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Considerations in the design of clinical trials for erectile dysfunction

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The naissance of the phosphodiesterase-5 inhibitors has dramatically fueled the research engine in pursuit of novel therapies for erectile dysfunction (ED). The epidemiological product of reports on penile implants, to multicenter, randomized, double-blinded, placebo-controlled trials on oral therapy and intracavernosal/intraurethral injection therapy, has translated into substantial assets for the treatment of patients with ED. However, at the heart of this issue, is that prior to the imbursement of effective and safe advents, investigators must consider several key points in the design stages of clinical trials. The scope of the following review of the ED literature over the past two decades represents a methodological approach and a prospective quest for enriching current quality of evidence, focusing on considerations in the design stages of Phase III clinical trials of ED and highlighting the emphasis that needs to be placed in the process of subject enrollment, partner involvement and standardization of outcome assessment.

Keywords: erectile dysfunction • intracavernosal alprostadil • intraurethral alprostadil • PDE5i • penile prosthesis • randomized controlled trials

The umbrella of male sexual dysfunction overlies a number of disorders, including erectile dysfunction (ED), premature ejaculation, delayed or absent ejaculation, loss of libido, hypogonadism and Peyronie's disease [1]. The vast majority of evidence that stems from the literature has blossomed following the advent of pharmacological therapies for ED in the mid 1990s, consequently revolutionizing the management of male sexual dysfunction. A NIH consensus defined ED as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance [2]. Population-based studies have derived an estimated prevalence of combined mild, moderate and severe ED to be 52% [3]. Across age groups, ED prevalence has been reported at 7% in men aged 18–29 years, 40% at 40 years of age and 70% at 70 years of age [3,4]. From an etiological perspective, ED can be stratified into 3 groups: organic, psychogenic or, most commonly, a combination of both [5]. Treatment modalities for ED include first-line: oral phosphodiesterase-5 inhibitors (PDE5i); second-line: intracorporal and intraurethral injection therapy and vacuum constriction devices; and third-line: penile prosthesis.

The foreseen objective assessment of the efficacy of therapy lies at core in the process of designing clinical trials and is foundational to the pursuit of novel treatments for ED. The use of randomized controlled trials (RCTs) that are double-blinded and placebo-controlled is no doubt the optimum design for addressing clinical questions in ED and of paramount importance being the systematic and standardized approaches in the stages of design in order to avoid undesirable bias. Such processes are conducted in a step-wise fashion, whereby each phase serves to answer a certain question. Phase I entails observing the safety,

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tolerance and pharmacokinetics of novel drugs on a small group, followed by the critical and determining step of acquiring dose-specific safety and efficacy on a larger group (Phase II), with intention of no harm of advent therapy, consequently facilitating studying the clinical efficacy and safety in Phase III leading to approval. Specific subpopulations can be studied during Phase I and III, or following the marketing of new advents (Phase IV).

Evidence extrapolated from ED trials has demonstrated high success rates; however, in congruence with such positive outcomes, the critical review and appraisal of ED literature has yielded a number of considerations pertaining to the methodological design of trials. Limitations can be regarded as either inherent or acquired. For example, the inherent drawback of studies on prosthetic implant therapy in ED includes the inability to enrol control arms in the design stage, and the untouched approach of comparing different implants in RCTs, both of which can be attributable to ethical and fiscal constraints. Applying sound principles of critical appraisal, the acquired limitations mainly generated from oral and injection therapy trials, which constitutes the majority of available literature at present. The most striking of such includes the bias in selecting subjects who differ from the general population of ED patients with respect to underlying comorbidities (metabolic and cardiac risk factors), the absence of standardized outcome measures, recruitment of subjects with less profound severity of ED resulting in more favored outcomes, which are not necessarily generalizable, and paucity of data on objective assessment of partner satisfaction.

The current review endorses a perseverant approach to the literature on ED, considering the present quality of RCTs, with the aim of addressing the drawbacks in the methodological design. In a systematic approach, stratified by treatment modalities, the objectives of this review are to identify major clinical trials on ED, to exploit major inherent and acquired limitations in the design of these trials using a standardized tool (The Consolidated Standards for the Reporting of Randomized Controlled Trials [CONSORT] 2010 checklist; Table 1), to produce a table demonstrating this and to propose suggestions that can possibly be implemented to further enhance the magnitude of evidence in the ED research arena.

Search strategy

Using the Medline database, relevant articles from 1996–2011 were identified and deemed eligible by two investigators independently. Mesh terms used for the search process included: 'Erectile dysfunction', 'Phosphodieterase-5 inhibitors', 'penile prosthesis', 'intracorporal injection' and 'intraurethral alprostadil', with restriction to RCTs, meta-analysis and systematic review. The yielded articles were then searched by hand to elicit further relevant references (the snowball effect). Inclusion criteria included focus on ED patients, randomized control design in the case of oral and injection therapy and large case series on penile implants approved by the US FDA.

Drawbacks in methodology and design of clinical trials in ED

■ Overview of current therapy

Since the approval of sildenafil in 1998, the efficacy and safety of use was soon replicated in many clinical trials rendering it the first-line therapy for the treatment of ED [6–8]. Subsequently, following the favorable action and outcome observed with sildenafil, continuing efforts lead to the development of newer PDE5i agents in 2003: vardenafil and tadalafil. RCT testing all three agents independently, uniformly demonstrated improvement in erectile function amongst men with ED, with efficacy extending to problematic subgroup patients including those with diabetes [9–11], metabolic syndrome, spinal cord injury [12] and post-prostatectomy patients (Table 2) [13]. Amidst the triumph of PDE5i in the management of ED, the implications in the design of RCTs of oral PDE5i is an area that has been lightly touched upon and deserves a carefully contemplated approach.

Despite the well-known notion of invasiveness with intracavernosal and intraurethral injection therapy, dating back from the approval by the FDA in 1996, their use has no doubt been shown to be highly effective, with tolerable side effects by some [14,15]. The availability of oral PDE5i has by far diminished the role of local injection therapy early on in the management of ED; however, amongst nonresponders, alprostadil intracavernosal injection is usually an option for patients who qualify for home use following an in-office trial. Having been deemed eligible, the issues of compliance and tolerance of side effects (penile pain, fibrosis, hematoma and priapism) remain the detrimental factors for outcome satisfaction and point to those who will proceed for alternative modalities. The advent of intraurethral alprostadil injection introduced a mechanism of action similar to intracavernosal injection, although, with a more favourable side-effect profile (mainly penile pain) via a less-invasive route of administration. Intraurethral alprostadil has also demonstrated a high percentage of satisfaction amongst subjects [16–18]; although, not of superior magnitude to the effect observed in intracavernosal injection therapy. Similarly, the design of trials on injection therapy warrants a closer perspective, considering the selection of patients based on an in-office trial; hence, raising issues of blindness and selection bias.

For many years, the only options for treating ED were surgical. Mechanical device implantation was the favored approach, with alternative procedures including vascular bypass procedures. The era of penile prosthetics has matured over the years and, despite the advent of oral therapy, remains the final option in the algorithm of treatment in ED and occasionally first-line in selected groups. Prosthetics can be divided into inflatable and malleable, with the majority of implanted prosthesis being inflatable. The main prospects of a successful outcome are those of prosthetic infection rate, mechanical failure and device survival. Overall, penile prosthesis implantation equates with a reported satisfaction of

Table 1. The Consolidated Standards for the Reporting of Randomized Controlled Trials checklist used in the appraisal of selected studies.

Section/topic	Item no.	Checklist item
Title & abstract		
	1a	Identification as a randomized trial in the title
	1b	Structured summary of trial design, methods, results and conclusions
Introduction		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
Methods		
Trial design	3a	Description of trial design (such as parallel or factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomization		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomization; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses

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Table 1. The Consolidated Standards for the Reporting of Randomized Controlled Trials checklist used in the appraisal of selected studies (cont.).

Section/topic	Item no.	Checklist item
Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment and were analyzed for the primary outcome
	13b	For each group, losses and exclusions after randomization, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group
Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision and, if relevant, multiplicity of analyses
Generalizability	21	Generalizability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

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up to 92% [19–26], with reports of device survival up to 5 years amongst 80–90% of patients [19–26]. Additionally, recent modifications, including antibiotic coated implants, have proven to reduce the incidence of infectious complications [27–30]. Early reports on prosthetics comprises case series and uncontrolled studies, and despite advents and modifications to prosthetics (e.g., antibiotic coating) leading to widespread implementations in the guidelines on management, the current lack of trials comparing standard versus modified prosthetics in a prospective or randomized approach, points to the need to improve study design in order to extrapolate evidence for use in the clinical setting.

Ethical considerations

Approaching a patient with ED can be fairly awkward. One can be faced with either of two dilemmas – first, one in which the partner is unaware of or is disinterested by the patient seeking medical attention, or second, one whereby the encounter involves the attendance of the patients spouse. Whenever feasible, the assessment should include both parties in a relationship because uninterested or unwilling partners may have a large impact on the outcome and the assessment may also identify concomitant partner sexual dysfunction [31–33]. In addition, this may also raise issues in compliance, whereby the subject

Table 2. Devised table for critically appraising randomized controlled trials in erectile dysfunction.

Author	N	Sample-size/power calculation reported?	Randomization/allocation concealment method detailed?	Baseline comparability reported?	Comparable data collection of arms reported?	Blinding method clearly detailed?	Treatment clearly detailed?	Efficacy and side-effect assessment reported?	Outcome assessment defined?	Partner assessment attempted?	Intention to treat analysis?	Ref.
First-line (oral)												
Dinsmore *et al.*	220	No	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	[38]
Goldstein *et al.*	861	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	[6]
Montorsi *et al.*	514	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	[7]
Tan *et al.*	254	No	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	[55]
Carson *et al.*	2102	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	[39]
McMahon *et al.*	152	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	[44]
Padma-Nathan *et al.*	179	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	[54]
Porst *et al.*	268	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	[45]
Rajfer *et al.*	287	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	[57]
Yip *et al.*	242	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	[46]
Hatzichristou *et al.*	323	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	[40]
Hellstrom *et al.*	805	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	[41]
Porst *et al.*	590	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	[42]
Potempa *et al.*	336	No	No	Yes	No	No	Yes	Yes	Yes	No	Yes	[56]
Montorsi *et al.*	303	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	[13]
Goldstein *et al.*	452	No	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	[9]
Rendell *et al.*	252	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[10]

Table 2. Devised table for critically appraising randomized controlled trials in erectile dysfunction (cont.).

Author	N	Sample-size/power calculation reported?	Randomization/ allocation concealment method detailed?	Baseline comparability reported?	Comparable data collection of arms reported?	Blinding method clearly detailed?	Treatment clearly detailed?	Treatment clearly detailed?	Efficacy and side-effect assessment reported?	Partner assessment attempted?	Intention to treat analysis?	Ref.
Second-line (intracavernosal/urethral)												
Godschalk *et al.*	15	No	No	Yes	Yes	No	Yes	Yes	Yes	No	No	[15]
Williams *et al.*	159	No	No	Yes	Yes	No	Yes	Yes	Yes	No	No	[18]
Padma-Nathan *et al.*	996	No	No	Yes	Yes	No	Yes	Yes	Yes	No	No	[17]
Hellstrom *et al.*	68	No	No	Yes	Yes	No	Yes	Yes	Yes	No	No	[16]

may feel greater pressure when partner support is absent, therefore, compliance and subsequent follow-up in trial phases may be endangered. As such, partner involvement is crucial in the early stages of subject recruitment into trials. Of consideration are the cultural and religious disparities in sexual practices, and the need for studies looking at different sexual orientations (i.e., homosexuals). Similarly, subjects might not be competent or able to use certain treatments, specifically alprostadil injection and prosthetic pump inflation, hence, the need for partner involvement is inevitable and mandatory for compliance purposes.

Following rigorous explanation of the study purpose and enrollment to subjects for consent purposes, the increment from Phase II to III may pose ethical threats when external funding from pharmaceutical companies pressures researchers to expedite trials. The innate desire to publish selective results and suppress unfavorable outcomes may translate into hidden, undesired side effects that are firstly never published and, more importantly, are not made known to the general population of ED patients [34,35]. Hence, the dualities of interest between researchers and external funders should be declared to the patient and examined for the presence of conflict to avoid ethical endangerment.

It is worthy of note that the use of placebo-controlled arms in alprostadil injection therapy trials may not be considered appropriate from an ethical perspective, due to the invasive nature of the treatment. Congruently, designing prospective penile prosthesis trials on antibiotic-coated versus noncoated implants can also be unethical, given the present evidence on favorable infection rate with the former.

■ Study population

As a general rule in selection of a study population, the experimental population is derived from a reference population. The reference population may be restricted by certain desired demographics – age, sex, pathology and comorbidities – that are thought to modify the existence of the effects seen in the proposed trial. In other terms, the reference population is what represents the scope of the public-health impact of the desired intervention. Thus, when recruiting subjects with ED from the general (reference) population, certain inclusion criteria are to be considered (discused below).

Having been deemed eligible for enrollment, voluntary will to participate versus non-willingness poses a significant impact on generalizing study findings and the development of end points under investigation [36]. Of epidemiological and statistical relevance, volunteering individuals tend to experience lower rates of morbidity compared with those who do not volunteer, regardless of the hypothesis under study and the actual treatment they are assigned to [37]. Confounding factors in the issue of volunteerism include baseline age, socioeconomic status, education and public-health awareness. Looking at the ED literature in all treatment modalities, most studies do not report baseline demographic differences between eligible subjects who choose to participate versus those who do not [6,14,30,38–42]. These data are extremely valuable as they may point to differences between participants and nonparticipants, and hence identify influential factors on generalizability. A multicentered approach in investigating efficacy of an intervention aids to magnify the potential outcome under study. The majority of trials on oral therapy and some on intracavernosal/intraurethral alprostadil identified in our search have adopted a multicenter approach; hence, the favored outcomes observed are of high statistical significance and quality. Of note is the literature on second- and third-line therapies that had been published before or amidst the birth of oral PDE5i, hence inherently inclusion or eligibility had not taken into consideration the availability of oral therapy, therefore, valid response to injection treatment could be overestimated, calling into question the generalizability to the reference population.

Sample size & power calculations

In the early planning of any analytical epidemiological study, the calculation of sample size to ascertain clinical and statistical significance is of paramount importance. Any clinical trial must have a sufficient sample size to detect reliably any difference between treatment groups, regardless of the magnitude of difference desired. Most clinical trials have been criticized for having little scientific value, attributable to the fact that sample size is inadequate to detect the differences hypothesized [43].

The sample size in most trials on oral therapy ranged from 140 to 861 patients; however, only two trials on sildenafil [10,44], one of the trials on vardenafil [40] and four trials on tadalafil [13,44–46] had reported their sample size calculation (Table 2). Based on the calculated sample sizes necessary to detect a power of 90%, authors predicted the need for at least 120–250 subjects. These numbers differed based on discrepancies in the desired statistical difference between treatment groups, accounting for a certain percentage of dropout and losses to follow-up, screening failure, and dose-related effects. Despite most trials achieving these numbers, adopting a uniform approach in describing sample-size calculation is mandatory. None of the trials on intracavernosal and intraurethral injection (Table 2) and penile prosthesis had reported sample size calculation.

Inclusion & exclusion criteria

A general consensus on criteria for inclusion included: age of 18 years or older, the presence of ED for at least 3–6 months, having a stable partner in a heterosexual relationship for 3–6 months and willingness to participate in the trial and comply with key requests of the trials – which include maintaining regular sexual activities over the course of the trial, abandoning any confounding erectile-function-enhancing treatment, completing regular patient sexual diaries and abiding with the scheduled visits [1]. Diagnosis of ED is initially based primarily on self-reported history and physical exam, with the aid of diagnostic questionnaires. Diagnostic imaging and invasive tests (e.g., intracavernosal injection, penile Doppler studies, cavernosography and Rigiscan®) are not considered standard in inclusion criteria, partly because ED is a self-reported entity, hence, diagnostic tests may not correlate with the burden of the disease. Inclusion criteria of most trials on oral or injection therapy overlap and with the exception of trials addressing specific subgroups, discrepancies in inclusion on the definition of ED duration and the severity of ED can lead to over or underestimation of outcome.

Common exclusion criteria in oral therapy trials include: severe vascular, neurogenic and/or endocrine disease, non-nerve sparing radical prostatectomy patients, penile anatomical defects, primary diagnosis of another sexual disorder, psychological disorder, poorly controlled diabetes, myocardial infarction or stroke within 6 months, regular use of nitrites, hematological, hepatic or renal impairment, active peptic ulcer disease, and previously failed PDE5i therapy. Issues that arise here are the potential bias of selecting favorable patients on the basis of disease severity and the exclusion of previously failed therapy without clear definition of failure of therapy (see 'Bias in ED trials' section). However, certain trials have addressed the question of efficacy on select populations such as diabetics [9–11], spinal cord injury [11] or post-prostatectomy patients [13], further adding to the success of PDE5i treatment in such patients. Noteworthy is the exclusion of patients with premature ejaculation. Recent evidence and guidelines have shown congruent improvement in premature ejaculation amidst treatment for ED, highlighting the potential dual effect of treatment with PDE5i [102].

Follow-up & termination of study

To achieve the desired number of end points, trials adopt two strategies: recruit a population that

is highly likely to develop the outcome of interest and ensuring adequate follow-up length. Ascertaining a precise length of follow-up is cumbersome and should anticipate that accrual of end points may precede the initially planned follow-up time. Reasoning behind this may be attributed to the fine selection and volunteerism of participants (those likely to develop the end point of interest), which, as previously mentioned, differ from the general population of ED patients and, hence, may distort the actual course and length of treatment needed. Additionally, the secular changes of ED itself are difficult to establish and can sometimes be as large a magnitude as the effect of PDE5i themselves. This points to considering the mechanism by which PDE5i exert their pharmacological effects. Based on the pharmacokinetics of PDE5i, they exert their action within 1–2 h and lasting from 3 to 17.5 h, hence their effects are seen immediately [47] and compliance here depends on the efficacy and side-effect profiles. On the other hand, the point in time (months to years) whereby subjects begin to develop tolerance and seek second- and third-line therapy is variable and undetermined. Generally, most trials (oral and injection therapy) have conducted a run-in period ranging from 1 to 4 weeks, followed by the actual treatment of 3–24 weeks. Whether this length of follow-up period is adequate to conclude that injection therapy and PDE5i exert a durable long-term effect is unclear. However, the run-in period is essential to ensure that the population for which the study was designed is studied. A period of a week seems to be optimal. Nevertheless, interim assessments are clearly defined, with drop-out and losses to follow-up accounted for in the analysis.

The length of the follow-up required to ascertain device survival in penile prosthesis studies based on current evidence is controversial. One review has demonstrated a 10-year device-survival rate (revision-free) of 68.5% and a 15-year device-survival rate of 59.7% [48]. These figures point to the need to ascertain a standardized length of follow-up in future prospective trials, ideally between 10 and 15 years. In perseverance of designing studies with such long-term follow-up, Porst *et al.* have proposed the approach of two follow-up periods: a mid- and long-term follow-up [1]. The midterm should assess the short-term mechanical failure rate (e.g., cylinders or pump), surgical failure rate (infection), patient and partner acceptance and satisfaction, ease of device operation, penile length and shape, additional use of PDE5i or alternative regimens. The long-term follow-up, along with the above mentioned, should look mainly at revision-free device-survival rate at 10–15 years [1].

Assessment of outcomes

Objective assessment of ED treatment is primarily based on questionnaires. The questionnaires used in assessing efficacy of PDE5i include: the International Index of Erectile Function (IIEF) 15- and five-item questionnaire [49,50], Global Efficacy Question and the Sexual Encounter Profile. Other validated questionnaires used for assessment of outcome exist; however, they are not used frequently in major trials [1]. The use of the IIEF score has been validated in the assessment of ED severity, and baseline and post-treatment efficacy assessment, correlating well with the observed outcome of treatment. The Sexual Encounter Profile, though not validated, has been shown to closely correlate satisfactorily with the IIEF with respect to erection and intercourse satisfaction [51]. The inherent drawback of all of these questionnaires is the lack of simultaneous assessment of partner satisfaction and the inability to differentiate various etiologies of ED (hence, it does not substitute diagnostic workup).

Pertaining to PDE5i trials, there appears to be an investigator preference towards the use of one or multiple questionnaires simultaneously, without a universal standardization of using a solo questionnaire for the purpose of comparing trials. The IIEF 15-item questionnaire, and later devised five-item questionnaire, encompasses five main domains: erectile function, libido, orgasmic function, sexual satisfaction and overall satisfaction. The period over which the questionnaire addresses sexual function is 4 weeks prior to completion of the inventory, hence the potential recall bias (see 'Bias in ED trials' section). The post-treatment assessment in most trials emphasizes mainly questions 3 and 4 of the inventory:

- 3: the ability to obtain an erection of sufficient rigidity to achieve penetration;
- 4: the ability to maintain the erection.

The original validation of the IIEF was based on the entire 15-items, hence the deviation towards focusing on two of these points to weakness of assessing end point outcomes.

Pertaining to injection therapy, most trials have addressed outcomes using the Erectile Assessment Scale [17]. This tool assesses penile response to therapy and encompasses five grades:

- 1: No response;
- 2: Some enlargement;
- 3: Full enlargement (but insufficient rigidity);
- 4: Erection sufficient for intercourse;
- 5: Full rigidity.

Although replicated across trials, this tool assesses mainly the erection hardness with poor insight into sexual satisfaction, partner satisfaction, orgasmic function and sexual desire. Hence, this points to the need to implement outcome assessment of injection trials based on the standardized outcome assessment used in oral therapy trials.

Incident infection rates, mechanical failure and device survival remain the main factors in the outcome assessment of penile prosthetic devices. Despite the relevance of the former for assessing outcome, the use of a standardized questionnaire tool to assess patient and partner satisfaction, as opposed to surgical success, should not be undervalued.

Statistical analysis

In pursuit of high-quality evidence, RCT's should abide by the CONSORT criteria [52]. Among the CONSORT criteria, one important methodological aspect is the intention-to-treat (ITT) analysis. ITT means that during the statistical analysis, patients are analyzed on the basis of the treatment arm to which they were randomized, whether they have received that form of treatment or not. This ensures that the baseline characteristics of patients in the different treatment groups are comparable [53]. The majority of trials in PDE5i used the ITT analysis, rendering the data statistically plausible on outcomes of different treatment arms. None of the trials on injection therapy used the ITT statistical approach (Table 2).

Of importance is the approach to adjustment of baseline variables and subgroup analysis. In the case of ED trials whereby the outcome is based on a numerical scale (IIEF score), adjustment for baseline score is considered plausible and should be implemented. The need for center adjustment in multicentered trials is not mandate unless it is foreseen to be a strong predictor of ED therapy success (i.e., high case volume and expertise centers) and the proportion of patients in the treatment group differs dramatically between institutions. The strong relationship between certain risk factors for ED (e.g., hypertension and diabetes) must be accounted for in trials enrolling subjects with a mix of etiologies; this is eliminated when trials enrol specific subgroup of patients. A common notion is the observed flaw in the approach to subgroup analysis outcome in most RCTs; however, this is not the case in ED trials. Certain populations, including individuals with diabetes, hypertension and spinal cord injury differ in the pathophysiological pathways of the disease, hence the need to study a population of mixed etiology, with restricted subgroup analysis on such patients, is deemed necessary. This approach has been adopted by most trials on ED, rendering their approach plausible.

Bias in ED trials

Selection bias

Any factor that influences the way participants are enrolled or selected into a trial can threaten the validity of its outcomes. In clinical trials, the two major kinds of selection bias are sampling bias and attrition bias. Despite the literature clearly displaying baseline demographics and characteristics of patients enrolled into ED trials, certain inclusion and exclusion criteria translate into selecting patients with less severe disease, hence demonstrating favorable outcomes. For example, the exclusion of all patients with diabetes by some [54] and those with poorly controlled diabetes by others [6,38,46,55,56], despite evidence demonstrating the efficacy and safety of PDE5i in diabetics [10], is a form of selection bias whereby investigators choose patients with less morbid etiologies of ED, hence overestimating the positive response to PDE5i therapy. A two-way argument can be generated here, whereby deferring such subgroups of patients ensures that compliance and follow-up is optimized by selecting less-morbid subjects who are more likely to participate and abide by the trial restrictions; on the other hand, certain patients with severe ED and comorbid conditions might actually represent a more coherent group that is more eager for ED treatment, hence a more disciplined sample. Certain investigators have answered the question of the efficacy of PDE5i in these patients by restricting their experimental population to those with diabetes [9–11], spinal cord injury [12] and post-prostatectomy patients with ED [13]. With respect to intracavernosal and intraurethral alprostadil, the restriction of in-clinic responders during the Phase III studies translates into selection bias, whereby only those who responded to the first instillation in the clinic were enrolled in the at-home RCT, thus diverging the trial towards more favored outcomes [17]. The demonstration of lower infection rates amongst antibiotic-coated versus non-coated penile implants in retrospective study reviews might also be biased. If more *de novo* antibiotic-coated implants are inserted, the infection rate will inevitably be lower in a certain cohort, hence the selection bias here. Of importance is the diabetic population with ED, who are more prone to infections, yet disproportionately receive more nonantibiotic coated prosthesis and hence will most likely have a higher incidence of infection [30].

Allocation concealment

Optimum random allocation between arms of the study requires blinding both the subject and the investigator to the intervention. This can be enhanced; for example, by using computer-based random allocation. Despite all trials stating their randomized approach,

out of the trials included in our review, one of the trials on sildenafil [10], three trials on tadalafil [44,45,57] and one trial on vardenafil [40] had clearly detailed the random allocation method and allocation concealment. Our findings are further supported by previous meta-analyses on oral therapy that demonstrated this paucity in description [8,58]. This scarcity was also identified when reviewing RCTs on intraurethral and intracorporeal injection therapy [14,16,18].

■ Measurement bias

A systematic standardized approach to classifying or measuring an outcome is mandatory in clinical trials. The use of IIEF scoring system has been validated as previously mentioned and has been replicated across all trials assessing oral and injection therapy. However, certain trials have focused on the use of certain aspects of the IIEF questionnaire for outcome analysis, which deviates from the original validation that emphasizes incorporating all items of the questionnaire; hence potential measurement bias operating. Furthermore, the IIEF does not assess partner satisfaction nor does it serve as a surrogate measure of underlying etiology. There remains a need for a more robust tool to assess treatment response in both partners simultaneously, such as the use of the Treatment Satisfaction Scale [59].

■ Recall & reporter bias

The purposeful or accidental inability to accurately recall and report correct information pertaining to the history, severity and course of disease will inevitably bias the treatment outcomes. The fact that the IIEF questionnaire assesses sexual function on the basis of a 4-week period, the room for potential recall and reporting bias is undisputable. Fear of nonacceptance for enrollment based on strict inclusion criteria and failure of therapy with subsequent drop out, place pressure on subjects pursuing treatment desperately. This may potentially lead to purposeful reporting bias to mask unwanted habits (e.g., smoking or concomitant use of aphrodisiac herbal remedies). However, these confounding factors are sometimes burdensome to identify and might never be unmasked.

■ Publication bias

The tendency to report findings that conform precluded notions and outcome expectations by investigators and their sponsors is common. Two major influential factors of publication bias are sponsoring companies and journal editors. Pressure on investigators from sponsors and the innate bias of editors towards favorable outcomes translates into a 'positive-or-none' culture in publication. Although this dilemma concentrates in observational studies to a greater extent than clinical trials [18], nonetheless, the large amounts of money pumped into advocating the use of all modalities of treatment in ED is not beyond the eyes of the public. The success of current treatments in ED is unbeatable and the impact on the quality of life and sexual health cannot be overemphasized. However, the process of deferring publication of negative outcomes on certain populations overestimates the magnitude of effect seen by certain interventions and impedes the continuum of future research prospects on populations nonresponsive to treatment and, hence, their underlying distinguished characteristics that fuel the search for alternative therapeutic modalities.

Future perspective

The immersion of PDE5i in the treatment of ED is a landmark to the birth of the revolution, deferring the need for invasive therapies in the early course of the disease. The growing body of literature that stems from ED trials has forced us to attend to certain aspects of the design that warrant future modification to further enhance the magnitude of evidence. In the coming 5–10 years, the core of the modification process will entail a more rigorous approach that amends the recruitment process, the insight into partner involvement and assessment, the potential use of diagnostic testing in the diagnosis and assessment of satisfaction, the comparison of agents under study, the use of succinct validated outcome assessment tools more adherently and will adhere to standardized timeframes for follow-up.

In oral and injection therapy trials, recruitment of a more representative and generalizable study population that addresses the hypothesis is warranted. In addition, the study population should include patients with diversity of ED severity, or opt to study a subgroup of specific underlying etiology, like post-prostatectomy ED, with standardized inclusion and exclusion criteria. For all treatment modalities, the need to place greater emphasis on partner involvement in the process of recruitment and outcome assessment, with a potential to incorporate a domain reserved for partner satisfaction in the currently available validated questionnaires is needed – pre- and post-treatment – especially in patients with penile prosthesis. The study of more diverse populations, including homosexuals, and the confounding role of lifestyle modification amidst treatment is also warranted and plausible. The current data on side effect and safety is well imbursed; however, data on long-term efficacy and tolerance remains scarce and yet to be determined.

With the inherent limitation of current data quality, meta-analysis of different treatment options is not feasible; hence, the need for trials exploring outcomes of combination therapy of different treatment modalities, rigorous RCTs comparing the available different PDE5i simultaneously and prospective penile prosthesis trials is demanded. In future, novel therapies should be compared with PDE5i, the gold standard in ED therapy, not only to placebo.

From a methodological viewpoint, practical indications in any future RCT investigating existing or novel therapies for ED should place emphasis on the following points: a valid justification to implement Phase III based on *a priori* evidence of safety, tolerability and proposed efficacy from Phase I and II. A robust approach to participant recruitment, ensuring that the study population truly represents the reference population (ED patients) and not merely an accrual of nested subjects within secondary and tertiary care centers, while neglecting the need to enrol subjects suffering in the community centers that lack the services and expertise. Ensuring that outcome assessment using validated tools (IIEF) should not incorporate certain preferred domains, neglecting other important features of a disease spectrum (including libido, sexual drive and ejaculation).

Executive summary

Introduction
- Randomized, double-blinded, placebo-controlled trials remain the gold standard for addressing clinical hypotheses, and all erectile dysfunction (ED) studies should adhere to this design strategy when feasible.
- The arrival of PDE5i inhibitors far outweighs previous advents in the treatment of ED; however, considerations in the Phase III design stage remain detrimental to the quality of present evidence.

Recruitment & analysis
- The absence of clear description of randomization methods, allocation concealment, blinding methods and sample size calculations, points to the need for qualified epidemiologists and biostatisticians to be involved in the design and analysis process.
- Robust definitions of follow-up periods and termination of study are needed, especially in penile prosthesis studies where long-term follow-up is needed to ascertain device success and survival.

Study population & outcome assessment
- Acknowledging partner role in the treatment and outcome assessment of subjects with ED is crucial. Incorporating a domain for partners in current outcome assessment is mandatory.
- Clinical trials of ED should enrol subjects more representative of the reference ED population, with standardized and clear definitions of inclusion and exclusion criteria, but not so strict as to threaten the generalizability of study results.
- International Index of Erectile Function questionnaire has been validated and replicated; however the discrepancy generated by selecting specific questions for outcome assessment (questions 3 and 4) and neglecting other domain questions poses a great impact on the validity of results and hinders the systematic comparison of trials.
- The implementation of use of the International Index of Erectile Function in intracavernosal and intraurethral trials is also encouraged.

Bias
- Selection, reporter and recall are the commonest forms of bias operating in clinical trials of ED. Selection bias mainly stems from intraurethral and intracavernosal trials whereby subjects are enrolled based on response to an in-office positive response.

Advents in prosthesis
- Recent results favor the use of antibiotic-coated penile prostheses; however, it is now unethical to compare coated versus non-coated prosthesis.
- Trials exploring combination therapies simultaneously and a prospective design for penile prosthesis studies are mandated.

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