treating a much smaller population than people who have hypertension and are on antihypertensive medication or who have diabetes and have neuropathy. So ideally, you'd like to include it and power it and control for those things, but if the budget is limited, then you start with a stricter inclusion criteria.

DR. DeROGATIS: My first response is to say no, don't include conditions like depression because it is an unregulated, uncontrolled source of variance that's going to have an impact on your outcome and it'll confound the outcome. But then when I start thinking with more of my brain as opposed to less, then I think well, wait a minute, why couldn't you

have an arm of the trial with HSDD plus depression, then have HSDD, then have placebo, just to pick three. So then you could then systematically possibly -- now, obviously, this is not a register. You don't want one of your pivotal trials to be doing this but you could certainly do a phase three trial and so you would demonstrate efficacy for the drug with the condition and then you might, if you're lucky, be able to generalize the condition to a broader -- and in the case of women and depression, we know that it's disproportionately prevalent in women so that you would increase enormously the population to which you are efficacious treatment would have been demonstrated to be effective, so I mean that's just a thought.

DR. GASS: Well, speaking on expediency, I would like to see one drug get on the market and so I think the best way to do that would be a very clean, tight study with good criteria and then hopefully in the future, it could be expanded to other populations.

DR. GELENBERG: Yeah. I share everyone else's ambivalence. Every drug for any indication I've ever seen in a long career has been bedeviled by

the fact that the patients in the pivotal trials are pure, no comorbidity, no nothing and then it goes out into the real world and hundreds of times the number of subjects originally studied take it with all kinds of comorbidities and drug abuse and various health problems and nasty things are discovered the long hard way. And so the best of all worlds would be to ask a sponsor to do a relatively clean study in an uncomplicated patient who probably represents less than 10 percent of the universe of patients with the condition and then another study, much larger, of necessity more expensive with appropriate stratifying and blocking and so forth so that you can make statistical sense out of results in case you've got a difference of women with depression or with various medical conditions.

DR. GOLDSTEIN: I rarely disagree with Dr. DeRogatis but I'm going to disagree. I think you have a DSM and you have a DSDS that says that you should not include in this population of women, HSDD, depression in your trial. You want to show drug effect in your condition description of what HSDD is.

I would not put women with depression in the trial. That doesn't make sense.

DR. GUESS: So I actually agree with Dr. DeRogatis and the idea that I think we lose something by not including people who are depressed given the prevalence of depression and the number of people who are being treated for it. I do think it muddies the water but I think having a specific arm to look at those people would be important, so that would be where I would be biased to do.

DR. HEIMAN: Depression is such an important disorder for women in common that after doing a clean sample, quote, unquote, with fewer complications, I think it should be considered. And then coming to Dr. Clayton's comment, you know, where she cited 60 percent of folks did not have depression who had HSDD, I think that's worth paying attention to. There's still that 40 percent so another question could be how you approach depression which would be -- I certainly wouldn't exclude somebody who had been depressed in the past though that might get a -- you know, begin to get into the genetics of things but still, I wouldn't

exclude those people in the trial, even in the clean trial, quote, unquote.

But somehow coming back to depression in particular, particularly since at some point, I hope both premenopausal and postmenopausal women will be looked at, not that depression is necessarily greater but certainly other medical conditions are. And we're not talking about other medical conditions because I really think -- I don't know what to do about that. That's so complicated. Maybe there are some that could be included but that, maybe it would depend on the drug being tested. So I like the idea of first a clean trial but then making room potentially, as Dr. DeRogatis said, for an arm in the second round.

DR. KINGSBERG: I am disagreeing with Dr. DeRogatis on this one. If -- I'm not even sure that ideally you're thinking pivotal trials should include depression or other conditions, but I think number one, it makes for an undue burden for the clinical trial and for the drug. Number two, I think, to Dr. Goldstein's point and I think to Dr. Basson and others, that depression is depression and the

downstream effect that if it has on sexual dysfunction makes depression the primary disorder that you would want to treat and to include them in a trial is inappropriate. You don't really know what would happen, so I think that is very messy.

It could be a nice phase four trial but let's get a drug approved and then do the phase four to see what combining the treatment with women who have depression and women who are effectively treated on antidepressants who have sexual side effects which, actually, would probably be the better trial than the depression itself which you want to treat.

DR. MESTON: I would start with as clean a sample as possible and screen out as many medical issues as possible including depression and then move to a study that included depressed people and also depressed people on antidepressants and look at both of those populations.

DR. MIRKIN: So I believe that if we are talking about the phase three clinical trial, the trial needs to be as representative as possible to the

target population and that's a world concept. So I wouldn't exclude anybody that will be the target population and the population that will be treated with the given drug.

If we're taking depression as an example, so we need to discuss okay, is a patient being depressed part of a given diagnosis, so using the DSM-5, I'm seeing that the patient would fall out of DSM-5. Therefore, developing a drug for this specific condition, she would be out. But the concept of having clinical trials in which you are testing a test article, not -- without including the population which is representative of the target population is a dangerous one because at the end of the day, what you want to prevent is to be treating someone with a drug that won't be efficacious for her or for him. Therefore, you know, there are two ways to think about that and I think that as human, a drug effect is as dangerous as not seeing a potential side effect, you know, in a test article.

DR. WIERMAN: I don't think I have any additional comments.

DR. JOFFE: Dr. Basson.

DR. BASSON: I think agreeing with the second to last speaker (inaudible) quite hear all of it but because in many people's experience, comorbid depression that is treated is a very, very common entity. To include women on antidepressants would be a very helpful and very relevant population notwithstanding that we know the (inaudible) for the drugs themselves would be a complicating factor. We know that and we know depression is also complicated but treated depression, including those women, maybe working out the benefit for them as opposed to the benefit for women not taking those medications because they're not depressed, I'm not sure I'd be comfortable with idea of just treating depressed women with a so-called sexual drug. The depression needs to be treated and it's their right. So it's more the people who are up to this point in time excluded because they're taking an SSRI or another antidepressant.

So I would advocate including them even though we know, in some ways, it's interfering with the drug. And of course, someone has to be sure

there's not a pharmacological interference with the two drugs, whichever the future drug is going to be doesn't mix with SSRIs, etcetera. Thank you.

DR. JOFFE: Okay. Let's turn to the last question which is an interesting one. I guess we've all had interesting questions but let's see what folks think about this one. So here we're talking with folks who have expertise in sexual medicine but if we have a drug approved that will probably mostly be prescribed probably by primary care physicians and folks who really don't have the same expertise in female sexual disorders that you all have, and when we do trials for female sexual dysfunction, subjects undergo structured clinical interviews conducted with folks who have expertise in the diagnosis and treatment of female sexual dysfunction, the subjects are completing instruments that capture what her assessment of her symptoms are, they capture -- and we use that as baseline in the trials and then we give those instruments again later on and we see what her response to treatment has been. But in clinical practice amongst primary care physicians who are going

to be using this product, how do we apply the findings from trials to the population at large and what challenges do you see for these busy primary care docs -- I think someone alluded to it earlier -- who have 10 minutes to see a patient and they've got to cover five different systems and what challenge do you see for these docs who are trying to make an accurate diagnosis, assess response to treatment, determine whether the drug is an appropriate drug for that patient, whether the patient should continue on it or come off it and what thoughts do you have for addressing these challenges? So I forget where we started -- do you want to take a stab at it, Dr. Wierman?

DR. WIERMAN: Yes. I think it would somewhat depend on the type of drug that was coming to mark and its mechanism of action. I think during the trial, it sounds like we're talking about using at least two detailed scales and the interviews, and during the trial, the outcome measures or the aspects of the changes that occurred that were the most dramatic could be use devise some type of a short

scale.

I think about in the erectile dysfunction range that there are tear-off sheets now that every primary care doc can use in their office that got evaluated and tried after multiple different clinical trials were done and they got shortened and shortened and shortened to be at least valid and possibly be used. On the other hand, we have lots of examples of, in other situations, abuse of drugs that are approved such as the data recently on testosterone in men.

So I think, you know, it can be developed and I don't think that these kinds of scales that we're talking about used in a clinical trial are quite what a primary care or an endocrinologist or an obstetrician/gynecologist has time to use so I think we'll need shorter evaluation tools to determine the right patient population.

DR. MIRKIN: I agree. That's why I think that it is important the result of a phase three clinical trial are representative of what's going to happen in a clinical setting and I would try to prevent the lack of (inaudible) between a clinical

trial and a clinical intervention.

How to help clinicians around trying to tease out the facts and trying to determine whether a drug will work on a given patient, I think that, you know, an easy fix will be trying to make the labels easier to read. I mean sometimes, you know, those that don't work so much with the labels, they get lost among all the information that is buried in these very small pamphlets that come in every single product approved in the U.S.

DR. MESTON: I would strongly recommend putting together some sort of patient screener for the physicians to use. The two measures we've been talking about, the FSFI, it's a short measure, and the --

UNIDENTIFIED SPEAKER: (Inaudible).

DR. MESTON: -- yeah, you could use just question 13, one item. Both of those measures have shown to have a sensitivity and specificity of, correct me if I'm wrong Ray Rosen, but around 85 percent and linear measure about 90 percent which my guess is it would be a lot more accurate than most

primary care physicians who are not trained in diagnosing sexual dysfunctions.

DR. KINGSBERG: So the good news is there is a screener that has been validated. In fact, I think Dr. Clayton validated it, and it is the decreased sexual desire screener, DSDS, and it has been used in clinical trials and it is five items. And I think the busy clinician who is not an expert can use this and easily discriminate who meets the criteria for the diagnosis and also who would be more likely to benefit from drug treatment versus psychotherapy. So I think it's already been done. I think the FDA has been very proactive and wanting those screeners developed, so credit to them in advance. So I think rue points are well-taken and we have something for this condition.

DR. HEIMAN: A screening idea is a very good one, obvious. The question for me is how will it come up. Will it come up in a sexual medicine -- well, a sexual medicine clinic is certainly not a primary care sitting -- will the patient raise a question or will the physician be doing just a systems and history in which case it would it probably need to be embedded

with other questions about sexual functioning which would include orgasm, etcetera, etcetera. So this is actually not so easy. It might be easy for a particular drug but there are other conditions you might need to check on to make sure they weren't preceding the condition under study.

The only other sort of side thing that I wonder about for patient is coming in would be the fact that everybody is switching to electronic records and in big medical settings, these things are shuffled around. There is a fair number of patients that I've seen who kind of don't want this in their medical record and that's a different issue but it's an issue going forward and maybe would deserve discussion at some late point.

DR. GUESS: So I like the idea of a screening tool but I would like to also emphasize the idea of physician education or provider education. I find that -- we do it with incontinence all the time and people are putting on drugs because they don't really understand what type of continence it's supposed to be treating, so really advocating for our

patients, making sure it's a plenary sessions, at national meetings, making sure that grand rounds are being done annually to verbalize and tell people what these drugs are and what they're clinical use is so that we can ensure that our providers are well-educated about their use.

DR. GOLDSTEIN: Being a sexual medicine physician, the only patients I see are people with sexual dysfunction. So every day, I see men and I have FDA-approved drugs and I see women and there are no FDA-approved drugs. Should there actually be an FDA-approved drug for women and it would likely not be prescribed in general by sexual medicine physicians, it would be prescribed by internists, it would sort of follow the pattern in 1998 of the first in class sexual medicine drug for men with erectile dysfunction. There was an enormous investment by Pfizer in education. There was, as you say, grand rounds in every hospital. We have a society called the International Society for the Study of Women's Sexual Health. ISSWSH does nothing but education. We educate doctors in courses. We educate nurse

practitioners and physician assistants. I would see ISSWSH having a huge role in education.

Primary care doctors are incredibly conservative. I would find that a lot of doctors who wouldn't feel comfortable would actually refer maybe to more sophisticated primary care doctors who had more experience as what happened in erectile dysfunction. There -- a cadre of primary care doctors ended up becoming experts that weren't sexual medicine doctors but experts within their own sphere.

I just want to bring out the fact that it would be prescription-driven medications. So we have over-the-counter many drugs including like Tylenol where there is no regulation or doctor oversight, and Tylenol has associated with liver disease if you take too much of it. So I think it would be all positive, all good. We have an unmet need. We need drugs for women now.

DR. GASSMAN: Well, the reality in terms of access to primary care and how conservative or less conservative the primary care doctors are has to do with patients who can afford to go to boutique

practices, to concierge internists and be referred to high-end sexology clinics where they pay out of pocket and how live in very privileged zip codes and drive very expensive automobiles and other people who are on Medicaid where the primary care doctors are not so conservative and not so diligent and not so attentive to all of the rules. And the analogy would be that if any of us on our way out today gets a call from a spouse that honey, the refrigerator died, we're going to whip out our Smartphone and look at what's the latest of GE versus, you know, some other brand of refrigerator. And the only way we're going to make sense of a population-based medicine, especially as more drugs come in about which we know so much initially, is to have algorithms, decision support for physicians, electronic screening instruments for patients, patient coaching, the whole wraparound services for population health so that people with chronic conditions, whether it's hypertension or a sexual dysfunction will be able to get appropriately screened and track through algorithms of extenders to primary care physicians to the rare instance where a

patient will be referred to a high-end specialist if the patient doesn't live in Beverly Hills.

DR. GASS: I don't see this as being a big problem. I think the DSDS is a great screening tool. It can be given to the patient while she's sitting in the office waiting for you to come in there and then answers are very easy to review with the patient. I would liken it to what happened with PMS when we were diagnosing PMS and treating it with SSRIs. Little questionnaires came out so you could make a rather succinct diagnosis without too much time. A lot of primary care physicians are prescribing antidepressants and they're not therapists or psychiatrists. So I don't think this would be a big problem.

Low libido is a household word now and in every magazine so people are coming into all kinds of doctors mentioning low libido, so I think this could be handled very nicely.

And if you remember the patients yesterday, think about the number of them that talked about receiving testosterone pellets. We have no clue how

widespread this practice is of physicians having picked up this pattern of prescribing compounded testosterone. We have no data to speak of on how widespread that is, so the compounded testosterone, I would love to make a request to the FDA that those prescriptions start being tracked by gender. I called the Ohio State compounding pharmacy group to ask them about the prescriptions, how many prescriptions were being written for women, just out of curiosity, and they said, "Oh, we do have to track that but we don't track it by gender." So it is really hard to even know how widely used medications like this are already.

So I think this would really fill a need and would do it appropriately with medical and evidence-based products.

DR. DeROGATIS: At the simplest level, I think screening with the DSDS, which has very good sensitivity, specificity, reliability, everything, would be very beneficial to busy docs. And then it occurs to me that if you wanted to be more elaborate and had lots more money, and don't ask me where the

money comes from, you could develop a network of interested -- because some docs are not -- it's just not their thing, you know, and they're not -- but you could develop a network of docs and develop some additional screening instruments perhaps.

I can remember years and years ago, when ECDU was around instead of NCDU, a long time ago, and there was a network of physicians in Pennsylvania, general practice docs, had their own bulletin. They were very interested in psychiatric disorders, particularly depression at the time.

And so all I'm saying is this idea of having mechanisms for GPs, internists, and primary care guys to screen and effectively treat people with female sexual dysfunction could be elaborated into a network in which -- I mean this is grandiose but why not, it's the last question -- into a network of research. These would not be research institutions but they would be practices who contributed to a network of research. It's pie in the sky right now but why not.

DR. CONNELL: I think everybody was pretty extensive. I guess if you're going to really pie in

the sky, you could almost apply it to men and then you'd really have primary care doctors prescribing it all the time.

DR. JOFFE: Dr. Basson.

DR. BASSON: Well, I agree -- am I still on the line?

DR. JOFFE: Yes.

DR. BASSON: Okay. I'm agreeing with, I think, both sides that we've heard but yes, definitely as much education as possible for residents and medical students and physicians in practice. But ultimately, there are going to be physicians prescribing because, ah, finally, there's something to prescribe and that's again agreeing with previous speakers why it's so important that trials are in women who are representative of those who are going to be given the drugs. Thank you.

DR. JOFFE: I'll ask follow-up question for the folks who said we should have a screener. What I'm hearing, it sounds like, is using an instrument that wasn't tested along with the drug in the clinical trials. And I wanted to explore that a little more

and ask shouldn't we be -- if we're going to use something in clinical practice to diagnose patients in the trial and asses their response to treatment, wouldn't you want to use the same instrument that was used in the trials? This is a question for the folks who recommended a screener. Thoughts?

DR. MIRKIN: I didn't.

DR. KINGSBERG: Was the question would the DSDS be useful in a clinical trial?

DR. JOFFE: Well, what I'm hearing is on the one hand use this FSFI and distress instruments in the trial, but then I'm hearing use the DSDS in clinical practice so what I'm trying to understand is wouldn't we want to use whatever we used in a trial as the basis for screening and assessing response to treatment in practice? How do we know that the DSDS is going to respond in the same way to the treatment if it hasn't been studied with the treatment in the trial?

DR. KINGSBERG: Well, I think that they're answering two separate questions. It's sort of like including women on SSRIs in a clinical trial. In a

phase three clinical trial, the FSFI and the FSDS-R are the, you know, gold standards and would be really effective and I think some of the clinical trials have included the DSDS and that would be fine, too, but that's for the clinician diagnosis in a busy clinical practice to make it practical.

What the FDA, for the most part, has required in phase three clinical trials is an extensive diagnostic interview to make sure we get the right population. So I think it's fine to use it in addition but we're looking at efficacy with all these other endpoints, not just screening for the diagnosis.

DR. DeROGATIS: The DSDS has very good, as I said a minute ago, sensitivity and specificity against detailed clinical interview to establish diagnosis. So I don't know how many trials but in a number of trials, the patients upon whom the FSFI and the FSDS were completed and were the prime principle outcomes measures were DSDS certified to have HSDD. So it's -- while it's not the same instrument, it certainly establishes the condition that the outcomes measures then go on to reflect changes in.

So it's my experience, the hard way--I have to tell you, in getting docs to use psychological instruments is -- they don't want to and the longer the instrument, the more they don't want to. And so the DSDS is four or five -- five items if you involve the doc. So it's quick, it's sufficient, it's reliable, it's valid, all the good things. It's not comprehensive but that's obvious. So I think it would be useful and -- but because of my nature, perverse as it is, I would like to initiate this program in a research mode, that is find a group of docs who are interested, utilize this instrument and establish how effective it is in the real world, not clinical trials world but the real world and have, you know, so-called experts do the evaluations against which it would be monitored and the doc would do the kind of referrals to the program. Anyway, it's something to think about and…

DR. JOFFE: Yes.

DR. GASS: There's probably not really precedent requiring that for other products though, right, that everybody use the same screener or -- so I

don’t know why we would have to feel that that needed to be here.

DR. GOLDSTEIN: For the erectile dysfunction complementary male world, Pfizer developed a screener, actually a series of screeners. Actually, Dr. Although was very engaged in the SHIM, Sexual Health Inventory for Men, so that the same construct could theoretically be applied using the DSDS.

DR. JOFFE: Why don't we turn to questions? We've got about 10 minutes or 25 minutes -- 20 minutes of questions and then we'll do open the public hearing. Come on over to the mic.

DR. TIEFER: I'm Leonore Tiefer. I want to ask about question two, the one about adjunct sex therapy. It seems that most people were not in favor of that and I think there ought to be more options that are being considered and I wanted to offer something under the rubric of sex education. I mean if we think about what sex therapy is really all about, it consists of two components, right, relationship work and psycho-educational work. And we all know that they're equally important, that the

amount of misinformation that people have about sexuality is incalculable, bottomless. And it just seems so inappropriate not to try to enter that foray.

There's a paper in Dr. Goldstein's journal, this issue, that I rather like that has to do with women experiencing oophorectomy and they were given a very brief sex educational intervention, right. It was a half-day workshop, group workshop -- group work is very important for women, does many, many things so I'm not talking about one-on-one kind of sex education -- half a day group work, take home educational materials and two follow-up phone calls, and it had a very substantial influence on these patients' sexual adjustment post oophorectomy.

So I just want to suggest that there might be some kind of ways to deal with the massive myths -- we heard a lot of myths from patients yesterday, with all due respect, myths -- reminded me of Bernie Zibergeld, 10 feet long, hard as steel and can go all night, right. Myths and facts, a big part of sex education and intervention that wouldn't cost a million dollars and it would be very respectful of

many of the needs we've heard about.

DR. JOFFE: Comments from the panel on that?

DR. MESTON: Well, I certainly agree. I think that my response to that question, the earlier question was that absolutely, adjunctive therapy is a very important question and a very -- something that I think definitely should be studied. I think the fact that we see such an enormous placebo effect in women for sex drugs. The Viagra studies, I think some of them showed almost a 40 percent placebo effect. So there is significant benefit to non-drug interventions. We've seen that.

My only point was let's see what -- if we're talking about drug development, let's see what the drug does first and then I would be interested to see -- add on some of those components and see if it intensifies the effect or makes it more sustainable. That's sort of what's happened in the depression antidepressant literature.

DR. JOFFE: I think Dr. Basson has a comment from the phone.

DR. BASSON: Thank you. Yes. Adding on to

Dr. Tiefer's comment and going back to one of my earlier ones, to fully assess the patient and the partner, if there is one, to give them feedback of the formulation of the factors involved in her/their particular problem is providing the education, the validation of the concern and, therefore,, some of the components of the placebo effect. Then take a baseline measure on what instrument is going to be used and then see what additional benefit there might be from the medication so that you give them the chance of the information itself to have more benefit and then to see does a drug do more than that. And that would be considerably less than what was being proposed earlier before the break, that was should it be formal CBT or sex therapy.

DR. JOFFE: Next comment.

DR. PARISH: Yes, hello. My name is Sharon Parish. I'm a general internal medicine physician at the Weill Cornell School of Medicine. What I'd like to say, particularly to the comment about the Beverly Hills clinic and that that's where these kinds of things happen effectively, so I was at Bellevue

Hospital, North Central Bronx Hospital, Montefiore Medical Center, and the Bentances Health Clinic in the South Bronx, and I took care of for over 25 years with many colleague physicians a large population of patients who were uninsured, had Medicaid and Medicaid managed care and often couldn't pay at all anyway. And my experience was that my colleague primary care physicians astutely, competently and with zealous vigor carefully learned to use screening and identification instruments for analogous conditions such as depression, for example, and alcohol use disorders.

Instruments like the PHQ-9 and the Audit-C were widely disseminated through responsible international and national societies that promoted wide-scale education around the use of these instruments. And then in these settings, I saw them over the past, say, five years implemented in electronic medical records where the instruments were embedded and the clinicians learned to use them. And they often used the results to treat patients, often with medical interventions, sometimes medications like

antidepressants or anxiety drugs. These are primary care physicians who work in clinics. We see patients every 10 minutes and we use an EMR and we referred them, sometimes, depending on the clinician's self-assessed competency and the clinicians, I found, were responsible and capable of treating or triaging.

And I think that we need to understand that this can happen here with this disorder similarly and effectively. I'd like to see if any of the panelists would like to make a comment.

(Applause.)

DR. GELENBERG: Yeah, I would. Your patients are very fortunate and there are some absolutely wonderful physicians throughout the United States. What goes on in Manhattan is not generally the same as what goes on around the rest of the country including the other boroughs of New York City. So if you cross the Hudson --

DR. PARISH: Manhattan and the Bronx are not the same borough, right.

DR. GELENBERG: Well, okay, then I --

DR. PARISH: Foresight's --

DR. GELENBERG: -- then three of the other boroughs.

DR. PARISH: I worked in Brooklyn also if you want to get --

DR. GELENBERG: But it's not uniform throughout Brooklyn, it's not uniform throughout Queens or Staten Island, and it's not uniform in most of the country where you don't have the caliber of physicians that we're lucky enough to have in these urban areas. So the goal for U.S. healthcare as we move forward to ensure all Americans should be to make the caliber of care you're describing universal throughout rural and urban America for everyone.

(Applause.)

DR. PARISH: Well, I think that's a wonderful mission and I think the internet and large-scale education initiatives can make this possible. It's not like it was 20 years ago. I started in New York City in 1990. We didn't have the educational resources we have today. So I think we can be very confident that we can be far-reaching, even to like remote points of Vietnam, for example, based on some

of the people that attend some of our meetings.

DR. GELENBERG: Sure.

DR. PARISH: So I think that this is a solvable problem and I'm glad you made the point that it's not just Beverly Hills. It can happen everywhere.

(Applause.)

DR. SILCOX: My name is Christina Silcox. I'm from the National Center for Health Research and my question actually kind of bridges topic two and topic three. Yesterday we learned that the diagnosis is a diagnosis of exclusion which basically means that you all have the -- there are similarity in the symptoms but the causes are probably extremely different.

And so today we talked about -- there was some talk about subgrouping -- subgroup analysis. And I was just interested in learning a little bit more about what the panel thought those subgroups should be. Are we just talking about separating out pre and postmenopausal women or people with HSDD? Or are we going to go more in depth and say, okay, well, what's

the testosterone levels in these women? Do they have life -- is this a lifelong thing? Is it slow onset? Is it sudden onset? You know, there are a lot of different things and I'm just interested in what kind of subgroup analysis you guys would be interested in seeing.

And along with that, I would actually just like to make a comment that given the fact that a subgroup analysis, it should absolutely be made public and not confidential in the FDA files, as so many subgroup analyses are, so that other clinicians who aren't on the privilege of being on the advisory committee can see it and help their patients, make the right decisions for them.

DR. JOFFE: Any thoughts from any other panelists on these various subgroups? You know, FDA doesn't own these data. These data belong to drug companies so regarding your comment about making subgroup data available, that's on the companies. They have to be willing to do that. But any comments on the question of subgroups and how these drugs should be looked at?

DR. GASS: There may have been a difference as to whether or not people thought those who had usually been excluded should be included in this trial or whether or not they should be a separate study later. And so I think the one that was coming to mind for most of us would be those people who have depression who are on antidepressants and then get a sexual side effect from the antidepressants. It would be nice if they could still take their antidepressants and yet have some fix for that problem. So I think that's the most common group that comes to my mind. I don't know if other people had other groups that would be of interest as well.

DR. GOLDSTEIN: I mean the drug that's most close to being approved is non-hormonal so it would stand an unbelievable chance of helping these very poor women with sexual dysfunction and breast cancer. I would die to see a phase four trial of this drug in breast cancer patients. I think -- I've so many patients who would be ready to see how we could change their lives.

DR. SILCOX: Just to clarify and I might

just be completely mistaken, in topic two, there did seem to be discussion about whether, at the very least, premenopausal versus postmenopausal people should be separated out for analysis of this data. And so I guess that's kind of where my question was coming from. Are we just talking about pre and postmenopausal? Are we not even talking about that?

DR. GOLDSTEIN: If you're talking of the drug Flibanserin, it's a non-hormonal drug approved --

DR. SILCOX: (Inaudible).

DR. GOLDSTEIN: -- yeah, well, but you have to talk about each individual drug. So the Flibanserin drug is primarily for premenopausal but they actually have data in a large double-blind placebo-controlled trial in postmenopausal women, so you would have data in both groups. I'm pretty sure that's true.

UNIDENTIFIED MALE: It's true.

DR. GOLDSTEIN: Yes, it is true. Okay. For other drugs, you'd have to see what their indications are but they haven't come as far so we just don't have those data.

DR. GUESS: I would just add that I think the whole point would be to make these drugs as generalizable as possible so if the data were available, to go back and do a sub analysis and there were enough people, it would be reasonable to look at some of these other factors. I don't necessarily think that everything has to be evaluated for every drug. I think, again, going with what the indication of that specific drug is important for the getting out of the starting gate and then we can always go back and see if there are other things that we may be able to figure out from these studies.

DR. SILCOX: Thank you.

MR. SHIELDS: Hi. My name is Wayne Shields. I'm President and CEO of the Association of Reproductive Health Professionals and I represent the frontline providers who provide the care, so the results of your conversation today will go to them. And I'm here kind of to ask you in relation to this particular section -- you know, I'm just struck particularly by question two but also all four questions.

There seems to be a level of intense focus and nuances given to this conversation about female sexual dysfunction and how the clinical trials have been designed. I'm just struck by the elephant in the room which I'm sorry but I have to bring up. Can the panel give examples of similar rigor and intense nuance that was given to any clinical trial process for male sexual dysfunction? I mean it seems to be clearly something we're not discussing that my folks want to know about. They want to hear this from you.

I want to wrap up by saying I complement the FDA. This is a fantastic two days. I really appreciate being here and thanks for doing it.

(Applause.)

DR. GOLDSTEIN: I'm dying to say something but I'm going to hold.

(Laughter.)

DR. GOLDSTEIN: It's so frustrating to -- it's just so frustrating and so unfair and so underserved, the women with sexual problems. Just seeing it every day and I have with short studies, quickly approved and 11,000 patients, not approved. I

don't know how to express the frustration other than to just say that.

UNIDENTIFIED FEMALE: (Inaudible). Are we racing to that step?

MR. SHIELDS: I'm actually asking them about (inaudible)

DR. JOFFE: I think we've mentioned this a few times already, we really want to stay focused on female sexual dysfunction. We're trying to have a productive meeting. As you can see, FDA is not afraid of having folks who disagree with us. In fact, we invited a broad panel of experts here, some of which have expressed very clear differing views from what you've heard from the FDA. But we feel this is important. We feel this is how we get to the truth and so it's very important. We're very carefully listening to what you all have to say. We're listening very carefully to what the patients had to say yesterday. We're going to take this back and we are -- we take our jobs very seriously and we -- I think we all have the same goal. We want products that are effective and reasonably safe for our

patients. And I think we heard earlier about collaboration, working together, so I think let's try to stay on that positive note. We've only got about another hour to go so let's see if we can do it.

Any other questions for the panelists?

DR. WHITTAKER: Dr. Joffe, I have received a written question from the audience.

DR. JOFFE: Okay. That person is welcome to come up and ask it if you'd like or otherwise, Dr. Whittaker can read it. Who's the question from?

DR. WHITTAKER: This is from Adrianne Monsef and she's from the Strategic Science and Technologies, LLC in Cambridge, Massachusetts. And her question, it says, "Based on the discussions thus far and your clinical experience with patients, do you agree that HSDD is primarily a CNS-mediated condition and conversely FSAD is primarily a peripherally-mediated vasculogenic condition and if so, do you feel that the drugs in development should aim to treat each condition separately? And furthermore, do you feel the prevalence of FSAD patients is high enough to justify drug development for a peripherally-mediated

drug to treat FSAD?

DR. JOFFE: Any thoughts from our panel members?

DR. GUESS: I guess I would just go back to my statements about I don't think we know. I think if you use urinary incontinence, which is what my experience is in, we originally thought that much of this was centrally-mediated, but now we're figuring out that the afferent signaling plays a crucial role in the continence mechanism. And I think that this inter-relationship between the autonomic peripheral and central nervous system is something that, as a whole, we don't fully understand. And I think that's my whole point of really trying to understand symptoms land what these drugs do to all the symptoms so that then we can go back and try to figure out if it is indeed more centrally modulating versus peripherally modulating.

DR. GOLDSTEIN: I do not want to give the impression that we have zero research in female sexual dysfunction. I have 50 peer-reviewed manuscripts on research in female sexual dysfunction.

Dr. Noel Kim -- I think he's still here, raise your hand -- going to his PhD in discussing and researching female sexual dysfunction.

In particular with drugs, we have identified that in animal studies, if you put needles in certain places of the brain and you give the drug, you can measure the changes in serotonin and dopamine, norepinephrine, and that would imply that that's one of its actions. We have FMRI human studies showing that in women with HSDD -- this is published in Neuroscience out of Stanford, Leah Millheiser is one of the authors -- against control versus HSDD. They have different FMRI patterns in different parts of the brain and that on medications, you can change those issues.

I think the evidence of SSRIs causing -- well, it wouldn't be HSDD, it would medication-induced low interest gives us a comfort level that this is brain chemical imbalance and that this drug theoretically has an opportunity to change that imbalance, and that's just Flibanserin. There is a drug, Bremelanotide, which very strong dopamine

agonist that also has early positive benefits. So it would be incorrect to say there is limited research in this area. It's just very poorly funded and we desperately need more research.

But the way this works is it all comes from the top down. If a drug gets soon approved, there will be much more interest in everybody learning and understanding this drug. We will then have education in medical schools for women's sexual health. We'll have doctors being trained. We'll have research being generated. The best analogy I could give you is Peyronie's disease because there's a brand new drug just approved last year, and in the Sexual Medicine Society of North America, there are over 100 abstracts on Payronie's disease that has never existed before. Why? Because there's a drug out there and now you can provide it to patients and give it now for different indications, different reasons. I can only see that that will happen if we could get this unmet need needed and approved.

DR. JOFFE: Thank you. Let's take the last comment from Dr. Basson and then we'll go to the open

public comment.

DR. BASSON: I'm just going to address that last question as to whether there was a large enough group of women with peripheral vasocongestion entity. I think, you know, this is, as opposed to something that's quite central, and that is more a brain entity, I don't think it's anything like or simple as this. I think when women are complaining of lack of genital reaction, sensations, perhaps their words clinically are often genital deadness, this isn't necessarily lack of congestion because often, if they are postmenopausal, that can be corrected with estrogen. It's something else. As others have said, we're not quite sure what it is but the symptoms are, at least for a duration of time, peripheral, i.e., genital.

However, that's not to say that that's not in response to signaling from the brain. So I really don't think we can be very simple here and say there's this FSAD as in DSM-4 which is all due to lubrication swelling response and then there's a desire issue. I think it's way more complex and way more inter-related.

DR. JOFFE: Thank you. With that, if we could give a round of applause to all our panelists.

(Applause.)

DR. JOFFE: And now I'm going to turn it over to Pujita who will manage the open public comment.

MS. VAIDYA: Hello, everyone. We're now moving into the open public comment session so please keep in mind that we will not be responding to your comments but they will be transcribed and be part of the public record. For the sake of transparency, we request that you disclose if you are affiliated with an organization that has any interest in drug development in FSD or if your travel here today has been funded by an organization or if you have a significant financial interest in FSD drug development. If you do not have any such interest, you may also state that for the record.

We've collected signup before the meeting and we have 15 people signed up and 30 minutes for this session, so please be respectful for your other colleagues her and try to stick to the two-minute

limit that we have. I have a timer up front and when the light turns from green to red, that means your time has ended and I'll move on to the next speaker.

So I'll run through the order of speakers and then we can begin. So first, I have Cindy Pearson, then Leonore Tiefer, Thea Cacchioni, Barb Depree, Laurie Watson, Raymond Rosen, Eileen Beard, Jos Bloemers, Sally Greenberg, Stanley Althof, David Portman, Michael Krychman, James, Simon, Sharon Parish, and Anita Clayton. So first, could I have Cindy Pearson.

MS. PEARSON: Hi, I'm Cindy Pearson. I'm the Executive Director of the National Women's Health Network. We don't take money from drug companies or medical device companies.

We're in this room today talking about a scientific workshop on female sexual interest and arousal disorder because there are no treatments for it. What are the reasons? Is it the FDA? Is that the reason why there's no treatment all these years after an approved treatment for men? Is it the sponsors? Or is it women themselves?

There has been a lot of scientific conversation today about the extent to which the heterogeneity of women's experience of problems with sex create scientific problems in evaluating effective treatments. There hasn't been as much conversation today about women themselves being the source of difficulty in reaching successful approval for a product because our experience of sexuality being culturally mediated, our experience of sexuality being influenced by social factors. But women themselves are part of the reason why it's taken so much longer than it took for men.

I would also argue that sponsors are part of the reason to the extent that sometimes their inclusion criteria isn't good, sometimes their design isn't' as good as it could be, and sometimes their drugs just aren't good as they could be.

But the question of whether the FDA is the reason why there aren't drugs, I disagree with my good friend Wayne. The elephant in the room is not that the FDA is stricter with women's sex drugs than it is with men. The elephant in the room right now is there

is a marketing campaign going on to try to force the FDA to change its standard for approval to gender equity rather than safety and effectiveness. I see the yellow light's on so I'll just conclude quickly that, yes, we do want gender equity in sex as well as in everything else and we want drugs that are truly effective, definitively effective, and the safety is well enough known that women can make informed decisions. Thanks.

MS. VAIDYA: Thank you, Cindy.

(Applause.)

MS. VAIDYA: Next we have Leonore.

DR. TIEFER: Leonore Tiefer, no funding. So for the past year, there has been something unprecedented going on that requires public scrutiny and I refer to "Even The Score dot org"[eventhescore.org]. It involves sexuality professionals behaving unprofessionally and drug companies funding alleged patient advocacy campaigns to publicly shame the FDA with accusations of sexism and pressure it into using political instead of scientific and safety criteria in approving drugs for

FSD. The whole spectacle is shocking, deceptive, unethical, cynical, and despicable.

It began with social media blogs, urgent meetings at the FDA to examine non-existent sexism, recruitment of uninformed but well-intentioned women's group and women-elected officials, friend groups, more letters to the FDA and finally and most inappropriately of all, a letter from ISSWSH to its members offering travel grants for their patients to attend this meeting. These kinds of tactics are inappropriate and have created a rowdy and adversarial atmosphere that's made it difficult, if not impossible, to gather information useful for the FDA's deliberations. I would never burden my patients and exploit our sacred relationship with this kind of request. They deserve my integrity. It upsets me even to think about this. The availability of millions of dollars and the promise of billions of dollars is destroying the integrity of sexology and Even The Score was the final straw.

My New View Group has posted a petition defending the FDA, the last thing we thought we'd ever

do, from false accusations of sexism. We have prepared timeline of ISSWSH and Sprout tactics. We have fact sheets. It's not just us. This week the BMJ featured an article about Sprout, ISSWSH and Even The Score calling it a marketing masquerade.

I hope this meeting will signal a shift from a marketing masquerade and science theater to an important moment in a long and complex story. We say to the FDA --

MS. VAIDYA: Excuse me, Lenore --

DR. TIEFER: -- don't let the cart drive the horse.

MS. VAIDYA: Thank you, Leonore.

(Applause.)

MS. VAIDYA: Next, we have Thea Cacchioni and then Barb Depree. I don't think Thea's --

MS. WATSON: May I cut in? I need to catch a flight? I'm Laurie Watson.

MS. VAIDYA: Sure. Is she next, she there? I don't think Thea's here. Okay. Who are you?

MS. WATSON: I'm Laurie Watson, number five.

MS. VAIDYA: Okay.

MS. WATSON: I'm a certified sex therapist and the author of *Wanting Sex Again: How to Rediscover Desire and Heal a Sexless Marriage*, and I blog for *Psychology Today* and married and still doing it with over 1.4 million reads. I've paid for my own expenses.

I've worked over 6500 patient hours in this last 3-1/2 years myself, primarily with low libido women and frequency discrepancy couples. As a clinic, we've seen over 1,000 different couples' work that I supervise. I have deep experience in the narrative of female low libido. Along with the women yesterday who found desire and arousal as discreet states, my patients do identify this and want for themselves particularly subjective desire. Subjective desire infuses life itself with spice and excitement. I think this is what the patients were saying yesterday when they referred to wanting to desire 365 days a year. The hyperboles didn't mean that they wanted sex or desire every day but that they wanted or yearn, pine, long, crave, and feel.

I do think drugs would help. Pharmaceutically aided intrinsic female sexual motivation would help her not to just lie down and think of England but to have an erotic core with equal demands for physical pleasure. Erectile dysfunction does not always have an etiology of a disease state but can be caused by a poor self esteem, anxiety and depression. Regarding sexual functioning, erections are not even necessary for sexual pleasure nor for orgasm and yet men still prefer them.

I don't believe also that the min in my practice, no matter how distraught would grind up the pill and force feed it to women despite yesterday's fearful allegation about male domination. I found the implication male bashing. Thank you.

MS. VAIDYA: Thank you, Laurie.

(Applause.)

MS. VAIDYA: Next, we have Barb.

DR. DEPREE: Hi, I'm Dr. Barb Depree. I'm a gynecologist and I have no financial implications to being here. I came at my own expenses. I just want to say thank you to the FDA for people like myself who

are out there practicing, in the frontlines seeing women every day, that you give us the opportunity to express our interest for helping our patients address this.

And I think for me, it was helpful to hear the women's voice yesterday and mentioned to colleagues that that's me in the room every day. And I think Victoria especially, she wept. She didn't intend to, I don't think so, but women find the words around this so strong. I don't know how anyone in the room could not understand what the diagnosis might be. I understand the structure of setting up your clinical trials is complicated and trying to bring in the best information, asking the right questions, making sure patients report it in the right way may be complicated. But when I'm in the room talking to a Victoria, there's nothing -- sorry -- there's nothing complicated about understanding her situation.

And I also feel like the point number four about how are we going to have our primary care providers consider this drug, I'd like you to give more credit to the practitioners that really -- our

motto for our patients is to do no harm, and I think improving the conversation around this and allowing us to talk about "Grey's Anatomy" and chocolate and strawberries is a find opportunity. But in the end, that just isn't going to do it for our patients. We really need a medication and hopefully that in the privacy of our practice and the long relationship we've had with our patients we can together make a decision about whether a medication may have an indication. And in the end, maybe it is efficacious. Maybe it's only efficacious for a small percentage of our patients but at least we can have the conversation, allow them to have an option and to have hope that they might have some resolution to this life-changing condition. Thank you.

MS. VAIDYA: Thank you, Barb.

(Applause.)

MS. VAIDYA: Next, we have Raymond Rosen and then Eileen Beard.

DR. ROSEN: Excuse me. I got caught up in the last speaker's comments. My name is Raymond Rosen. I'm a Chief Scientist at New England Research

Institute, formerly Professor of Psychiatry at Rutgers.

I currently consult to three companies in this area: Apricus, Palatin and Sprout and our organization also ahs funding from Actavis, Pfizer and Shionogi, formerly from BI, for research somewhat related to this. My travel support was partially supported by Sprout.

I want to return to just one very specific issue and even though I really credit the FDA with putting this meeting together, which I think has been really exceptional overall, I also want to do a little bit of gentle --

(Automated voice timekeeper announcement.)

MS. VAIDYA: Sorry.

DR. ROSEN: -- a little bashing of the Division around the issue of PRO development. It's really been quite shocking to me, having been involved in the male area and the female area and having worked with this Division at the FDA for a long time, to see, quite honestly, the double standard. Three instruments in particular, the International Prostate

Symptoms Scale, IPSS; the primary endpoint in every trial of male BPH LUTS that I'm aware of is a 28-day recall instrument and has so little validation in comparison to the FSFI or the other tools; the IIEF, an instrument I was involved in myself, has so little validation compared to the FSFI and most recently, the Peyronie's disease questionnaire, PDQ.

I really invite the Division to look carefully at the validation literature for those three widely accepted male PROs and ask why PROs for women are being held to so much higher a standard. I was encouraged to hear that 12 out of 13 panelists strongly endorse the FSFI and the distress measure as good validated instruments, and I really hope the Division will finally consider these points. This has been a real frustration to myself and others that women's instruments are held to so much higher a standard. Thank you.

(Applause.)

MS. VAIDYA: Thank you, Raymond. Next, we have Eileen and then Jos Bloemers.

MS. BEARD: My name is Eileen Beard. I work

for the American College of Nurse Midwives. I have no other interests. I am the Senior Practice Adviser. I'm a Nurse Midwife and a Family Nurse Practitioner and I have been in clinical practice for more than 30 years.

The American College of Nurse Midwives, obviously, the focus for us -- women are at the core of our practice and we've been to a lot of meetings where this particular issue has been discussed. We're very distressed that there is no pharmacologic agent for women for hypoactive sexual desire disorder. You know, I see women, I listen to them, I offer every possible option but for some women, there are no other options. And I really implore the FDA to take serious consideration. Obviously, safety is paramount. No one wants a drug out there that's not safe but my understanding from looking at the drug trial information is that there is a drug that is available that does have a safety record and I hope that you will move forward.

I can only tell you that the patients can really speak. I can't speak.

BARBARA: My name is Barbara. I was a panelist yesterday and I just wanted to go over a few points. One thing I'd like to do is to make an illustration for all of you. I want you to think that you're going to go bed one day and wake up the next morning, you are perfectly fine the night before, you wake up the next morning and you have HSDD. What are you going to do? Where you going to go? There's nothing out there that's proven safe and effective for women.

So I was fortunate enough to be on a Flibanserin trial and I want to tell you that I have had this issue for about 25 years and I was on the placebo for the first duration of that clinical trial and that placebo did not work and I wanted it to work. Believe me, after 25 years, I wanted this to work so if I was going to have this positive placebo effect, it was going to be me. Didn't work. Nothing. Oh, I got the red light.

MS. VAIDYA: Thank you, Barbara.

BARBARA: But I was on the real Flibanserin after that. I was given the opportunity to take that

and I want to tell you that I was an amazing woman, initiating sex, my desire came back.

MS. VAIDYA: Thank you, Barbara.

BARBARA: It works. I'm living proof. Thank you.

MS. VAIDYA: Sorry.

(Applause.)

MS. VAIDYA: Next, we have Jos and then Sally Greenberg.

DR. BLOEMERS: My name is Jos Bloemers. I'm an employee of Emotional Brain. It's a small Dutch R&D driven company that is investigating two on-demand therapies for female sexual interest and arousal disorder. Yesterday it was rightly so stated that women should have a choice between on-demand or continuous pharmacotherapies for FSIAD.

I would like to argue that event logs be used for the primary endpoints for on-demand medication because this type of therapy is designed specifically to increase satisfaction during and around sexual encounters and decrease distress in that manner. Our event log assesses whether a sexual event

is satisfying or not but it also contains six Likert scale items assessing different aspects of sexual functioning, like sexual excitement, desire, arousal, genital pleasure, all aspects which underlie the core FSD symptoms. This enables us to observe how satisfaction relates to sexual functional domains per event, over multiple events, and which percentage of the events show adequate excitement, pleasure and arousal.

There's a strong relationship between the functional domains we measure following each event and whether a participant experiences an event as satisfactory or not, as would be expected. For each item, 80 percent of the unsatisfying events scored low, a zero or a one on a five point Likert scale, and 80 percent of the satisfying events scored high, a two, a three, or a four showing that SEEs are not as distal as was suggested.

Yesterday and today it was pointed out once more that sexual satisfaction is multifaceted and that all these facets show inter and intra individual variation. Adding Likert scale item scores to an

event log results in a combined satisfaction score that covers this variation or mostly covers it and is a valid endpoint for trials in FSD. The predictive power of such a satisfaction score is higher than that of any individual Likert item in predicting if a sexual event is satisfactory or not.

MS. VAIDYA: Thank you, Jos.

DR. BLOEMERS: Thank you.

(Applause.)

MS. VAIDYA: Next, could we get Sally Greenberg. She's not here, okay. Stanley Althof and then we'll have David Portman after him.

DR. ALTHOF: Good afternoon. My name is Stanley Althof. I am Professor *Emeritus* at Case Western Reserve University Medical School. I am also Executive Director of the Center for Marital and Sexual Health of South Florida, the past President of the International Society for Women's Sexual Health, the past President of the Society for Sex Therapy and Research.

I work for a number of -- consult to a number of male and female drug companies. The female

ones are Palatin, Trimel, Sprout, which paid for my travel here, and SST.

I want to focus just briefly on a number of issues. One, let's start with satisfying sexual events. Respectfully, I say to the FDA I think you started on the wrong foot years ago by asking for satisfying sexual events. And we have a chorus of papers that have come out year after and year and have seen this as a very difficult measure. As Dr. DeRogatis said, this is a crude measurement, it's counting, and I think we can really do better and have done better and have better PROs. It's distal to the concept. It doesn't have a great correlation with desire.

And the other issue, it's really not in the criterion for -- either in DSM-4 or 5. In fact, on the male side when we tried to -- I've created two or three instruments on satisfaction. When you tried for a premature ejaculation to introduce satisfaction as a primary endpoint, we were told we couldn't do that by the FDA and it wasn't in the criterion for premature ejaculation based on DSM-4.

Enough on that. I hope -- I think there is a sense that you're moving that down perhaps to a secondary, a tertiary endpoint. I hope you will please consider that.

I also want to thank you for putting this meeting together and for listening. I greatly appreciate that. I also appreciate the women that spoke yesterday.

The other thing I think is --

MS. VAIDYA: Dr. Stanley (sic).

DR. ALTHOF: I'm out. Okay, I'll stop.

MS. VAIDYA: Sorry.

DR. ALTHOF: Thank you.

(Applause.)

MS. VAIDYA: Next, can I have David Portman and then Michael Krychman.

DR. PORTMAN: Dr. David Portman, a Clinical Instructor of OB/GYN, Ohio State University. I'm also on the Board of Directors and a Fellow of the International Society for the Study of Women's Sexual Health.

My industry disclosures I have already put

on the record for research grants and advisory board participation. Part of my travel has been funded by Sprout but not only am I not being paid to be here today, I gave up two days away from my practice where I actually do make a living to proudly stand here on behalf of my patients.

I want to thank the FDA for giving voice to those patients just like mine who we heard so poignantly from yesterday. It's been a long time that they've suffered in silence and my colleagues give that same sense of commitment to hearing their voices.

I also want to commend the Agency for recognizing that FSD is a serious unmet medical need. Dr. Chang mentioned Dr. Schifrin's (ph) paper where 12 percent of the U.S. population identified as sufferers of FSD with distress so it is a widespread condition, a real condition. So hearing Dr. Basson state that it's not a pathology and it's been discredited and that we hear from pundits that it no longer exits, well, I'd like to tell you on behalf of my patients that they did not get that memo. They're suffering severely from these symptoms of low desire with

distress.

And as a researcher, I'm very concerned and interested in understanding etiology, understanding the way these instruments work. We've heard from Dr. DeRogatis it takes years to perfect instruments. It takes decades to understand etiology. We already have very good instruments. We understand somewhat the source of this disorder and we cannot let the perfect be the enemy of the good. We have good and right things to do now and we need to act on behalf of our patients because if not now, when?

(Applause.)

MS. VAIDYA: Thank you, David. Next we have Michael and then James Simon.

DR. KRYCHMAN: Thank you for the opportunity to speak. My name is Michael Krychman. I'm a sexual medicine gynecologist, sex therapist, and clinical researcher.

My disclosures in Shionogi, Pfizer, Palatin, Noven and my funding was partially supported by Sprout.

I'm also the social media chair for ISSWSH

and I want to clarify that ISSWSH did not provide any grants for anyone to be here.

I have been here for two days and heard the word "complex." I stopped counting after 20. We have oversimplified men and overcomplicated women. We agree it's multifactorial and multifaceted. I am the sole financial provider for a family of four, 8-year-old twins anticipating an overnight flight to give an educational lecture on sexual medicine and sexual psychology at a major University tomorrow morning so please don't minimize my stress or fatigue.

We have heard today that women respond in implement different treatments to address their symptoms. As a clinician, I provide ingredients so we can uniquely provide a safe, effective recipe for individualized women who are impacted by this medical issue. Woman choose pills or not, counseling or not, hormones or not. No medically approved option hurts women.

I'm cautiously concerned that the FDA is now scrutinizing and getting involved in healthcare provider prescribing behavior. I believe in women.

Let us learn from history. We did not think women were smart enough to vote. We denied them this privilege. We have been taught wrong. We didn't think women were strong enough to defend our country and we again have been taught wrong. Allow the philosophy of the sanctity of the therapeutic alliance between healthcare provider and patients. Healthcare providers want to help. Women want to be helped. Women will not remain on treatment if not effective or experience adverse events. Allow women their constitutional autonomy to be smart and strong.

MS. VAIDYA: Thank you, Michael.

(Applause.)

MS. VAIDYA: Next, could I have James Simon and then Sharon Parish.

DR. SIMON: I'm Dr. Jim Simon. I'm a Professor of Obstetrics and Gynecology at the George Washington University School of Medicine, Secretary of the International Society for the Study of Women's Sexual Health, an Associate Editor of the *Journal of Sexual Medicine*, and I have a private practice here in Washington, DC. You had an opportunity to hear from

my patients yesterday.

I've been an investigator, a consultant to many companies in women's health generally and in sexual medicine specifically. They include Abvi (ph) Actavis, Amgen, Amnil, Apotex, Ascend (ph) , Bayer, Dr. Reddy, [A-ZI]i, Endoceutics, Everett, Lupin, Merck, Novartis, Noven, Novannordisc, Palatin, Pfizer, Shionogi, Sprout, SST Therapeutics MD and Teva. I've also performed contract research for the NIH and the American Heart Association.

And in full disclosure, I have a book that sold out and I have royalties from that and I develop slide sets for medical education. I get royalties from that.

You heard yesterday from my patients and others how distressing an impactful female sexual dysfunction can be and the toll it can take on their relationship and the havoc it wreaks on their quality of life. You heard that patients with sexual dysfunction are willing to inordinate risks to get help in overcoming their problem. They go to the internet. They get junk of questionable value, much

of which is tainted with undisclosed additives, both commercial, pharmaceutical and others. They use compounded therapies of questionable purity, sterility, and reliability. The FDA, believe me, they know this.

This may be contributing to the extraordinary variability, for example, to the testosterone response noted yesterday including excessive hair growth varying to absolutely no effect. Let's not forget the patients receiving testosterone pellet therapy also undergo minor surgical procedures every six months with attendant risks of infection and bleeding just to get their pellets.

No medication is perfect and no medication has absolutely no side effects. Let's not forget, as Dr. Goldstein, Tylenol may cause severe liver failure and it's over-the-counter and yes, the FDA regulates over-the-counter products the Agency recognizes the benefits of proper use of Tylenol --

DR. VAIDYA: Thank you, James.

DR. SIMON: -- and that Tylenol's benefits outweigh the risks. Sexual dysfunction is a huge

problem.

DR. VAIDYA: Thank you, James. Sorry.

DR. SIMON: Women can make their own decisions. No drugs are perfect. Waiting for perfection was a waste of time.

(Applause.)

MS. VAIDYA: Next we have Sharon Parish and then finally, Anita Clayton.

DR. PARISH: I'm Dr. Sharon Parish. I'm President of the International Society for the Study of Women's Sexual Health, Professor of Medicine and Clinical Psychiatry at the Weill Cornell Medical College, and a general internal medicine physician. I've been on the scientific advisory board for Pfizer, SST, and Sprout Pharmaceuticals.

I understand that there may be concern that once a drug is approved about widespread use and clinicians abilities to diagnose and treat only appropriate patients. ISSWSH and its collaborators can handle this. ISSWSH is the largest international multidisciplinary academic scientific organization dedicated to research, clinical practice and education

exclusively for women's sexual disorders.

For the past 15 years, we have run extensive, live and web-based educational programs for a wide array of clinicians including primary care physicians, gynecologists, urologists, psychiatrists, psychologists, sex therapists, pelvic floor physical therapists, nurse practitioners and others.

We comprehensively address evidence-based clinical practice guidelines for prevalence, screening, diagnosis, management, coding, and the indications for pharmacologic and non-pharmacological therapy for female sexual disorders.

In addition, we actively collaborate and develop consensus publications with other large organizations dedicated to clinical practice in women's health such as the North American Menopause Society, the American College of Genecology, and the International Menopause Society. Thus we are confident that this large multi society, international network provides a robust infrastructure to ensure appropriate, safe, and selective management and treatment of female sexual disorders in the United

States and worldwide. Thank you.

MS. VAIDYA: Thank you, Sharon.

(Applause.)

MS. VAIDYA: And finally, we have Anita Clayton.

DR. CLAYTON: Anita Clayton. You've heard, Professor of Psychiatry and Clinical OB/GYN at UVA. Disclosures include research grants and consulting in sexual medicine to Palatin, S1 Biopharma, Sprout and Trimel.

The first speaker at this public mic yesterday opened with the following comment: "Today has been surreal." Let me close the second day by echoing her comment, this is surreal but let's all be honest about exactly why. We sat yesterday and heard from woman after woman after woman on her experience with FSD. Dr. Kweder summed up, well, we all heard. It was striking how similar their stories were, the consistency among them that arousal and desire were distinct, that their lack of desire was not a daily phenomenon but rather a state of being and that the impact it having on their lives and their

relationships is profoundly distressing. They were seeking access to a potential solution, not a magic pill, not some idealistic version of sex, their own normal which none of us should pretend to be an authority on.

What is surreal here is that it is 2014 and we are still debating whether or not what the patients so clearly told us is valid or whether we know better. The science and the voices of countless women have already given us that answer. Let's make good on the spirit of a patient-focused meeting. This time, let's listen and do something for them.

(Applause.)

DR. VAIDYA: Thank you, Anita. And that ends the open public comment round.

Now I'd like to call Dr. Audrey Gassman here to the stand for the closing.

DR. GASSMAN: Thank you. In the interest of knowing that many people have cabs to catch and flights, I will keep my closing remarks as painless and brief… First, I would like to thank Drs. Basson, Meston and DeRogatis for providing excellent

presentations this morning that assisted this scientific workshop.

(Applause.)

DR. GASSMAN: Second, I would like to thank all the members of our panel today for taking time out of their very busy schedules and practices to come here and provide their perspectives and their input and recommendations on the three important panel discussion topics that we had: diagnostic challenges, the clinical endpoints and the clinical instruments. Your comments and recommendations will read carefully, consider, and take back and discuss so thank you for your contribution today.

(Applause.)

DR. GASSMAN: I would also like to thank the folks that came up and spoke in the mic, very passionately sometimes, with their comments and concerns. We also have a transcriptionist and we will take all of this information back.

Finally, I would like to let everyone know that if you did not get a chance to speak or you have additional comments that you would like, we do have an

open docket and you can provide additional comments to the docket. And I believe that docket does not close until December so don't think that you have to run right home and write something out. You do have time to provide additional comments to the docket.

I would also like to thank, as yesterday they mentioned, the patients who came up and provided their perspectives. We understand and recognize that your perspectives are important and when we go back and have our discussions and deliberations, we will also be including and reviewing the discussions from yesterday.

(Applause.)

Finally, I would like to thank our audiovisual and the staff and folks from Sodexo who provided lunch, so we can't forget them in our discussions.

And with that, I'd like to say thank you for coming and have a good night and have good travels.

(Applause.)

(Whereupon, at 4:39 p.m., the meeting was adjourned.)

CERTIFICATE OF TRANSCRIPTION

I, LUCY T. TURNBULL, hereby certify that I am not the Court Reporter who reported the following proceeding and that I have typed the transcript of this proceeding using the Court Reporter's notes and recordings. The foregoing/attached transcript is a true, correct, and complete transcription of said proceeding.

November 10, 2014 _____

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