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Seminar article

A primer on clinical trial design

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Abstract

A well-designed and executed clinical trial is the gold standard of evidence-based medicine. It is important for readers to understand the rationale for the study design, identify common pitfalls, and scrutinize limitations. Herein, we present a brief overview of types of designs used for clinical trials and discuss the use of appropriate end points, the selection of study participants, randomization, sample size calculation, blinding, and analysis of data. Finally, we emphasize the importance of accurate and transparent reporting. Our goal is to provide a primer for practicing urologists to enhance their understanding of the clinical trial literature. Published by Elsevier Inc.

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Introduction

A well-designed and executed clinical trial is the gold standard of evidence-based medicine. Each month, dozens of trials are published in top journals with the intent of guiding clinical practice with reliable evidence. Although it is assumed that by virtue of the peer-review process, a published trial has met certain standards, the reader is ultimately responsible for critical appraisal of the quality and applicability of the trial. Namely, the reader should be able to understand the rationale for the study design, identify common pitfalls, and scrutinize limitations. Herein, we present a brief overview of clinical trials to provide the practicing urologist with a basic methodological understanding of the clinical trial literature.

What is a clinical trial?

A clinical trial is a prospective study design that is aimed at understanding the effect of an intervention (e.g., surgical procedure, drug, or medical device) in a predetermined population over a defined period of time. High-quality clinical trials adhere to stringent design and reporting guidelines [1]. However, not all research questions are appropriate for a clinical trial. The benefits of a clinical trial are outweighed if (1) the intervention poses undue harm or risk to participants (e.g., a study that exposes participants to cigarette smoke), (2) the control group is denied a treatment that is known to work, (3) the trial is economically infeasible (e.g., a study that requires 15 y of follow-up). In these situations, a well-designed observational or simulation study can replace a clinical trial.

What are clinical trial phases?

Because many clinical trials involve the use of drugs, it is important to review the phases of clinical trials (Fig. 1). Phase I trials are designed to establish the safety of a new drug, to determine dosing, and to better understand the pharmacokinetics of the treatment. During phase I trials, a small number of healthy volunteers are used to determine the "maximum tolerated dose." The maximum tolerated dose is established by giving slowly increasing doses of the experimental drug to groups of 2 to 3 volunteers and observing for toxicity (i.e., dose escalation). As an example, investigators recently published a phase I trial using the liquid formulation of imiquimod in patients with non–muscle-invasive bladder cancer [2]. The investigators gave volunteers small doses of the intravesical agent and observed them for side effects.

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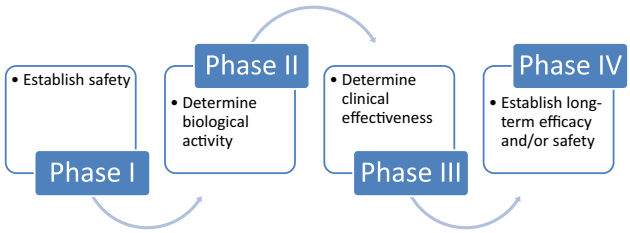

Fig. 1. Clinical trial phases. (color version of the figure is available online.)

Once the safety of the treatment has been established, drug trials typically move into phase II. During phase II trials, investigators use a larger sample of volunteers to determine whether the experimental drug has biological activity. For example, investigators recently published results of a phase II trial examining the efficacy of intravesical nanoparticle albumin-bound (nab-)paclitaxel for the treatment of non–muscle-invasive bladder cancer [3]. The authors of this study used the most common phase II design (i.e., "2-stage design"). In this design, patient exposure to ineffective interventions is minimized by first giving a safe dose (established in phase I) of the drug to a small number of participants. These participants are observed for a predetermined minimum level of biological activity before additional participants are invited to join the trial. In the aforementioned study, investigators enrolled only 10 patients initially. Once the efficacy threshold was met, an additional 18 patients were enrolled. At the end of their phase II study, the authors found that 37.5% of enrollees responded to the treatment. Toxicity in these patients was documented, and they were followed up for a year to determine the durability of the response.

Once efficacy is established, investigators then determine the clinical effectiveness using a phase III trial. The elements of the phase III trial are the subject of the remainder of this article. Finally, once the drug is determined to be effective and enters clinical practice, investigators may conduct a phase IV trial, which is often focused on long-term efficacy or safety of the intervention or a combination of both.

What are the primary and secondary end points?

The primary research question is typically a test of the effect of a specific intervention on a primary end point. Clinical trials typically have a single primary end point and secondary end points. Secondary end points may be tests of additional outcomes related to the primary research question; for example, if the primary end point is all-cause mortality, secondary end points could include serious cardiac events or specific causes of death. Investigators may also report exploratory end points or post hoc analyses. It is important to note that exploratory end points are different from primary/secondary end points because the trial was not designed to test these end points. Exploratory end points are typically used to drive future research.

Investigators may choose to examine the effect of the intervention in specific subgroups (i.e., men, patients older than 65 years, or patients at varying baseline risk of outcomes). All subgroup analyses should be determined a priori. In a study on nephrectomy followed by administration of interferon alfa-2b compared with alfa-2b alone for the treatment of metastatic renal cell carcinoma, subgroup analyses were performed on patients stratified by measurable disease (yes/no), performance status (0/1), and location of metastases (lung/other) [4]. Although subgroup analyses may prove to be clinically helpful, it is important for the reader to be cautious when interpreting the results. For example, if the findings are unremarkable, it may simply be a result of inadequate power, as the trial was designed around the primary question. On the contrary, if the findings are remarkable, one has to consider that in the process of testing many subgroups, some findings would positive owing to chance alone.

What are appropriate end points?

The selection of appropriate end points is critical for a successful clinical trial. Typically, a single end point is selected for the primary question. However, in select circumstances, the primary question may be best answered through a "composite" end point. For example, in a prospective study on the need for imaging in patients with low-risk prostate cancer, the investigators created a composite end point of negative imaging findings, which included results of bone scan, computed tomography, and magnetic resonance imaging [5]. The use of composite end points allows investigators to perform their trial with a smaller sample size.

"Surrogate end points" are often used in the interest of cost and time. For example, although survival is an important end point, it is time intensive and expensive to measure in a clinical trial setting. For men with castration-resistant prostate cancer, biomarkers have been suggested as appropriate end points to assess the treatment potential of new therapeutic agents [6]. It is important for readers to assess whether the surrogate markers truly reflect important clinical end points by assessing whether the association between surrogate markers and the end points has a strong causal relationship in the patients included in the study. For example, prostate-specific antigen (PSA) is not likely to be a good surrogate marker for prostate cancer in a general screening population, but it may be adequate in a population of patients being treated for advanced cancer.

Regardless of the end point selected, appropriate end points should be predetermined, assessed in all patients by reviewers blinded to treatment group, and measured in an unbiased fashion [7].

How are patients selected?

Patient selection is an important component of clinical trial design and interpretation. Investigators should document, in a highly transparent manner, specific inclusion and exclusion