Randomized and nonrandomized studies: Complementary or competing?

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Both randomized and nonrandomized studies are integral to orthodontic research and practice because they permit evaluation of relationships between exposures and outcomes, allowing the efficacy, effectiveness, and safety of interventions to be assessed. These designs allow clinical decisions to be informed. Nonrandomized designs include nonrandomized clinical trials, cohort studies, case-control studies, cross-sectional studies, case series, and ecological studies. There is debate surrounding the optimal research design; however, both randomized and nonrandomized designs are important to build a broad, informative evidence base. The designs are therefore complementary, with unique advantages and limitations. The applicability of either approach hinges on the clinical question posed, the feasibility of studying it, and ethical considerations. (Am J Orthod Dentofacial Orthop 2014;146:633-40)

Clinical research involves investigation of the cause of a disease, evaluation of associations between cause and effect, and assessment of the preventive or therapeutic value by isolating and recording potential associations. It is imperative that research findings are interpreted and used optimally.[1] Best conduct, use, and interpretation of research require an understanding of research methodology and study design complemented by adequate and transparent reporting.[2,3]

Clinical research can be broadly classified into nonrandomized and randomized studies. The nonrandomized category, also known as observational studies, includes mainly nonexperimental studies: nonrandomized clinical trials, cohort studies, case-control studies, cross-sectional studies, case series, and ecological studies (Fig 1). Randomized studies are usually known in biomedical research as randomized controlled trials (RCTs). The purpose of randomization is the creation of groups that differ only randomly at the time of allocation of the intervention. Thus, the key difference between randomized and nonrandomized studies is that in the former, the investigator allocates the interventions to participants randomly: eg, by throwing dice or coins, or by using computer software to generate an unpredictable sequence.[4]

There has been considerable debate as to which design is more appropriate to answer clinically important questions.[5-7] RCTs are considered the gold standard for assessing the efficacy and safety of the intervention of interest. However, it is not always possible or ethical to conduct an RCT. When RCTs are not feasible or unethical, nonrandomized studies, such as cohort or case-control studies, may be undertaken. In general, nonrandomized studies are more prone to systematic and confounding biases than are RCTs; consequently, it is also more difficult to make causal inferences concerning the effect of an intervention.[4,8]

Observational studies are used extensively to describe the distribution of disease and exposure in populations. They are also useful for hypothesis generation and testing; however, hypotheses may be assessed more adequately, when feasible, with RCTs.[8] On the other hand, RCTs, although highly controlled and often less biased because they are conducted in highly selected settings, may yield less generalizable results that lack relevance to other populations and settings. RCTs, therefore, tend to have high internal validity but low external validity.[9,10] For example, if we consider the assessment of Class II correction, Class II malocclusion is a multifactorial problem expressed with many variants including maxillary protrusion, mandibular retrognathia, or a

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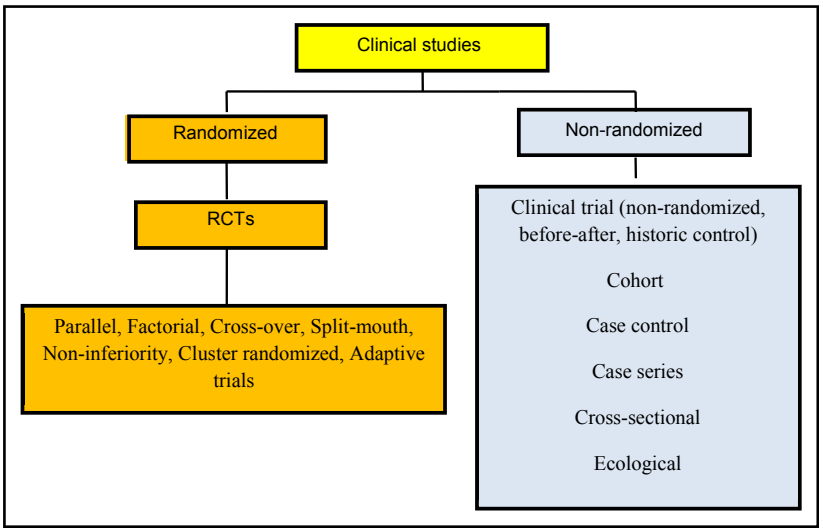

Fig 1. Types of clinical studies based on Cochrane collaboration classification.[4]

Table I. Examples of randomized and nonrandomized (observational) clinical studies

Study type	*Treatment*	*Outcome*	*Source*
Randomized			
Randomized clinical trial	Lingual retainer failures Chemical vs light cured bonding	Failure	Pandis et al, 2013[12]
Randomized clinical trial	Comparison of the Twin-block vs the Dynamax appliance	Class II correction	Thiruvenkatachari et al, 2010[13]
Nonrandomized			
Cohort	Self-ligating vs conventional brackets Wire size and material	Arch-wire ligation time	Turnbull and Birnie, 2007[14]
Case control	Self-ligating vs conventional brackets	Treatment efficiency	Harradine, 2001[15]

combination. A successful intervention for Class II correction demonstrated in an RCT with a highly selected group of participants may not apply to the wider Class II population. Consequently, we can say that the findings of RCTs are less generalizable.[11] Examples of published randomized and nonrandomized (observational) studies[12-15] are shown in Table I.

NONRANDOMIZED STUDIES

For the purposes of this review, the discussion will be limited to cohort and case-control designs, since these are most commonly used when an RCT is inappropriate.

Cohort studies

Cohort studies are also called follow-up, longitudinal, or incidence studies. The subjects are followed over time to monitor their health outcomes. Participants with different levels of exposures to risk factors or different characteristics at baseline are then compared to estimate differences in the rate of developing certain health outcomes later in life. These groups are defined as study cohorts. All participants must be at risk of developing the outcome. The participants are followed for a set period of observation (usually a long period), and all new cases of the outcome of interest are identified. Comparisons of outcome experiences are made within the study cohorts. Ideally, the exposure factor would constitute the only difference between the populations under comparison, although in reality people with different levels of exposures also differ in other characteristics.[16]

Cohort studies that are based on information concerning the exposure and the outcome collected from preexisting sources in the past are called retrospective cohort studies. This design is common in orthodontics when information on exposures and outcomes from patient records is retrieved and associations explored. However, the usefulness of such a study depends on the thoroughness of the certification of the outcome in the records for the time period under consideration. Moreover, information on confounding factors may not be available because there was no planning for the study during completion of the files. Cohort designs have key advantages and disadvantages (Table II).[16]