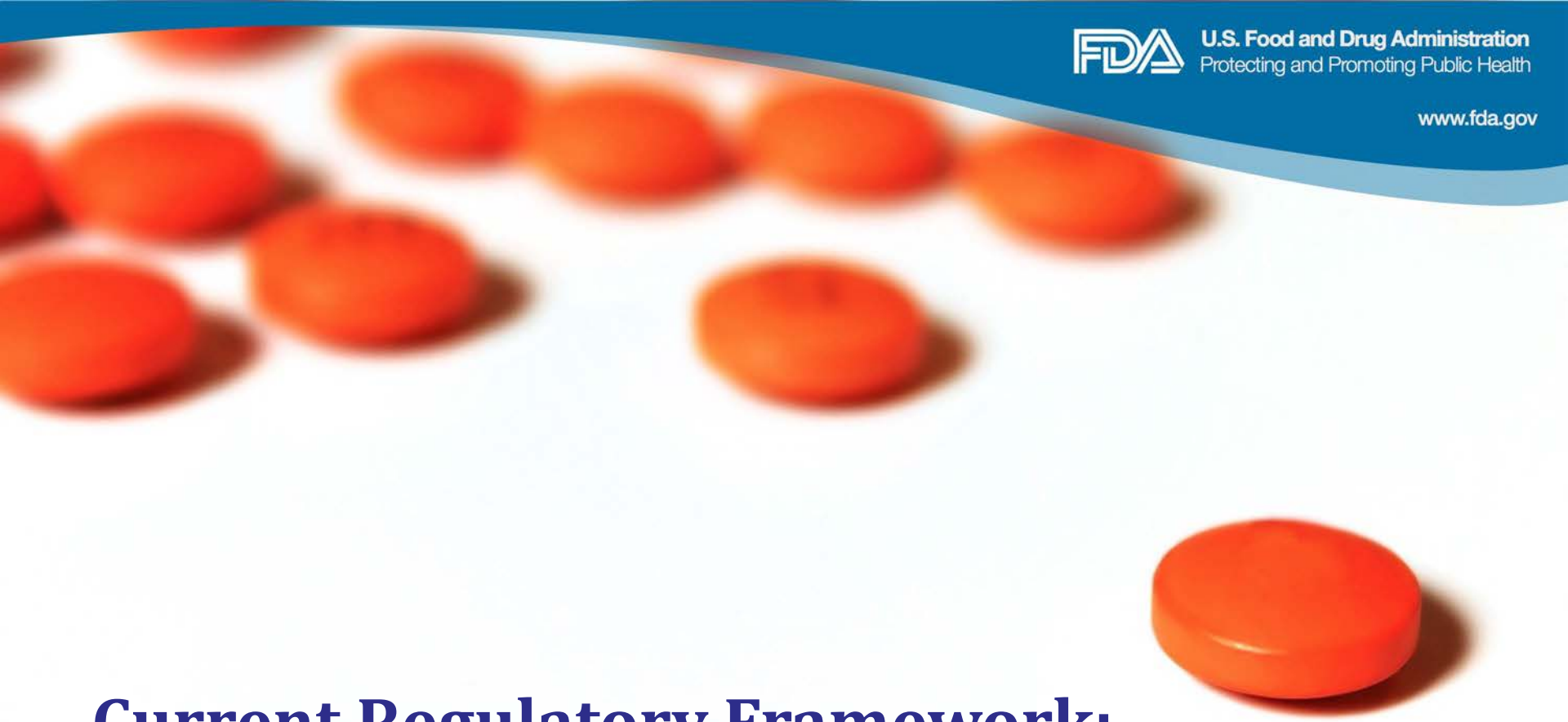


Current Regulatory Framework: Female Sexual Interest/Arousal Disorder (FSIAD)

Marcea Whitaker, MD
Clinical Reviewer, Division of Bone, Reproductive and Urologic Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

October 28, 2014

FSIAD

- New diagnosis in Diagnostic and Statistical Manual of Mental Disorders (5th Edition), DSM–5 (May 2013)
- Merged from two separate diagnoses - Hypoactive Sexual Desire Disorder (HSDD) and Female Sexual Arousal Disorder (FSAD) – in DSM-IV-TR

How is FSIAD currently diagnosed?

A. Absence or significantly reduced sexual interest/arousal for at least 6 months (with at least 3 of the following symptoms):
   1. Absent/reduced interest in sexual activity
   2. Absent/reduced sexual/erotic thoughts or fantasies
   3. No/reduced initiation of sexual activity; unresponsive to partner's attempt to initiate sexual activity
   4. Absent/reduced sexual excitement/pleasure during sexual activity in at least 75% of encounters
   5. Absent/reduced sexual interest/arousal in response to any internal or external cues (e.g., written, verbal, visual)
   6. Absent/reduced genital or non-genital sensations during sexual activity in at least 75% of sexual encounters

How is FSIAD currently diagnosed? (con't)

B. The problem causes clinically significant distress
C. The sexual dysfunction is not better explained by:
    1. Non-sexual mental disorder
    2. Severe relationship distress (e.g., partner violence) or other stressors
    3. Effects of a substance/medication or another medical condition

FSIAD in Clinical Trials – Challenges

- How to apply the new diagnostic criteria to patient enrollment?
- What combination of symptoms should be used to determine eligibility?
- How to differentiate whether the drug product treats primarily desire symptoms or arousal symptoms in the same trial?
- How should these products be labeled?
- Which PRO instruments should be used?

Patient Population

- Sexually active women with documented personal distress related to low desire or arousal difficulties
- Sponsors should:
  - Define the targeted patient population
  - Provide justification for the patient population selected
  - Provide sufficient details of the enrollment criteria

Patient Population (con't)

- Pre- and/or post-menopausal[†] women in the development program
  - Optimally, these two groups would be evaluated separately
  - If in the same trial, the studies should be powered for each subgroup due to possible differences in physiologic response to treatment

[†] See Guidance for Industry "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation"

Study Design/Location

- Two adequate and well-controlled trials (Phase 3)
- Rationale for North American trials is based on differences in:
    - Diagnosis
    - Practice of medicine
    - Cultural views
    - Subjective responses by patients

Study Duration

- Each Phase 3 trial subject evaluated for at least 24 weeks in duration to assess efficacy and safety
- An extension study that provides total exposure for at least 52 weeks will also be needed to better characterize safety in chronic use

Previously Used Endpoints

- Co-Primary Endpoints
  - Satisfactory Sexual Events (or SSEs)
  - Change in Desire or Arousal
- Key Secondary Endpoint: Distress
  - Patient-Reported Distress (5-point scale)
    - "How often do you feel bothered by low sexual desire?" †

0=never; 1=rarely; 2=occasionally; 3=frequently; 4=always

† Question 13 – Female Sexual Distress Scale-Revised

Considerations

- Magnitude of the treatment effect
- Concerns with using existing instruments (such as the FSFI) for determining efficacy in light of changing diagnostic criteria, recall period, multi-barreled concepts, etc.
- Possible constraints in the primary care setting
- Physiologic differences between populations (i.e. pre- vs. post-menopausal) that may impact efficacy and safety

Risk-Benefit

- Generalizability of trial results to patients with other co-morbidities (psychiatric and/or medical conditions)
- Potential for interactions with drugs or alcohol
- Uncommon side effects in clinical trials may affect many patients once the drug is approved

Dr. Rosemary Basson

"The Female Sexual Response"

Professor of Psychiatry
and
Director of Sexual Medicine Program
University of British Columbia

Back-up Slides

Hypoactive Sexual Desire Disorder (DSM-IV-TR)

- Persistently or recurrent 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 context of the person's life.
- The disturbances cause marked distress and interpersonal difficulty
- The sexual dysfunction is not better accounted for by another mental or medical disorder (except another sexual dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., drug or alcohol abuse, a prescription medication) or a general medical condition.

Female Sexual Arousal
(DSM-IV-TR)

- Persistent or recurrent inability to attain or to maintain until completion of sexual activity, an adequate lubrication-swelling response of sexual excitement
- The disturbance causes marked distress or interpersonal difficulty
- The sexual dysfunction is not better accounted for by another Axis I disorder (except another sexual dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medication.

Guidance for Industry

Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation

Postmenopausal Definition

- Women with 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.

Women's Sexual Response: Potential Role of Medications for Dysfunction

- Rosemary Basson MD., FRCP (UK)
- Clinical Professor, Director of Sexual Medicine
  University British Columbia
- Departments Psychiatry and OBGYN

Objectives

- Discuss current understanding of women's sexual response
- Identify women's common sexual problems
- Consider potential pharmacological intervention for dysfunctional response

Women with sexual difficulties
- otherwise healthy
- with medical conditions

Human Sexual Response

- Sexual activity is so much more than sexual intercourse or other form of penetration
- Sex is so much more than sexual activity
- Sex includes intimacy, pleasure, excitement, desire, physical sensations, physical changes
- Any model must allow variation to avoid pathologizing

Human Sexual Response

- Masters, Johnson, Lief, Kaplan 1960's & 70's
- Informed APA's DSM of sexual disorders
- Informed RCT inclusion criteria, endpoints and diagnostic instruments

Desire **extrinsic/ responsive**
intrinsic

Arousal
subjective excitement
genital & other physical changes

By the late 1980's

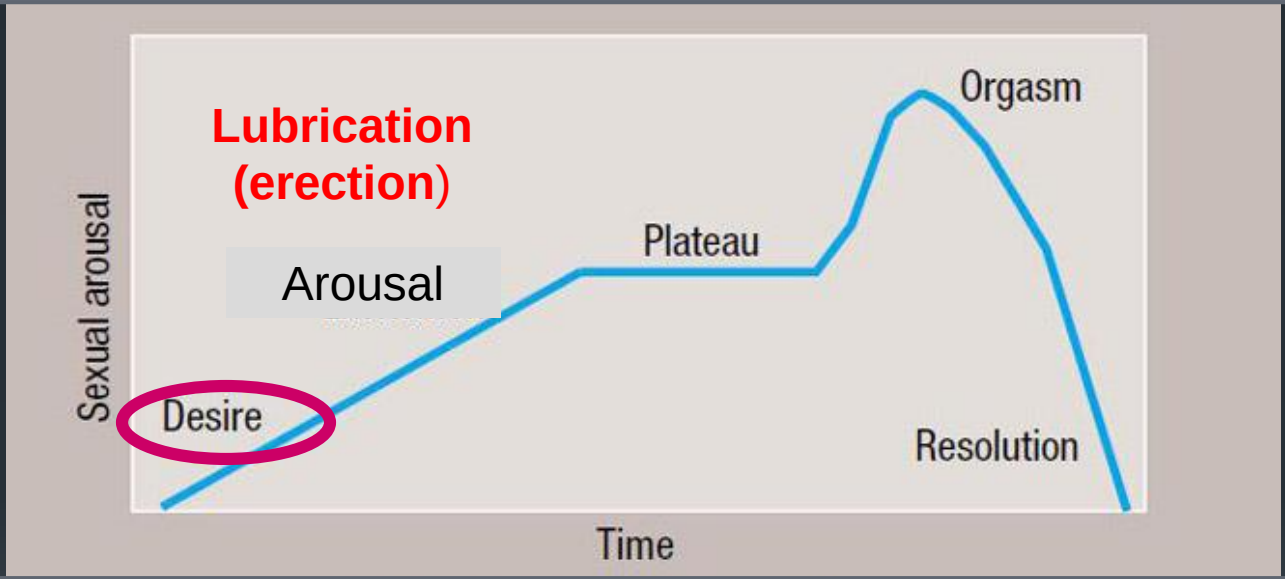
- **Responsive component of desire**
- **Subjective component of arousal**

were omitted

Tiefer 1991
Ann Rev Sex Res

Human Sex Response Cycle 1974 -1999

Linear, little variation, genitally focused, devoid of external triggers/ stimuli, desire is present (in both partners) at the outset



Not in keeping with:

- **clinical experience**
- **psychophysiological research**

other models emerged, their empirical validation followed

The Consequences of 1st Omission

- Initial, seemingly spontaneous desire confirmed by reporting sexual fantasies, became the focus of assessment of sexual desire. It's absence implied disorder.

- Women reporting responsive desire but less frequent intrinsic/ spontaneous desire would thus be deemed 'dysfunctional.' (Sand. J Sex Med 2007)

Not in keeping with the evidence

Desire/ Urge/ ‘Hunger’

- **A sense of desire at the outset and in between sexual encounters is rare or absent in most of** 3,200 mid-life women despite sexual satisfaction (Cain. J Sex Res 2003)

- **The wanting or motivation for sex is complex**
  237 reasons for – (possibly > 237 reasons not to !).
  Awareness of sexual desire / urge is not the most common reason women have sex (Meston. Arch Sex Behav 2007)

- **Desire reduces with relationship duration while sexual satisfaction & orgasm frequency increases-**
  as in 230 Australian women (Burri. J Sex Med 2014)

The Consequences of 2nd Omission

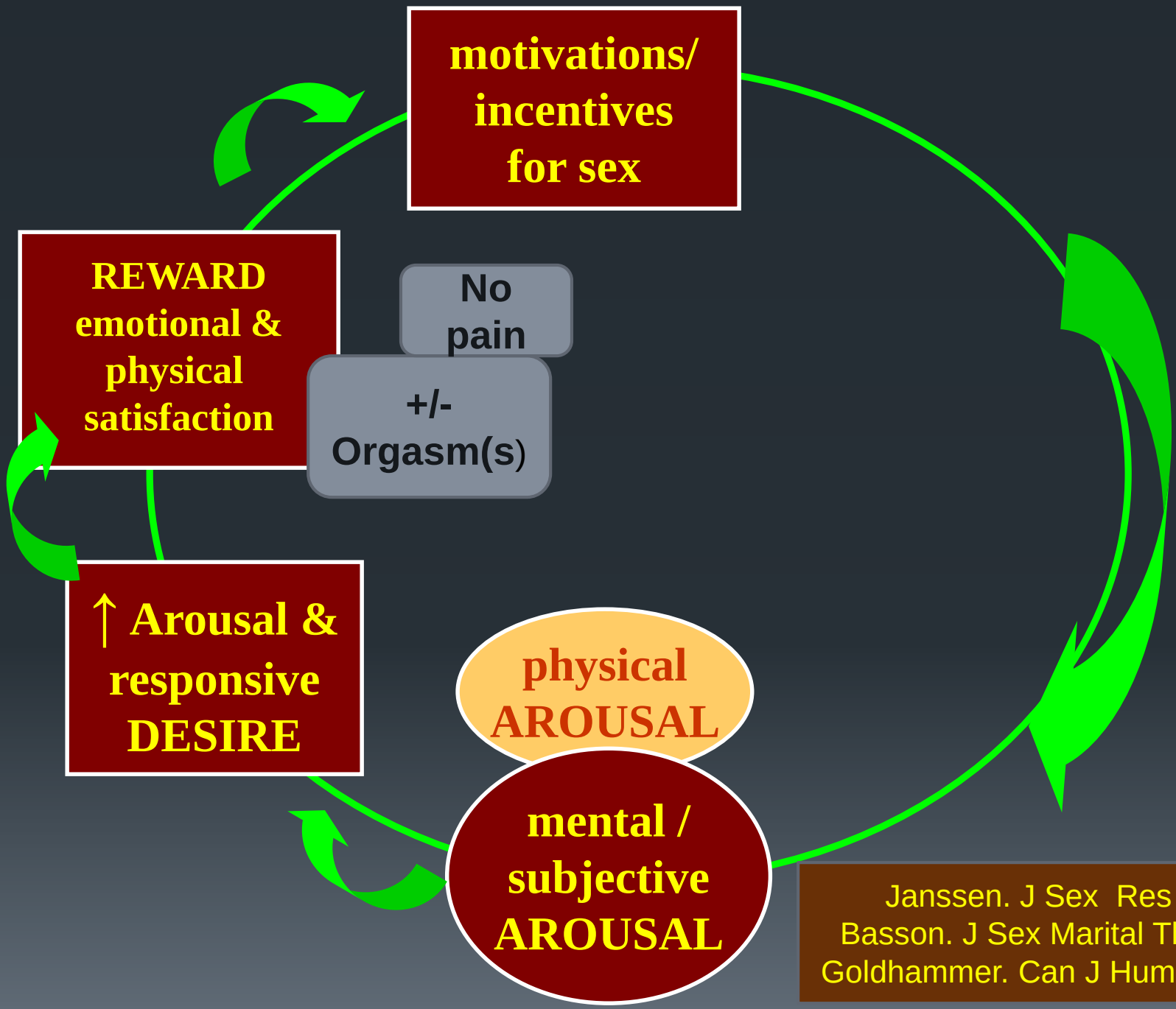
- Genital swelling/ lubrication became the focus of any assessment or enhancement of sexual arousal
- Until DSM5, subjective arousal/ excitement was ignored

Not in keeping with the evidence

Sexual Arousal

- Vaginal lubrication correlates poorly with degree of subjective arousal –sexual excitement, pleasurable sexual sensations, in women with and without sexual problems
  (Laan. J Sex Med 2008; Chivers. Arch Sex Behav 2010)

- Also vaginal changes correlate poorly with brain imaging data during visual erotic stimulation
  (Arnow J Neurosci 2009)



Janssen. J Sex Res 2000
Basson. J Sex Marital Ther 2000
Goldhammer. Can J Hum Sex 2011

motivations/ incentives for sex

Willingness to provide/guide

Sexual stimuli & required context

Emotional intimacy

Information processing

physica AROUS

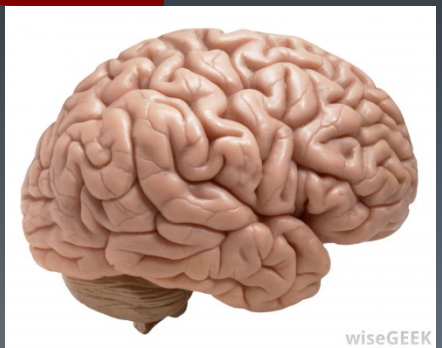
-Congestion
- ↑Sexual sensitivity

mental AROUSAL

↑ Arousal & responsive DESIRE

REWARD Emotional & physical Satisfaction

Sexual "hunger" fantasies thoughts



motivations/ incentives for sex

Willingness to provide/guide

Sexual stimuli & required context

Information processing

Physical arousal

Subjective arousal

↑ Arousal & responsive desire

REWARD Emotional & physical Satisfaction

motivations/ incentives for sex

Willingness to provide/guide

Sexual stimuli & required context

nformation processing

Physical arous

Subjective arousal

↑ Arousal & responsive desire

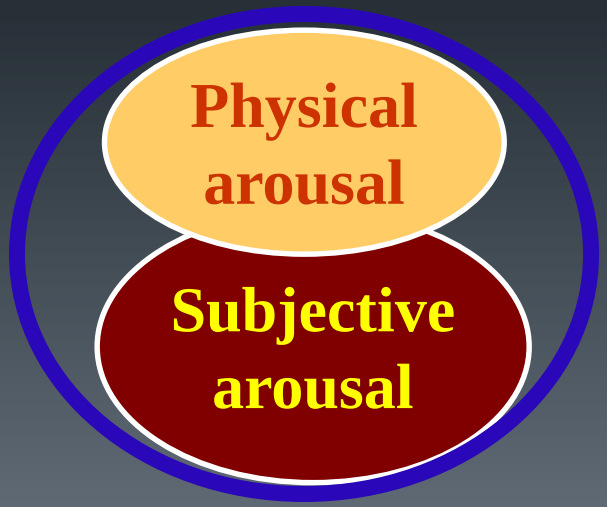
REWARD Emotional & physical Satisfaction

"I don't feel any thing"
"There is no response"
"Nothing arouses me"

Subjective (mental) arousal

1. No mental excitement
2. No sexual sensations – genital or breast tingling, throbbing
3. No awareness of genital wetness, swelling
5. Minimal sexual sensations from stimulating breast/ genitalia/ other areas

Physical (Genital) arousal



Sexual Satisfaction

- **Not equivalent to an absence of dysfunction** (Pascoal. J Sex Res 2014;51:22-30)
- **Mutual pleasure, intimacy** (Pascoal. J Sex Res 2014;51:22-30)
- **Nor is there a focus on performance or the act of intercourse** (Kleinplatz. Can J Hum Sex 2009;18 (1-2) 2009)

The Consequences of Accepting an Evidence-based Model

- Its explanation can constitute ‘therapy’.

  “There's nothing wrong with me !
  I don’t have to feel lust before I start and its OK to need emotional intimacy first”

- Feeling less ‘abnormal’, she has motivation to make the necessary changes to make sex more rewarding

- **BUT**

The Consequences of Accepting an Evidence-based Model

- HSDD criteria have designated pathology and have been the recruitment criteria for RCTs
- Medications have been trialed on women who may have been completely sexually healthy
- Dilemma – as in the (confusing) recent Endocrine Society guidelines designed to temper the widespread use of compounded and male formulations of testosterone: “harm reduction”

Meta-analysis &Guidelines on Testosterone from the Endocrine Society: 2014: many caveats due to inclusion criteria & that HSDD is discredited

- "studies recruited .. women still able to have on going sexual activity with an **average of 2-3 satisfying sexual events per month"**

- "An absence of sexual desire between sexual encounters appears to be common, **well within the range of normal female sexual experience.** Yet this absence is the target of therapy".

.. "desire for sex is just one of many reasons or incentives for sex. Studies are needed in women with low sexual interest/incentives and low arousal (and typically few orgasms) to reflect the prevalent clinical situation".

Reasons/ incentives for sex

Willingness to provide/guide

Sexual stimuli & required context

ormation ocessing

Congestion ↑Sexual sensitivity

Physica arousal

Subjective arousal

↑ Arousal & responsive desire

REWARD Emotional & physical Satisfaction

No pain

+/- Orgasm(s)

Appraisal of sexual stimuli

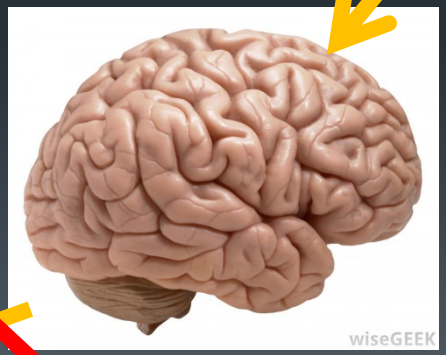
Distractions: self monitoring, expecting pain or insufficient response, thoughts & stressors irrelevant to sex
negative societal influences
no expectation of subsequent emotional closeness

Depression

Drugs

Fatigue

stimuli



Negative cognitions
Negative emotions
Nobre. Arch Sex Behav 2008

Inhibition proneness
'dual control system'
Bancroft. J Sex Res 2009

Arousal

Sexual Problems

- **Ongoing distressing difficulties may affect 10% of women - multifactorial etiology**
- **Robust evidence links to mood disorders & relationship**
  (Dennerstein. J Sex Med 2008; Mitchell. Lancet 2013)
- **Psychological factors well established**
  (Hartmann. Menopause 2004; Graham. Arch Sex Behav 2006)

Biological factors indicated:

- **Clinical Depression**
- **Medication Effects**
- **Genital problems related to estrogen-deficit**
- **Overproduction of prolactin**

Biological factors not confirmed

- Context of chronic illness - diabetes, renal failure, multiple sclerosis **comorbid depression** plus relationship factors determine dysfunction

(Lew-Starowicz. J Sex Med 2014; Bhasin. Lancet 2007)

Biological factors not confirmed

- **No correlation with testosterone deficit** – however testosterone activity is measured
  - Mass spec. testosterone
  - Mass spec. androgen metabolites to reflect both ovarian testosterone and intracellular production of testosterone from precursors - DHEA(S), A4
  - No group differences between 125 women with HSDD/ SIAD and 125 controls (Basson. Menopause 2010)

Biological factors not confirmed

- While sexual function is altered by medication affecting 5HT, dopamine, noradrenaline receptors- there is no evidence of intrinsic aberration of these neurotransmitters underlying any FSD

- Functional brain imaging while viewing erotica will be different (e.g., compatible with ↑ self monitoring) in women with and without desire complaints: this does not denote a brain disorder
  Woodard. Fertil Steril 2013; Arnow. Neurosci 2008

Common Sexual Problems

- ↓ Sexual Arousal
  - Neither mental nor physical stimuli arouse
  - Only genital stimulation is ineffective
- Chronic pain with penetrative sex
  - Premenopause – provoked vestibulodynia (PVD)
  - Estrogen-deficit related pain
- Absent orgasm despite high arousal “so close”
  - Often life-long
  - Or SSRI associated

Loss of sexual interest/ motivation

Needed Pharmacological Rx

- Effective sexually neutral antidepressants & anxiolytics

- Medication to augment cognitive therapy management of chronic dyspareunia from PVD

- Post menopause, (probable vaginal route)
  - SERM to benefit women with histories of estrogen sensitive cancers
  - Medication (likely hormonal) to restore menopausal loss of sexual sensitivity

Could a medication directly benefit lack of interest from ↓ arousal - where neither physical nor mental sexual stimuli are effective?

Probably not

- Strong link to mood.

- Often ‘adaptive’ to psychological etiology

- Meta-analyses support psychological therapies

Recent evidence: MBCT benefits low self image, mood, stress, distractions, acceptance instead of evaluation

But **medications can induce this dysfunction -** lack of interest from ↓ arousal - **theoretically supporting a pharmacological approach ??**

BUT data are scarce

- **RCTs to date have not recruited these women.**
  Women on average reported 2-3 sexually satisfying sexual events each month in published trials
- **Women reporting infrequent sex due to zero events being satisfying have not been studied**

Conclusions

- Incentives/ motivation-based sexual response
- For women, intimacy incentives predominate

- **Subjective Arousal** and **Responsive Desire** again acknowledged, coexist, triggered by stimuli

- Seemingly ‘innate/ spontaneous’ desire is variably sensed, typically fades with relationship duration and with age while sexual satisfaction mostly increases

Thank you for listening

TRANSITIONING FROM DSM-IV-TR TO DSM-5: DIAGNOSTIC CHALLENGES

Cindy M. Meston, Ph.D.
University of Texas at Austin

The Sexual Psychophysiology Laboratory
The University of Texas at Austin

Outline

- Critique of DSM-IV-TR HSDD
- Critique of DSM-IV-TR FSAD
- DSM-5 Female Sexual Interest/Arousal Disorder (FSIAD): Justification and Critique
- Practical implications of diagnosing desire problems with DSM-5 FSIAD criteria
- Practical implications of diagnosing arousal problems with DSM-5 FSIAD criteria

DSM-IV-TR Hypoactive Sexual Desire Disorder

A. 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.
B. The disturbance causes marked distress or interpersonal difficulty.
C. The sexual dysfunction is not better accounted for by another Axis I disorder (except another Sexual Dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Lifelong vs. Acquired

Generalized vs. Situational

Due to Psychological Factors; Due to Combined Factors

Main Criticisms of HSDD Criteria

- Focus on absent or deficient sexual fantasies and desire for sexual activity may not be a good definition of desire in women.
  - Absence of sexual fantasies normative for majority of women.
  - Women engage in sexual activity for reasons other than desire.
  - Implies desire is “spontaneous” versus “triggered.”

DSM-IV-TR Female Sexual Arousal Disorder

A. Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement.
B. The disturbance causes marked distress or interpersonal difficulty.
C. The sexual dysfunction is not better accounted for by another Axis I disorder (except another Sexual Dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Lifelong vs. Acquired

Generalized vs. Situational

Due to Psychological Factors; Due to Combined Factors

Main Criticisms of FSAD Criteria

- Exclusive focus on genital lubrication-swelling response not justified.
  - There are many “extragenital” physiological changes as well as cognitive/emotional changes that occur during sexual arousal.
  - Little evidence that women with FSAD have impaired genital response.
  - Desynchrony between subjective and physiological sexual arousal in women.

Recommendations From International Multidisciplinary Panel (Basson et al., 2002; 2003)

Three subtypes of FSAD:

(1) Subjective sexual arousal disorder;

(2) Genital sexual arousal disorder;

(3) Combined genital and subjective arousal disorder

DSM-5 Female Sexual Interest/Arousal Disorder

A. Lack of, or significantly reduced, sexual interest/arousal, as manifested by at least three of the following:
   1. Absent/reduced interest in sexual activity.
   2. Absent/reduced sexual/erotic thoughts or fantasies.
   3. No/reduced initiation of sexual activity, and typically unreceptive to a partner's attempts to initiate.
   4. Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (approximately 75%-100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts).
   5. Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (e.g., written, verbal, visual).
   6. Absent/reduced genital or nongenital sensations during sexual activity in almost all or all (approximately 75%-100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts).

DSM-5 Female Sexual Interest/Arousal Disorder (con't)

B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.
C. The symptoms in Criterion A cause clinically significant distress in the individual.
D. The sexual dysfunction is not better accounted for by a nonsexual mental disorder or as a consequence of severe relationship distress (e.g., partner violence) or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

Lifelong vs. Acquired

Generalized vs. Situational

Mild vs. Moderate vs. Severe

Justification for Combining Desire and Arousal Disorders in the DSM-5

- High overlap between desire and arousal in women.
  - Desire and arousal problem often coexist in women.
  - High correlations between validated measures of desire and arousal.
  - Treatments for desire often improve arousal.

FSFI Domain Intercorrelations

	Desire	Arousal	Lubrication	Orgasm	Satisfaction	Pain
D	1.00					
A	**0.76**	1.00				
L	0.56	0.75	1.00			
O	0.54	0.81	0.68	1.00		
S	0.60	0.80	0.62	0.70	1.00	
P	0.37	0.47	0.64	0.41	0.53	1.00

From: Rosen et al. (2000). JSMT, 26: 191-208.

Implications for Diagnosing Desire Problems with FSIAD Criteria

A. Lack of, or significantly reduced, sexual interest/arousal, as manifested by at least three of the following:
   1. Absent/reduced interest in sexual activity.
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Implications for Diagnosing Arousal Problems with FSIAD Criteria

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Measurement of Outcomes with PRO's

Leonard R. Derogatis, Ph.D.

Director, Maryland Center for Sexual Health
Associate Professor of Psychiatry
Johns Hopkins Univ. School of Medicine

Origins of the term PRO

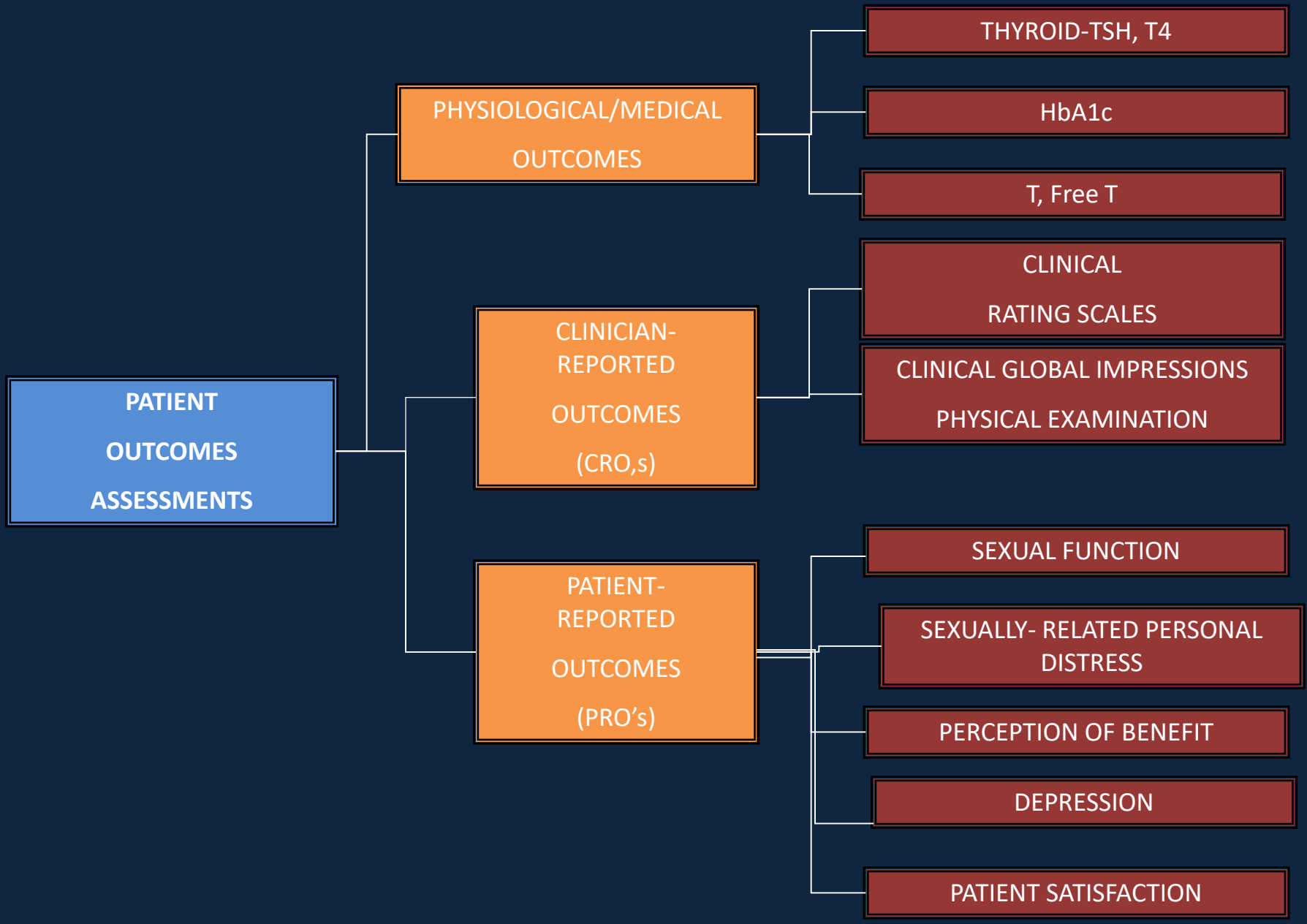
- The term “PRO” is an acronym proposed by the FDA to represent “patient reported outcomes”.

- It is meant to reflect any outcome based on self-report data provided by patients and used in the regulatory review process.

Burke, L. Acceptable evidence for pharmaceutical advertising and labeling. DIA Workshop on Pharmacoeconomics and Quality of Life Labeling and Marketing Claims. 2000, Oct. 3rd; New Orleans.

Acquadro, C., Berzon, R., Dubois, D., Leidy, N.K., Marquis, P., Revicki, D., Rothman, M., for the PRO Harmonization Group. Incorporating the patient’s perspective into drug development and communication: Value in Health,2003, (6): 5; 522-531.

OUTCOMES ASSESSMENT MODALITIES



Leonard R. Derogatis, 2014

Psychological Assessment & Precision of Measurement

- **Psychological Variables tend to be hypothetical constructs which are operationally defined by PRO's using psychometric methods, and are measured on ordinal-approaching- interval scales.**

- Physical e.g., physiological variables tend to reflect tangible physical entities measured on true ratio scales.

- These scale differences in the measurement of constructs versus tangible entities result in more sophisticated and powerful measurement for physical variables.

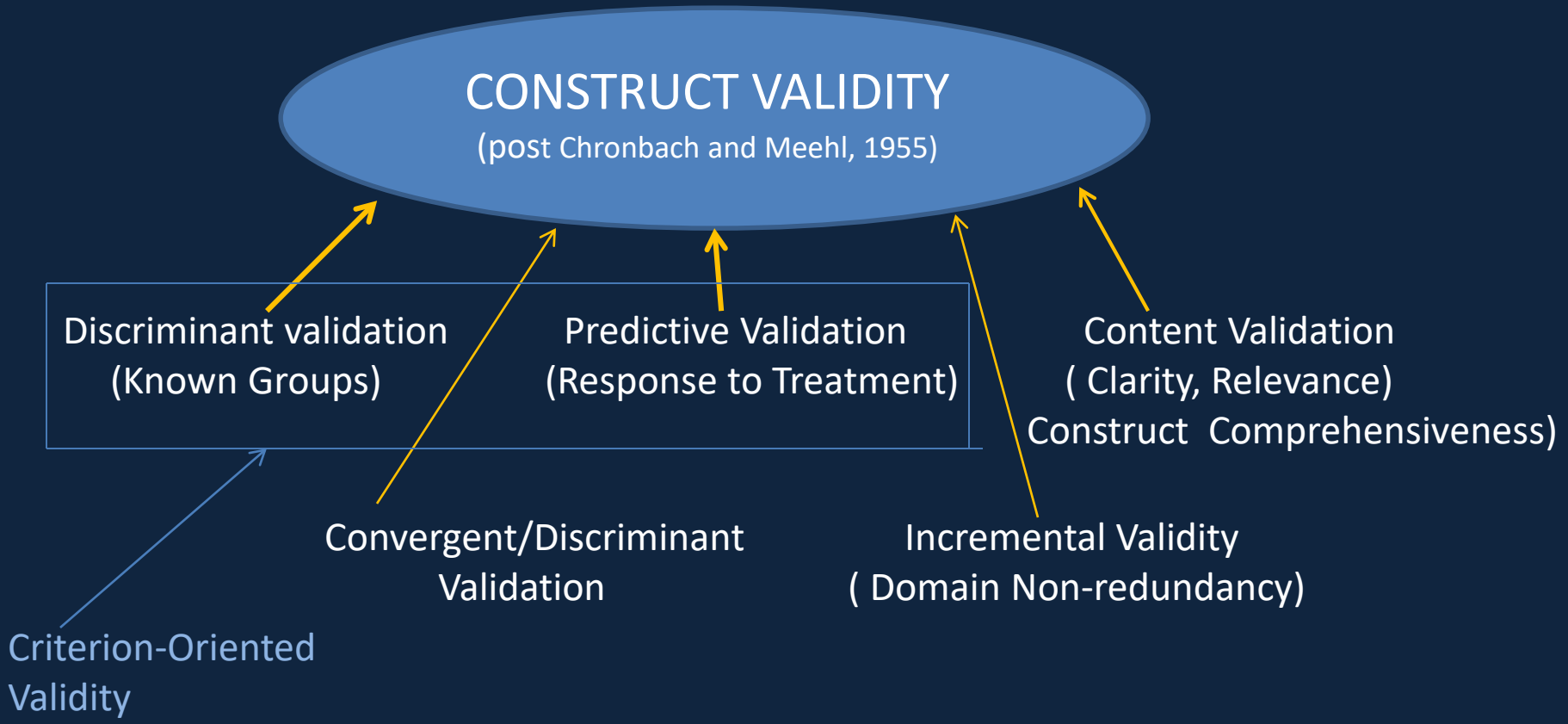
- This does not mean that psychometric measurement is "soft" or unscientific, it simply means that it is less precise.

Leonard R. Derogatis, 2014

“ It is often 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. ”

John Tukey

Construct Validation Process



Leonard R. Derogatis, 2014

“The validation process is [akin to] an expanding network of circumstantial evidence supporting the validity of the test instrument .”

J. Nunnally, *Psychometric Theory, 1967*

“The operations involved in validating a psychological instrument [equate] with those required in testing a scientific theory.”

S. Messick, Amer. J. Psychol., 1995;50:741-749

Reliability

PRO	Test-Retest	Internal Consistency	Inter-rater
ASEX	0.80	0.91	
CSFQ	0.45-1.00	0.64-0.80	–
DISF-SR	0.80-0.90	0.74-0.80	0.84-0.92 (interview))
FSFI	0.79-0.88	0.89-0.97	–
PFSF	0.67-0.84	0.80-0.94	
SFQ28	0.73-0.89	0.65-0.91	
DSDS Screener	0.89-0.96 Items # 1-4	0.79 Items # 1-4	
FSDS-R (Distress)	0.87-0.93	0.93	

General Description & Validation Data

PRO	No. of Items	Admn Time	Domains	Criterion Oriented Known Groups	Criterion Oriented Therap. Respon.	Ct. Val	Norms
ASEX	5	7-8 min	5 plus Total Scr.	YES	YES	NO	NO
CSFQ	35	20+ min	5 plus Total Scr.	YES	YES	NO	YES
DISF	25	15+ min	5 plus Total Scr.	YES	YES	NO	YES
FSFI	19	15 min	6 plus Total Scr.	YES	YES	YES	YES
PFSF	37	20+ min	7 plus Total Scr.	YES	YES	YES	NO
SFQ28	28	15+ min	8 plus Total Scr.	YES	YES	YES	YES
DSDS Screener	5	5-7 min	1	YES Sn/Sp=.84-.88	N/A	NO	N/A
FSDS-R Distress	13	10 min	Total Score	YES Sn/Sp=.93	YES	NO	YES

Recommendations Regarding PRO'S:

- concern issues have been the focus of consistent debate
- represent suggestions not directives or mandates
- intended to have a primary heuristic value
- addressing them should be undertaken via a collaborative effort

Recommendations Regarding PRO'S: HOW VALIDATED DO PRO's HAVE TO BE ?

Minimum Criteria for term "Validated"

- Clear evidence of acceptable Test-Retest and Internal Consistency Reliabilities.

- Clear evidence of comprehensive Content Validity (incl. content representation, clarity, relevance).

- Compelling evidence of relevant Discriminant Validity (e.g., Known Groups).

- Compelling evidence of relevant Predictive Validity (e.g., Responsiveness).

fRecommendations Regarding PRO's NORMS:

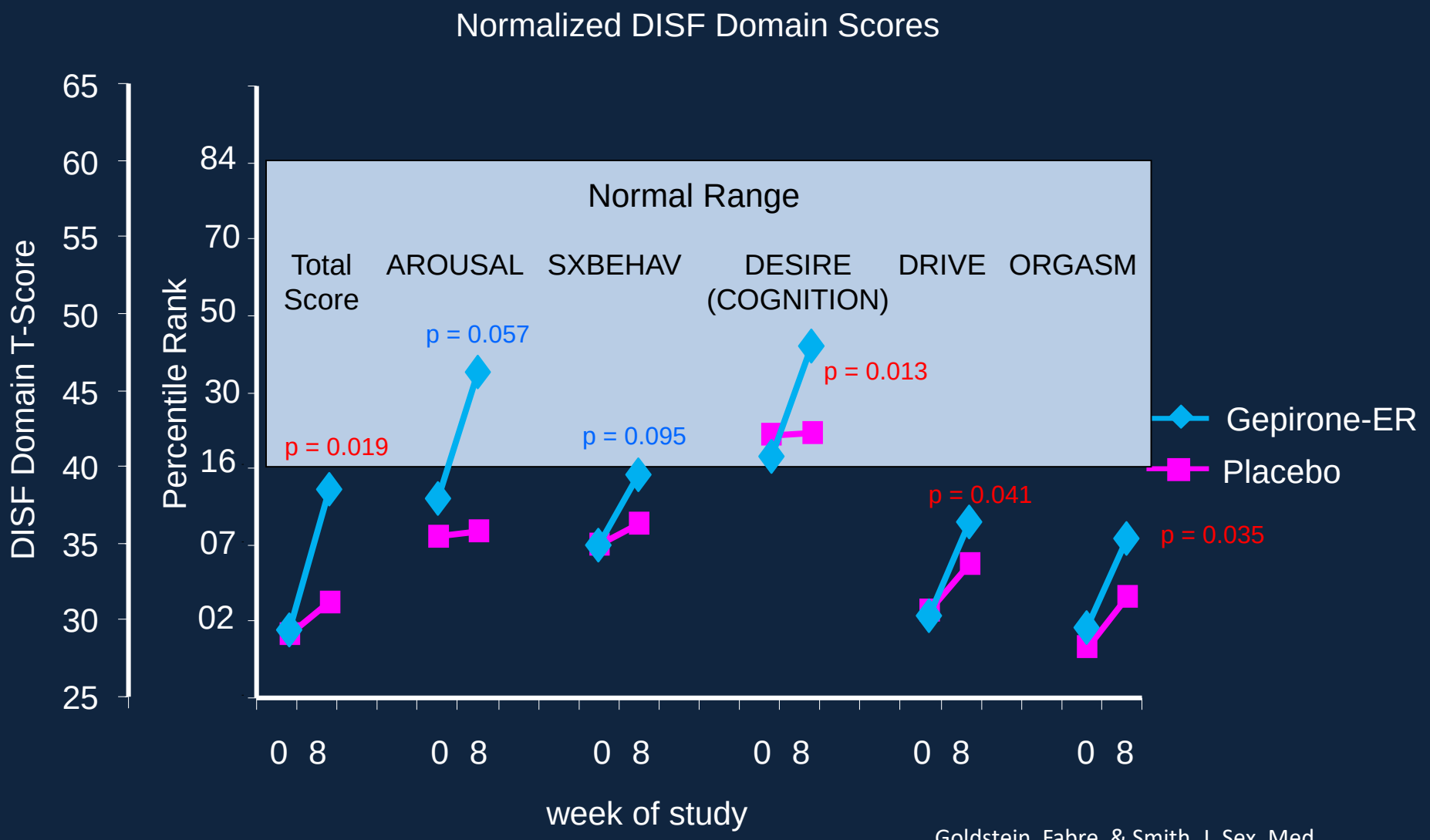
- True norms for outcomes instruments(as opposed to cut scores and raw score increments) are rarely developed and utilized.

- The failure to develop PRO norms results in the loss of a substantial amount of information about the absolute and relative efficacy of drugs.

- This is particularly true when issues such as *clinical significance are* being assessed.

Leonard R. Derogatis, 2014

Gepirone-ER Effect on Sexual Function in Women



Goldstein, Fabre, & Smith, J .Sex. Med., 2010

Recommendations Regarding PRO's

Recall Period: We have consistently debated the acceptable recall period for various PRO's in a variety of populations with uneven progress having been made on this issue.

- 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 recall with the use of longer periods.

- The counter argument is that a number of the PRO's on the previous list have already demonstrated high reliability, "known groups" validity and "treatment responsiveness with longer (e.g., 28 day) recall periods

In addition,

- Forgetting results in unreliability and increases in error of measurement. Since reliability is a necessary condition for valid measurement, if these PRO's have demonstrated responsiveness and discriminative validity (i.e., valid measurement), the issue of recall period should no longer be a issue of debate for the PRO (in that specific population) .

Recommendations Regarding PRO's CONTENT VALIDITY:

- PRO Guidance (Dec., 2009) states," …the items and domains of an instrument should be *appropriate and comprehensive* relative to its intended measurement concept, population, and use."

- The operations by which items and domains are deemed *appropriate and comprehensive should be m*ore explicitly defined.

  - What is the minimum number of patients required for focus groups and cognitive debriefing to be judged sufficient?
  - What specific criteria determine appropriateness?
  - How is comprehensiveness defined?
  - If "concept saturation" is to be formally accepted as a criterion for sufficiency of PRO content, what is the recommended number of respondents contributing *no new content* to establish that saturation has been reached?

Conclusions

- PRO instruments serve a very important purpose in measuring outcomes in clinical trials in FSD, through assessing and quantifying those variables and constructs for which there are no physical equivalents.

- They are distinguished from physical measurement not by scientific quality, but rather level of precision.

- Much more can be done to make optimum use of PRO's to elucidate the efficacy of our treatments. The effort needs to include the FDA, clinicians, and industry working together collaboratively.

Assessing Patient-Reported Outcomes: A Regulatory Perspective

Ashley F. Slagle, MS, PhD
Office of New Drugs Study Endpoints
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

October 28, 2014

Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

Purpose of "Outcome Assessment"

- To determine whether or not a drug has been shown to provide benefit to patients
- A conclusion of treatment benefit is described in labeling in terms of the concept of interest (outcome) measured
- One of the most important aspects of drug development is how that benefit is measured

Treatment Benefit

- Treatment benefit is demonstrated by evidence that the treatment has a positive impact on how a person with the condition or disease:
  - Survives
  - Feels or Functions in daily life

Evidentiary Standards to Document Treatment Benefit

- Documented by "Substantial evidence" (21 CFR 201.56(a)(3))
- Evidence from "Adequate and well-controlled clinical trials"
- The methods of assessment are "well-defined and reliable" (21 CFR 314.126)

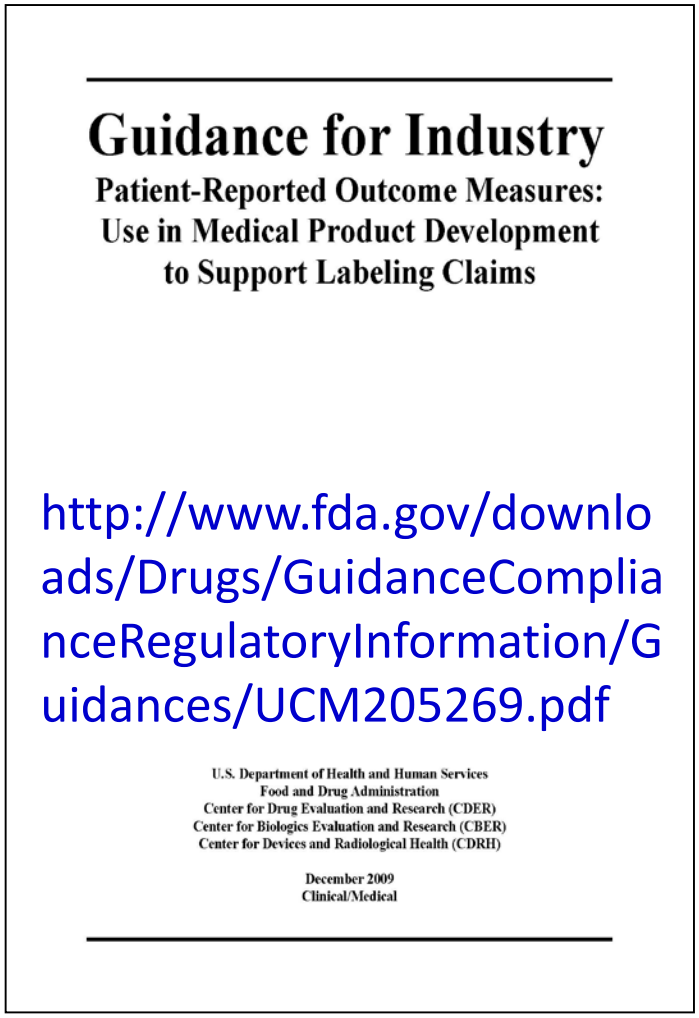
Types of Outcome Assessments

- Survival
- Biomarkers
  - A physiologic, pathologic, or anatomic characteristic that is objectively measured and evaluated as an indicator of some normal or abnormal biologic function, process or response to a therapeutic intervention
- Clinical outcome assessments (COAs)
  - Performance outcomes (PerfOs)
  - Clinician-reported outcomes (ClinROs)
  - Observer-reported outcomes (ObsROs)
  - **Patient-reported outcomes (PROs)**

When is a PRO Assessment Adequate for use in *A&WC* Studies?

- Regulatory standard: measures are *well-defined and reliable*
  - Empiric evidence demonstrates that the score quantifies the concept of interest in the targeted context of use
- What does this mean?
  - This means measuring the right thing (concept of interest), in the right way in a defined population (targeted context of use), and the score that quantifies that 'thing' does so accurately and reliably, so that the effects seen in the outcome assessment can be interpreted as a clear treatment benefit.

Good Measurement Principles



Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

- Defines good measurement principles to consider for "well-defined and reliable" (21 CFR 314.126) PRO measures intended to provide evidence of treatment benefit
- All COAs can benefit from the good measurement principles described within the guidance
- Provides optimal approach to PRO development; flexibility and judgment sometimes needed to meet practical demands

Well-defined and Reliable

- The tool adequately measures the concept of interest in the context or clinical setting of interest
- To assess this, we review the tool's measurement properties:
  - Content validity
  - Construct validity
  - Reliability
  - Ability to detect change
  - Information to support interpretation of meaningful change

Clinical Outcome Assessment Considerations

- Not all patient reported, clinical-reported, observer-reported, or performance outcome assessments are appropriate Clinical Outcome Assessments
  - May be useful for other purposes:
    - Diagnostic
    - Prognostic
    - Trial eligibility and trial enrichment
    - Epidemiologic or population studies
    - Clinical practice decision-making
  - Measures used successfully for these other purposes will not necessarily be appropriate for clinical trial outcomes assessments, for example:
    - "Validated" checklist of symptoms may not detect change in severity of symptoms
    - Diagnostic tools are broad to identify all patients, but may be too broad for use as outcome assessments as not all patients will experience all (or most) elements used for diagnosis

Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

1 Understanding the Disease or Condition

Natural history of the disease or condition
- Onset/Duration/Resolution
- Diagnosis
- Pathophysiology
- Range of manifestations

Patient subpopulations
- By severity
- By onset
- By comorbidities
- By phenotype

Health care environment
- Treatment alternatives
- Clinical care standards
- Health care system perspective

Patient/caregiver perspectives
- Definition of treatment benefit
- Benefit-risk tradeoffs
- Impact of disease

2 Conceptualizing Treatment Benefit

A. Identify the *meaningful health aspect* that is the intended benefit to patients in their daily lives
- Survives (e.g., length of survival)
- Feels (e.g., symptom severity)
- Functions (e.g., walking ability)

B. Identify the measureable *concept of interest* that represents the meaningful health aspect, which can be:
- Equivalent to the meaningful health aspect (e.g., patients' self-reported ambulatory activities in daily life) OR
- Distinct from, but related to the meaningful health aspect (e.g., 6-minute walk test)

C. Define context of use for clinical trials, e.g.:
- Disease/Condition entry criteria
- Clinical trial design
- Endpoint positioning

D. Consider appropriate clinical outcome assessment type(s):
- Patient-Reported Outcome (PRO)
- Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- Performance Outcome (motor, sensory, cognition)

3 Selecting/Developing the Outcome Measure

A. Search for existing clinical outcome assessment measuring the concept(s) of interest in the context of use :
- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

B. Begin clinical outcome assessment development
- Document content validity (qualitative or mixed methods research)
- Evaluate cross-sectional measurement properties (reliability and construct validity)
- Create user manual
- Consider submitting to FDA for qualification for use in exploratory studies

C. Complete clinical outcome assessment development:
- Document longitudinal measurement properties (construct validity, ability to detect change)
- Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- Submit to FDA for qualification as effectiveness endpoint to support claims

Updated on March 14, 2014

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
http://www.fda.gov/Drugs

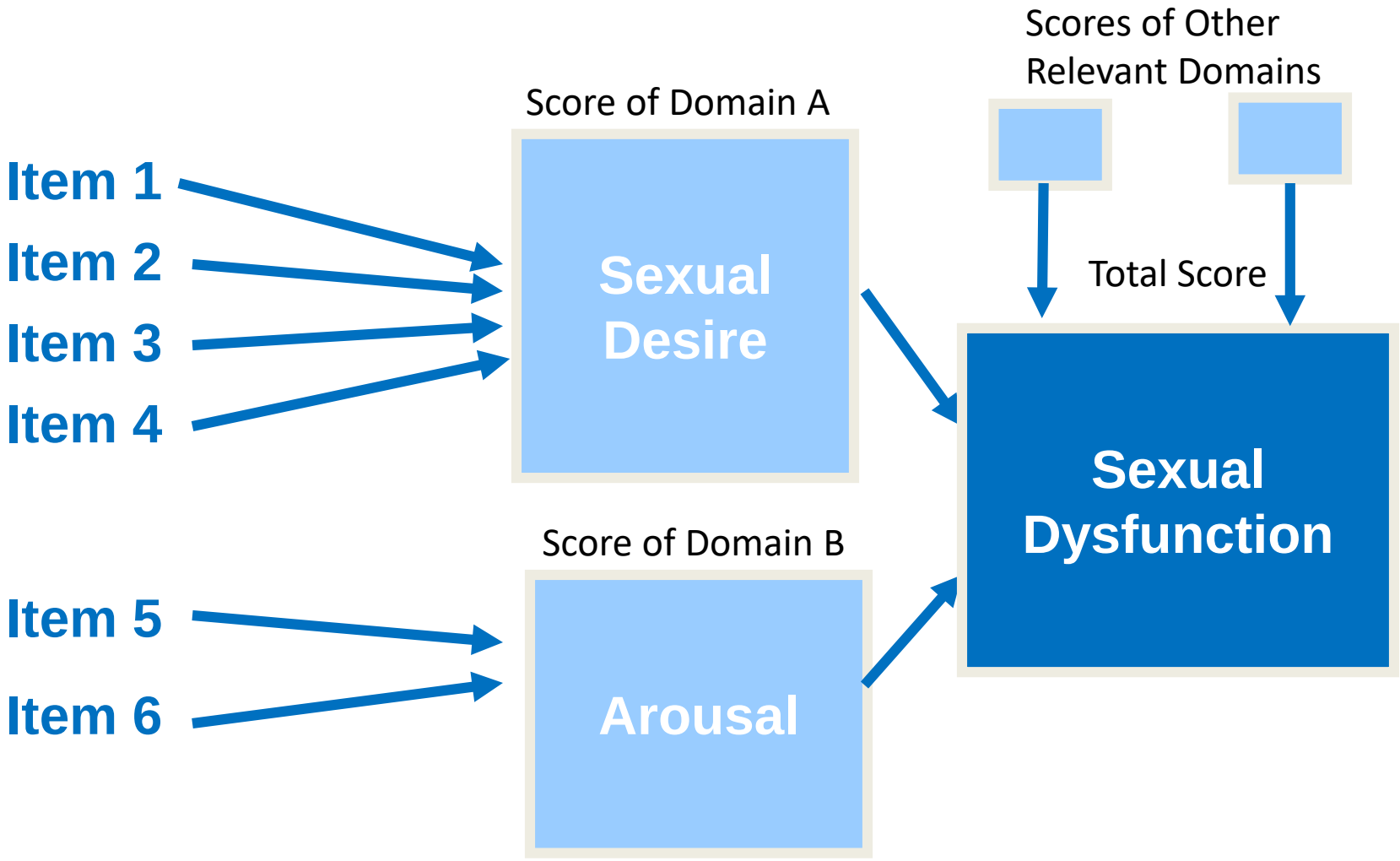
Context of Use

- Disease definition
- Disease characteristics
- Clinical characteristics
- Demographics
- Setting
- General plan for study design
- Characteristics of the study medication
- Endpoint positioning
- Type of claim(s) sought

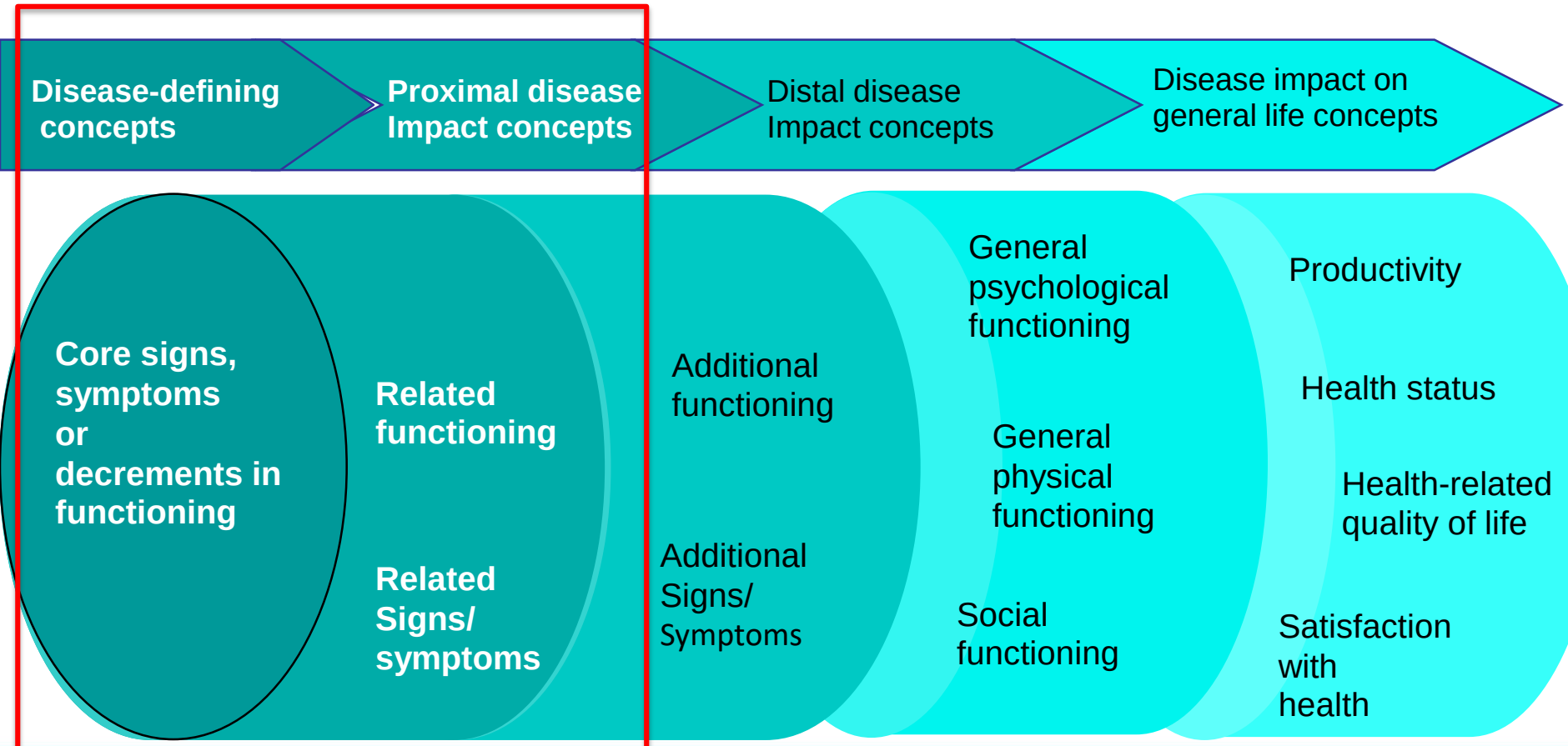
Concepts of Interest

- What concepts are relevant in that clinical context?
  - Satisfying Sexual Events
  - Sexual desire/interest
  - Distress related to sexual function
  - Arousal
  - Others
- Patient input is key

Conceptual Framework of a Clinical Outcome Assessment



Concept of Interest
Evidence of Treatment Benefit (Proximal to Distal)

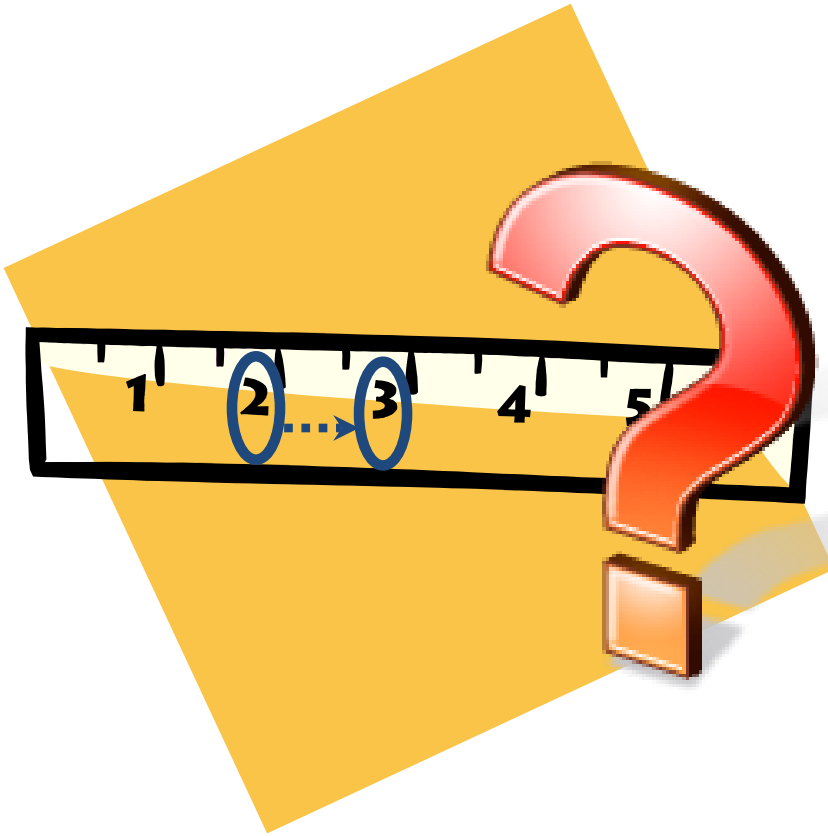


Challenges with some PRO assessments: Satisfactory Sexual Events

- Core disease defining symptom?
- Proximal or distal impact?
- What contributes to “satisfaction”?

Challenges with some PRO assessments: Content

- Multi-barreled items, unclear what is driving the score change
  - Imagine one single question asks: please rate your interest in sexual activity, initiation of sexual activity, feeling receptive to a partner's initiation, having erotic thoughts/fantasies, feeling pleasure during sexual activity, and genital sensations during sex

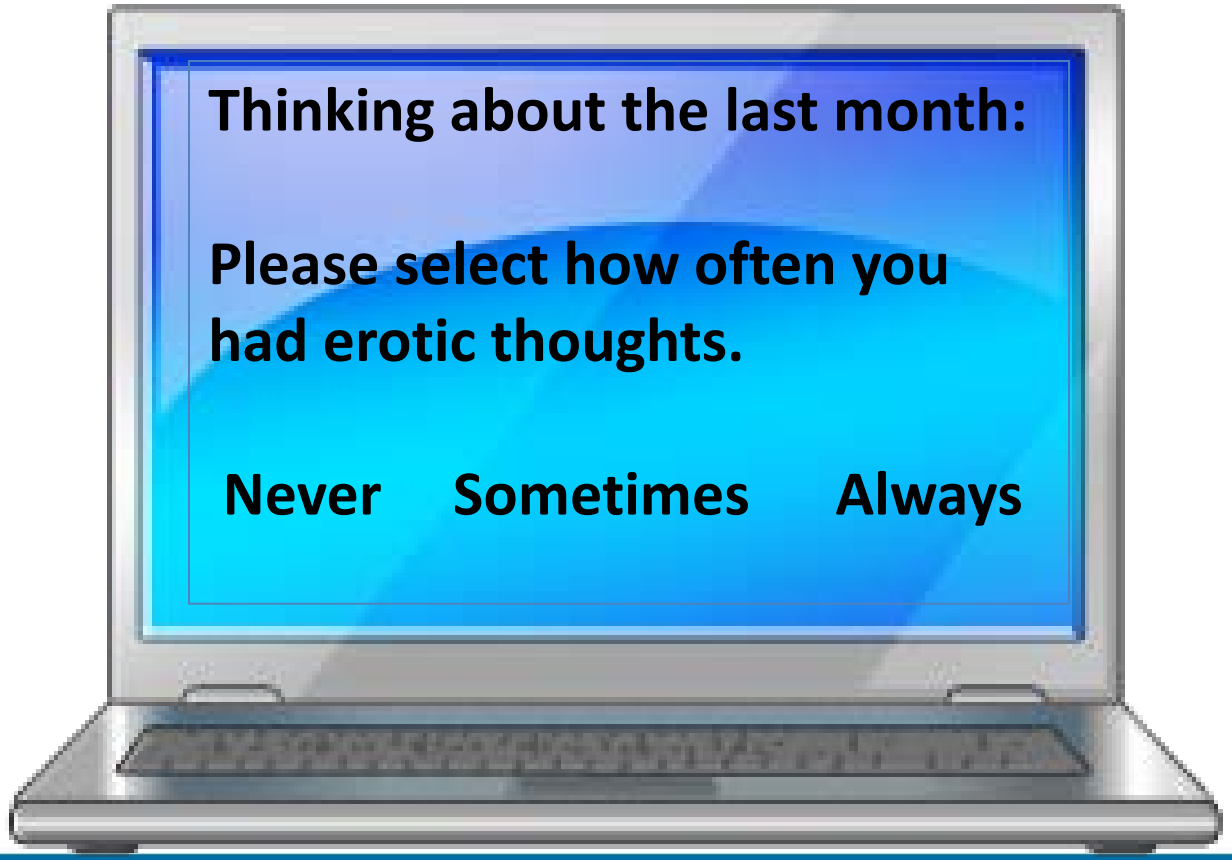


Challenges with some PRO assessments: Content

- Do clinical trial participants consistently interpret and understand the questions on the PRO assessment?
  - For example, what does *sexual activity* mean to different patients? *Genital sensations*? *Desire*?

Challenges with some PRO assessments: Content

- Response options make detection of treatment benefit difficult

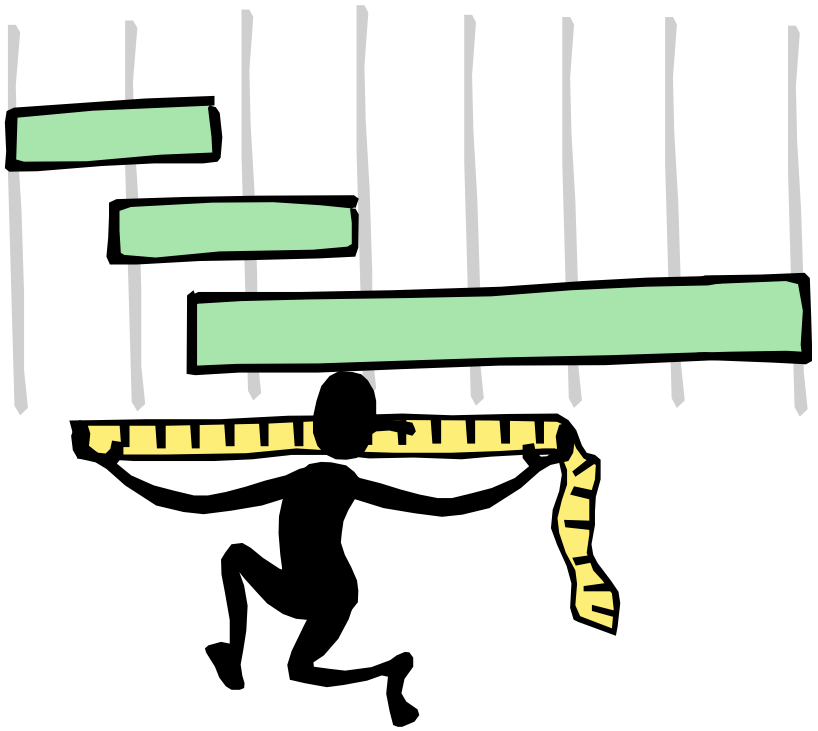


Challenges with some PRO assessments: Recall Periods

- What is the most appropriate recall period?
  - Depends on what is being measured
  - How do patients summarize daily or weekly variation of a symptom when reflecting back over a month?
  - Typical recommendations encourage more frequent (e.g., daily) assessments to help limit variability and potential bias
    - Think about PRO assessment administration schedules that can limit patient burden

Challenges with some PRO assessments: Meaningful Change

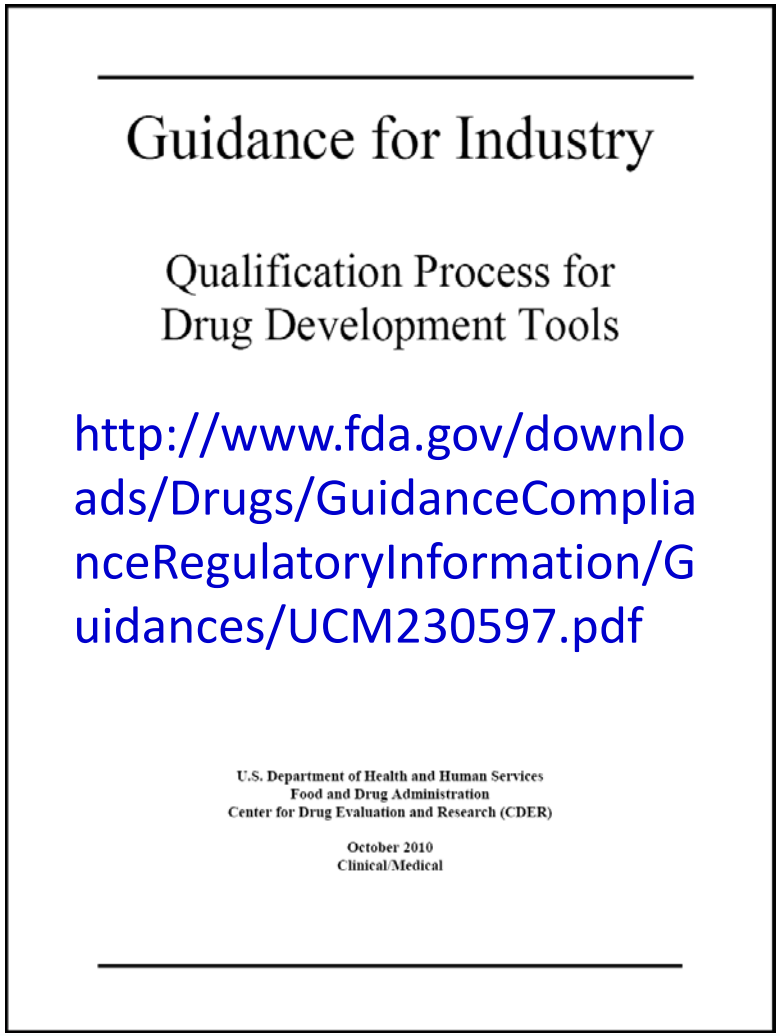
- How much change is meaningful?



How FDA Can Help: Providing Advice on PRO Assessments

- Provide advice and recommendations on PRO assessments:
  - For individual drug development programs (within an IND)
  - Through the Drug Development Tool (DDT) Clinical Outcome Assessment Qualification Program

DDT Qualification Guidance



Guidance for Industry

Qualification Process for
Drug Development Tools

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

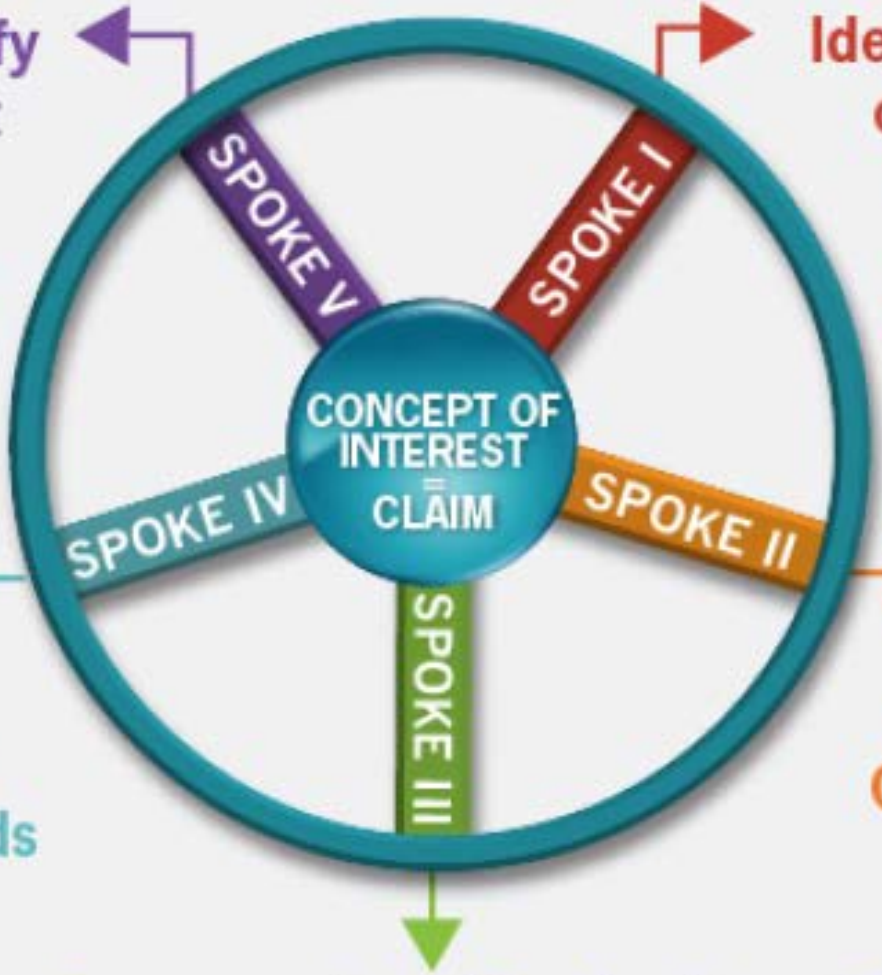
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2010
Clinical/Medical

- Describe a process NOT evidentiary standards
- Qualification process described for Biomarkers, Animal Models, and Clinical Outcome Assessments (COA)
- Final Guidance 2014

Qualification of

CLINICAL OUTCOME ASSESSMENTS (COAs)



Identify Context of Use (COU) and Concept of Interest (COI)

Draft Instrument and Evaluate Content Validity

Cross-sectional Evaluation of Other Measurement Properties

Longitudinal Evaluation of Measurement Properties/ Interpretation Methods

Modify Instrument

COA DDT Qualification Website

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm

Female Sexual Interest/Arousal Disorder Scientific Workshop

Panel Discussion Topics

October 28, 2014

Panel Discussion Topic 1: Diagnostic Challenges

1. What do you view as the strengths and weaknesses of these diagnostic criteria when used in clinical practice?
2. What do you view as the strengths and weaknesses of these diagnostic criteria when used for defining inclusion and exclusion criteria for clinical trials that will test drug products?
3. How would you precisely define and quantify each of the 6 indicators of absent or reduced interest/arousal? For example:
    a. How would you define and quantify “reduced frequency?” How much reduction in frequency is needed to meet the criteria for FSIAD?

Panel Discussion Topic 1: Diagnostic Challenges

b. How would you define other terminologies, such as “sexual activity”, “interest”, “arousal”, “sexual excitement/pleasure during sexual activity”, “internal sexual/erotic cues”, “non-genital sensations”?

4. How would you define or quantify “significant distress?”

5. How would you define or quantify “severe relationship stress” in patients who are not experiencing partner violence?

6. Is input from the sexual partner needed or useful?

Panel Discussion Topic 2: Clinical Trial Endpoints: Current Challenges and Future Directions

1. For a drug intended to improve female sexual desire, FDA has recommended that the drug show improvement compared to placebo in two co-primary efficacy endpoints (satisfying sexual events and sexual desire) and one key secondary efficacy endpoint (distress because of low sexual desire). What would you recommend as the key endpoints for assessing the efficacy of drugs intended to treat FSIAD or aspects of FSIAD? Possibilities include, but are not limited to:
   a. Improvement in satisfying sexual events
   b. Improvement in sexual desire
   c. Improvement in sexual arousal
   d. Reduction in distress experienced because of low desire or arousal
   e. Others

Panel Discussion Topic 2: Clinical Trial Endpoints: Current Challenges and Future Directions

2. What are the strengths and weaknesses of each of the efficacy endpoints above as well as any others that you are recommending?

3. What should be the appropriate recall period in a clinical trial for measuring:
   a. Satisfying sexual events?
   b. Sexual desire?
   c. Sexual arousal?
   d. Distress?
   e. Other endpoints that you are recommending?

Panel Discussion Topic 2: Clinical Trial Endpoints: Current Challenges and Future Directions

4. Should the recall period be the same for all of the efficacy endpoints?

5. Some drugs may be intended for use on an as-needed basis whereas others may be intended for daily administration. Should the recall periods discussed above depend on whether the product is intended for use on an as-needed basis or for daily use?

Panel Discussion Topic 3: Clinical Trial Instruments and Other Design Features: Current Challenges, Future Directions, and Generalizability to Clinical Practice

1. What do you view as the strengths and weaknesses of the following instruments for use as key efficacy endpoints in clinical trials that will test drug products?
   a. The Female Sexual Function Index (FSFI) to assess desire or arousal
   b. The Female Sexual Distress Scale – Revised (FSDS-R) to assess distress

2. Do you see a role for evaluating sex or behavioral therapy as an adjunctive treatment to drug therapy?

Panel Discussion Topic 3: Clinical Trial Instruments and Other Design Features: Current Challenges, Future Directions, and Generalizability to Clinical Practice

3. FDA has a long-standing interest of encouraging sponsors to include subjects in their clinical trials who are representative of the patient population who will use the drug in clinical practice. Otherwise, unnecessary exclusions can raise concerns about the generalizability of the findings. The presence of certain diseases or conditions (for example, depression or other medical conditions that may be associated with sexual dysfunction) may confound our assessment of the treatment effect in FSIAD clinical trials. How should this issue be handled during the clinical development program of a drug product intended to treat FSIAD?

Panel Discussion Topic 3: Clinical Trial Instruments and Other Design Features: Current Challenges, Future Directions, and Generalizability to Clinical Practice

4. To qualify for clinical trials evaluating a drug for female sexual dysfunction, subjects undergo structured clinical interviews conducted by clinicians with expertise in the diagnosis and treatment of female sexual dysfunction. The subject also completes instruments that are designed to capture her own assessment of her symptoms, which are then used as the baseline when assessing response to treatment. When applying findings from clinical trials to the population at large, what challenges do you see for clinicians who will be trying to make an accurate diagnosis and assessment of response to treatment in a busy primary care or outpatient setting? What approaches do you recommend for addressing these challenges?