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Standards for Clinical Trials in Male and Female Sexual Dysfunction: III. Unique Aspects of Clinical Trials in Male Sexual Dysfunction

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ABSTRACT

This series of articles, Standards for Clinical Trials in Male and Female Sexual Dysfunction, began with the discussion of a common expected standard for clinical trial design in male and female sexual dysfunction, a common rationale for the design of phase I to IV clinical trials, and common considerations for the selection of study population and study duration in male and female sexual dysfunction. The second article in this series discussed fundamental principles in development, validation, and selection of patient- (and partner-) reported outcome assessment. The third and present article in this series discusses selected aspects of sexual dysfunction that are that are unique to male sexual dysfunctions and relevant to the conduct of clinical trials of candidate treatments for men.

Key Words: Clinical Trials; Male Sexual Dysfunction; Standards

INTRODUCTION

This series of articles, Standards for Clinical Trials in Male and Female Sexual Dysfunction, began with discussion of a common expected standard for clinical trial design in male and female sexual dysfunction, a common rationale for the design of phase I to IV clinical trials, and common considerations for the selection of study population and study duration in male and female sexual dysfunction. The second article in this series discussed fundamental principles in development, validation, and selection of patient- (and partner-) reported outcome assessment. The third and present article in this series discusses selected aspects of sexual dysfunction that are that are unique to male sexual dysfunctions and relevant to the conduct of clinical trials of candidate treatments for men. The material that follows is a revised and edited version of content written by H. Porst and Y. Vardi (chairs), E. Akkus, J.A. Melman, N.C. Park, A. Seftel, C. Teloken, and M. Wyllie (committee) on Standards for Clinical Trials in Male Sexual Dysfunction for the International Consultation on Sexual Medicine in 2010.

Male sexual dysfunction symptoms are commonly experienced, although they are less commonly screened by, or brought to the attention of, health care providers.[1–4] Prevalent male sexual disorders include erectile dysfunction (ED), premature ejaculation (PE), and loss of sexual desire. Late-onset hypogonadism (LOH) and Peyronie disease (PD) are other male sexually related disorders of concern. With the exception of lifelong PE, which shows a consistent prevalence rate of 18% to 25% across 18 to 65 years of age, all male sexual dysfunctions and medical conditions that impair male sexual function are age dependent, with profoundly increasing prevalence rates from the fifth decade on.[5–14] Male sexual dysfunctions have a significant negative impact on quality of life and sexual satisfaction and on a broad range of psychosocial domains and partnership issues including partner sexual function.[5–17]

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Because there is a substantial body of evidence that male sexual dysfunctions have a clear negative impact not only on the sexuality but also on the psychological and general well-being of men afflicted with these disorders and often on their partners, there is a continuing medical need for the development of new efficacious and safe treatment options. This section focuses on specific issues in study design and study end points that are unique to male sexual dysfunction.

SPECIAL CONSIDERATIONS FOR CLINICAL TRIALS IN ED

Study Populations: Key Inclusion Criteria

The overwhelming majority of clinical trials conducted on ED have required the following criteria for enrollment:

1. Chronic ED for at least 3 months (in many trials 6 months)
2. Stable partner in a heterosexual relationship for at least 3 months
3. Willingness to participate in and comply with the key requests of the trial:
   a. To maintain regular sexual activities during the entire course of the trial with a mean frequency of sexual activities of at least once per week
   b. To give up any other erectile function (EF) enhancing treatment including hormonal (testosterone [T]) replacement therapy with study entrance
   c. To complete patient diaries where applicable
   d. To present at the scheduled visits and return all study drug material (drug accountability)

Key Efficacy End Points

ED Severity

The presence of chronic ED is ensured during the treatment-free run-in phase primarily by the following assessment tools.

Sexual Encounter Profile Questions 2 and 3[18]

The Sexual Encounter Profile (SEP) is a five-item questionnaire that is completed after each sexual intercourse attempt and contains the following questions:

1. Were you able to achieve at least some erection? (Some enlargement of the penis)?
2. Were you able to insert your penis into your partner's vagina?
3. Did your erection last long enough for you to have successful intercourse?
4. Were you satisfied with the hardness of your erection?
5. Were you satisfied overall with this sexual experience?

Many clinical trials for male ED have used the SEP question 2 and 3 data as the main inclusion criteria requiring that in at least 50% of sexual intercourse attempts question 2 and/or 3 were answered with "no." Because in most studies, only questions 2 and 3 are quoted, for the sake of patient compliance, we suggest using a short SEP consisting only of these two questions.

International Index of Erectile Function—Erectile Function Domain

The International Index of Erectile Function (IIEF) is a 15-item validated questionnaire that was developed with financial support from the pharmaceutical industry for the sildenafil clinical research development program.[19] The IIEF-EF domain, consisting of questions 1 to 5 and 15, served as the standard tool for categorization of the severity of the ED as subjectively reported by patients included in the clinical trials. The IIEF-EF domain is currently used in all clinical trials for new ED medications considered for market development. The data of the IIEF-EF reflect patients' recall of their sexual experience during the past 4 weeks. The maximum score that can be reached in the IIEF-EF domain is 30 and the categorization of the severity of ED according to the IIEF-EF domain is as follows:

- Severe ED score = 1−10
- Moderate ED score = 11−17
- Mild ED score = 18−25
- No ED or normal function score = 26−30

Per definition, all patients with an IIEF-EF domain score lower than 26 have some degree of severity of ED and therefore are generally included in most clinical ED trials.

Some trials in the past restricted the inclusion to a certain IIEF-EF score below and above which patients were not included in a trial and some ED trials randomized patients according to IIEF-EF severity at baseline (ie, assigned patients with mild, moderate, and severe ED at random to study arms).

In many ED trials the final IIEF-EF domain score and/or its change from baseline is used as the primary or secondary end point. Another quite common end point in clinical trials for ED involves the number or percentage of patients reaching a normal IIEF-EF score at study end indicating normal EF (ie, remitters). In recent years minimal clinically important differences in the IIEF-EF domain also have been investigated.

Global Assessment Question

The Global Assessment Question has been used as a patient-reported outcome (PRO) in clinical trials of treatment for ED[20]: "Has the treatment you have been taking over the past 4 weeks improved your erections? (Please compare your current erections after treatment with your erections before your participation in this study)": yes or no.

Numerous additional validated questionnaires have been used as efficacy end points in various clinical trials in ED and the interested reader is referred to relevant articles from the International Consultation on Sexual Medicine in 2015.[21] Key to selection of baseline and end-point efficacy PRO measurements in clinical trials of candidate treatments of ED are questions of "fit" of the measurement with the ED construct and psychometric validity of the PRO instrument, discussed in the second article in the present series.[22]