A practitioner's guide to developing critical appraisal skills

Interventional studies

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Editor's note: *This is the fourth in a series of articles summarizing research methods and design, research translation, statistical analysis and critical appraisal of the scientific literature. The purpose of this series is to help practitioners enhance their understanding of research and develop skills in interpreting research in the dental and medical literature.*

Authors of previous articles in this series have emphasized the need for well-designed and well-conducted studies to serve as the underpinning of evidence-based clinical practice.[1-3] The most definitive evidence for the safety and effectiveness of a therapeutic intervention is provided by randomized controlled clinical trials. In this article, we provide an overview of the design, analysis and reporting of these trials, with the goal of helping practitioners evaluate published clinical trials and their applicability to clinical practice.

TYPES OF CLINICAL TRIALS

Clinical trials often are categorized into four phases, each of which is

ABSTRACT

Background and Overview. Randomized controlled clinical trials are considered to provide the highest level of evidence for clinical practice, public health policy and evidence-based systematic reviews. Although all randomized controlled clinical trials share basic design characteristics, to assess the outcome of a particular trial one must carefully evaluate specific details of its design and analysis that might bias the study and influence its results. In this article, the authors review key points that practitioners should consider when assessing randomized controlled clinical trials so they can determine the applicability of study results to clinical practice.

Conclusions and Practice Implications. Dentists encounter a variety of types of evidence when trying to assess the utility of new therapeutic agents and procedures for their clinical practice. This article provides a background to use in evaluating data and selecting studies that provide the most rigorous clinical support for safety and effectiveness.

Key Words. Randomized controlled clinical trials; single-blind study; double-blind study; randomization; bias; crossover studies.
JADA 2012;143(10):1114-1119.

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intended to answer a different question.[4]

- In phase 1 trials, researchers investigate an experimental drug or treatment for the first time in a small group of healthy participants (20-80 members) to evaluate its safety and identify side effects. These trials usually follow animal studies that show promise for a particular intervention or drug that might be used to treat a specific disease in humans.
- In phase 2 trials, investigators evaluate a drug or treatment in a larger group of participants (approximately 100 to 200) to obtain preliminary information about treatment effectiveness, acquire information about optimal dose administration (if a drug is involved) and further evaluate safety.
- In phase 3 trials, investigators evaluate a drug or treatment in large numbers of participants (hundreds to thousands) to confirm its effectiveness, monitor side effects, compare it with standard or equivalent treatments, and collect information that will allow the drug or treatment to be used safely. In view of the large number of participants they typically require, phase 3 trials often are conducted at a number of different clinical centers (thereby the term "multicenter trials") with the use of the same experimental protocol design.
- Phase 4 trials are conducted after a drug or treatment has been approved and marketed. They provide additional information concerning the risks, benefits and optimal use of the drug or treatment.

Phase 3 trials are the key, or pivotal, trials used to document the safety and effectiveness of a new drug for the purpose of obtaining government regulatory approval (such as from the U.S. Food and Drug Administration) for marketing; in the case of nondrug trials, they are used to inform public health policy or influence clinical practice. All phase 3 trials are prospective: they begin before administration of an intervention (baseline) and follow participants forward in time with follow-up examinations at predetermined intervals after baseline and administration of the tested intervention. They are randomized such that each participant is assigned randomly to either an intervention (test treatment) group or a control group; they are masked (blinded) so that the researchers and, whenever possible, the volunteer participants are not aware of the group to which the participants have been assigned. Finally, before they initiate the study, the investigators must specify the key outcome criteria that will be used to judge treatment success, including the primary and secondary outcome variables, methods of statistical analyses and criteria for statistical and, if possible, clinical significance.

RANDOMIZED CONTROLLED CLINICAL TRIAL DESIGNS

Randomized controlled clinical trials generally have either a parallel-group or a crossover design.

In a parallel-group design, volunteer participants are assigned randomly at the outset of the study to receive either the test intervention or the control treatment for the entire duration of the trial. In a crossover design, participants are assigned randomly to receive either a test intervention or a control intervention for the first "leg" of the study and then are switched over to the other intervention for the second study leg. Because all participants are exposed to both the test and control treatments, each participant serves as his or her own control.

Crossover studies may require fewer participants than do parallel-group design trials, but they must be designed carefully to minimize the influence of one treatment on another. For example, in a crossover trial designed to test a drug intervention, it is necessary to have a pause (a "washout" period) before participants cross over from the test drug leg to the control leg so that any residual effects of the tested drug will dissipate before the control leg begins. Crossover trials have other limitations that can make analysis and interpretation of results challenging.[5] Overall, crossover designs are most appropriate for treatment of the symptoms of relatively stable chronic diseases and for interventions that have short-term, reversible treatment effects.[6]

Trials to test treatments for oral disease sometimes have a split-mouth design in which segments of the mouth (for example, right side versus left side) receive different interventions. This design is applicable only to interventions at specific locations in the mouth, because systemic drugs, for example, would affect all regions of the mouth. Split-mouth designs can be problematic because specific treatment sites within the same person (such as teeth or surfaces of teeth) are not independent of one another, and it is possible that an intervention at one site in the mouth—especially a locally delivered drug—can have a subtle effect on other sites in the same mouth. Although a trial with a split-mouth design can be efficient, it

ABBREVIATION KEY. CONSORT: Consolidated Standards of Reporting Trials. **JADA:** The Journal of the American Dental Association.