REVIEW
DOI: 10.5152/EssentDent.2025.24001

ISTANBUL UNIVERSITY CERRAHPASA

Randomized Controlled Trials in Dentistry

Doğa Naz Bahçeci, Selin Saygılı, Yelda Kasımoğlu

Department of Pedodontics,İstanbul University Faculty of Dentistry, İstanbul, Türkiye

Cite this article as: Bahçeci DN, Saygılı S, Kasımoğlu Y. Randomized controlled trials in dentistry. *Essent Dent.* 2025; 4, 0001, doi: 10.5152/EssentDent.2025.24001

Abstract

Randomized Controlled Trials (RCTs), acknowledged as a source of evidence regarding the feasibility of an initiative, are considered secondary level evidence for decisions in practice. However, they are also recognized as a fundamental source for systematic reviews and meta-analyses, which constitute primary-level evidence. Conducting an RCT requires a comprehensive understanding of study design, necessitating researchers to be well-versed in concepts such as PICO question, randomization, statistical tests, sample size calculation, bias, and protocol entries. Considering and adhering to the fundamental concepts of design, coupled with meticulous reporting, can facilitate the demonstration of the actual effects of interventions and the presentation of results with significant evidential value. Despite the ongoing evolution of RCTs over time, systematic deficiencies persist. This review addresses the methodology of RCTs.

Keywords: Bias, dentistry, randomized controlled trial, research methodology, validity

INTRODUCTION

In 1999, the American Dental Association developed the definition of evidence-based dentistry which remains valid today. Evidence-based dentistry is an approach to oral health care that requires the judicious integration of systematic assessments of clinically relevant scientific evidence, relating to the patient's oral and medical condition and history, with the dentist's clinical expertise and the patient's treatment needs and preferences.[1]

Randomized controlled trials, which serve as a source of evidence-based information regarding the feasibility of an intervention, are considered a secondary level of evidence for decision-making in clinical practice. Archie Cochrane, who played a crucial role in laying the foundation for modern evidence-based medical research, was a strong advocate of RCTs. While he critically emphasized the lack of reliable evidence supporting healthcare interventions, he dedicated a significant part of his career to promoting and advancing the use of RCTs.[2]

In a bibliometric study evaluating randomized controlled trials (RCTs) conducted in children and adolescents, it was determined that RCTs have been carried out in various disciplines, including caries management, orthodontics, endodontics, behavioral sciences and quality of life, oral hygiene, periodontology, and oral and maxillofacial surgery. However, the researchers argued that RCTs conducted on pediatric patient groups generally provide insufficient evidence.[3] A comprehensive understanding of

Corresponding author: Doğa Naz Bahçeci
e-mail: doganazbahceci@ogr.iu.edu.tr

Received: January 11, 2024
Revision Requested: February 9, 2024
Last Revision Received: March 25, 2025
Accepted: April 25, 2025
Publication Date: June 29, 2025

study design is critical to conducting a randomized controlled trial effectively. Researchers should be well-versed in the PICO question, randomization, statistical tests, sample size calculation, bias, and protocol entries.[4] The aim of this review is to explain the methodology of RCTs in dentistry and the potential misapplication in the studies.

PLANNING A RANDOMIZED CONTROLLED TRIAL AND CREATING A STUDY PROTOCOL

The initial stage in planning an RCT involves drafting a protocol for conducting the study. Sufficient expertise and financial support are necessary to fulfill the protocol steps. Three crucial points in defining the experimental study are the experimental/intervention group or unit, the intervention to be applied, and the evaluation of the intervention.[5]

PICO QUESTION

The ability to define the headings used in experimental studies is achievable through the formulation of the PICO question. The precision of the research question will facilitate the study design. The elucidation of PICO breaks down a research question into 4 fundamental components: the patients/population to whom the intervention will be applied, the intervention/treatment, the control or comparison, and the outcome measure.[4]

P: The initial stage of a well-planned study is identifying the group where the intervention will be applied and defining their issues.[6,7]

I: The second stage involves determining the intervention. In RCTs, the answer to this question may include any treatment, the use of a product, or a test.[4,6]

C: The control/comparison in the third stage refers to the intervention that will be compared to the intervention.[4] Comparison in the control group can take various forms. Study designs may include placebo, no treatment (though this would be unethical if a valid and standard treatment exists for the condition), administering a different dose of the drug (dose-response studies), or applying a known valid active and standard treatment.[8,9] If the condition to be intervened is symmetrical in the mouth, a split-mouth design can be used to create an individual control group.[10]

O: The fourth step involves determining the outcome measures. During this stage, differences between groups are statistically tested, and the intervention is evaluated.[1] The primary outcome measure is the targeted information, while secondary outcome measures, while not individually significant, contribute to a comprehensive interpretation when evaluated together.[11,12]

SAMPLE SIZE AND INCLUSION/EXCLUSION CRITERIA

Sample size determination is the process of identifying the required number of subjects during the planning phase to demonstrate the statistical power necessary to detect a significant difference between experimental groups. In RCTs, determining an appropriate sample size is crucial for the statistical design of the study. Working with an adequate sample size provides confidence in the reliability of the obtained outcomes. Oversizing the sample may result in statistical significance while undersizing may lead to a lack of observed variation and inconclusive results. An optimum and minimally effective sample size should be chosen. Working with excessively large samples raises ethical concerns due to the increased intervention of a larger number of individuals.[13]

The sample size can be calculated using various statistical methods, where calculating it through power analysis is considered the gold standard. The magnitude of the sample size relies on 4 primary factors: the type 1 error rate (α), the type 2 error rate (ß), effect size, and outcome measures. Type 1 and type 2 errors are not independent but are interconnected, necessitating a balanced consideration. In clinical trials within the health sciences, the type 1 error (*P*-value) is commonly set at 0.05.[13] Additionally, aiming for the study's power to be generally within the range of 80%-90% is preferred, not falling below 80%. Effect size is defined as the difference between the parameters of 2 distributions and is calculated using data obtained from prior literature or a pilot study planned and conducted before the main study.[14,15]

The next step involves establishing appropriate criteria for the inclusion or exclusion of individuals in the study. Primarily aimed at ensuring patient safety, these criteria also impact various aspects of the study and the interpretability of its outcomes. Stringent inclusion criteria can pose challenges in achieving the required sample size. Additionally, they may result in selecting a study group that does not adequately represent a broad target population, limiting the generalizability of the findings. In such cases, it is recommended to set exclusion criteria with strict boundaries to balance external validity.[16,17]

EFFICIENCY AND EFFECTIVENESS

There are concepts that need to be taken into account when planning an experimental study. It is necessary to decide on the measurement of efficacy or effectiveness in the study.[18] The study can be planned as a superiority trial, an equality trial, or a non-inferiority trial according to its conceptual structure.[19] The objectives and methodology of these trials differ, leading to variations in the interpretation of statistical results or in the analytical process. The most appropriate approach should be selected in the study design, with options including parallel, cluster, and crossover study designs. Bias risks and their management, evaluation of the outcome measure, determination of the sample group, and statistical planning should be done in advance.[18]

DEVELOPING THE STUDY PROTOCOL

Researchers should utilize the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT), developed by an international team to establish the standards essential in a clinical study protocol. The 33-item SPIRIT checklist can be applied to all clinical trial protocols, focusing more on the content than the format of RCTs. It provides guidance for key content, enhancing the transparency and integrity of the protocol, without including design and execution specifics.[20] Additionally, the SPIRIT 2013 Statement reflects applicable elements of the Consolidated Standards of Reporting Trials (CONSORT), facilitating the transition from the protocol to the final report based on CONSORT, thanks to a consistent structure used for common expressions in both checklists.[21]

FUNDAMENTAL CONCEPTS FOR RANDOMIZED CONTROLLED TRIALS

Bias

Bias is the absence of impartiality or presence of prejudice. It can be defined as a departure from the truth. In scientific contexts, it refers to any factor or process that systematically tends to steer the results or conclusions of a trial away from the truth. In clinical trials, errors can be observed as systematic - bias or variability. Variability can be defined as a random error. With the disruption of homogeneity, variation increases, expanding the CI. Bias can occur in various stages such as the design, implementation, analysis, or reporting of the trial, and can exist at different levels. It has been reported that there could be more than 35 types of bias.[22] It is expected that significant biases, which would considerably impact the study's outcomes, are particularly controlled throughout the study.[22,23] The underreporting of negative results, the selectivity of journal editors, and biases during the reporting phase are generally referred to as publication bias and dissemination bias, which are crucial in RCTs and systematic reviews/meta-analyses derived from them.[24]

In recent years, it has been recommended that RCTs are preferably registered on openly accessible websites specifically designed for this purpose, either during the planning phase or upon completion of the report, obtaining a registration number to be shared in publications.[25] This practice helps reduce publication bias, facilitates systematic reviews and literature examinations, informs potential participants and clinical practitioners, and enables the standardized presentation of study outputs in an accessible format to everyone.[26] The World Health Organization has declared that registering all clinical trials on the International Clinical Trials Registry Platform is a scientific and ethical responsibility and a necessity.[25] Obtaining a registration number is also included in the CONSORT 2010 items.[21,27]

CONSORT 2010 comprises a 25-item checklist and a flow diagram, providing guidance for all RCTs, although certain study designs may require additional information. Researchers can access supplementary lists on the CONSORT website for these designs. Adherence to the checklist items by authors ensures clarity, integrity, and transparency during the reporting process. Ortiz et al[28] identified deficiencies in RCTs published on dental caries concerning compliance with the CONSORT guidelines and recommended addressing this issue. A positive relationship has been demonstrated between the year of publication and compliance with CONSORT.[29]

Causality

The primary aim of research is to measure the relationship between an intervention/treatment and an outcome/result. One of the most critical requirements in evaluating outcomes is that all characteristics, apart from the intervention, of the groups should be similar in terms of confounders. Confounders are defined as variables that lie outside the investigated intervention but could influence the outcome. Variables like age, gender, race, dietary habits should be considered during the planning phase and distributed equally between both groups.[22]

The solution to this issue is ideal randomization. However, criticisms may arise regarding the selected method of randomization or the imbalance in group sizes. Selecting the most suitable method (simple randomization, stratified randomization, block randomization) according to the study will ensure this. It is crucial to statistically demonstrate that randomization has been achieved after forming the groups.[30]

The second requirement for causality is to clearly demonstrate that the changes occurring over time in the groups are due to the intervention. To fulfill this requirement, blinding techniques (single-blind, double-blind, triple-blind) may be employed, and depending on the suitability of the research topic, cluster or crossover designs can be considered. The importance of the scope of statistical evaluations in demonstrating causality should not be overlooked. Providing clear information about effect size, a 95% CI, and *P*-value is reported to be significant. Preventing biases is another factor ensuring the unaffectedness of causality.[31]

External Validity

External validity is defined as the ability to generalize findings obtained from a specific setting and a limited number of individuals to a larger population in real-life situations. Deviation from real-life conditions within the experimental setting makes generalization challenging. Within evidence-based medicine, there's a tendency to incline toward studies with high internal validity in evaluating the quality of studies to be included in clinical guidelines. This inclination raises concerns about the potential inadequacy of translating successful outcomes into practical applications.[32] It has been reported that it is challenging to achieve external validity in systematic analyses that evaluate RCTs, highlighting insufficient external validity and difficulties in applying findings to the population.[33] To enhance the external validity of RCTs,

reducing exclusion criteria is recommended. While single-center RCTs reduce external validity, multicenter RCTs have shown higher bias detection.[34]

Internal Validity

The level to which the results of an RCT reflect reality is directly associated with how far it can remain free from potential biases. The reliability of results in RCTs, their accuracy, and the assessment of reliable methods are termed internal validity.[35] At the same time, there needs to be a balance between internal and external validity. The generalizability of results in RCTs is achievable through external validity while ensuring that internal validity is not compromised in this process.[36]

Although there are several tools assessing the quality of RCTs, quality assessment tools primarily focus on internal validity.[37] If there is a bias in the methodological aspect of the study, the observed effect may not reflect the truth. Cochrane Collaboration's tool for assessing risk of bias, which evaluates the bias risk of the study in terms of internal and external validity dimensions, is widely accepted and recommended. This tool categorizes biases into 6 domains and signifies various methods developed to avoid each bias: Selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.[38]

Selection Bias and Randomization

Selection bias that may arise during the determination of intervention and control groups implies a difference in the fundamental characteristics of the groups being compared. During the group formation process, individuals believed to potentially respond more effectively or unfavorably to the intervention due to biases, either knowingly or unknowingly, might be deliberately or inadvertently separated. Randomization is recognized as the most effective method to control selection bias.[38]

Random Selection: It involves giving an equal chance to individuals chosen from a specific population.

Random Allocation: Individuals in a designated sample should have an equal chance of being allocated to intervention and control/comparison groups. One of the 2 crucial steps for effective randomization is random allocation, and the other is allocation concealment, which involves concealing the assignment process from the researchers involved in the study.[22,38]

Randomization is considered the cornerstone of RCTs, and the absence of randomization significantly impacts the quality of a study. Outputs obtained from non-randomized studies are considered weaker evidence compared to those obtained from RCTs.[39] Methods such as simple randomization, stratified randomization, and block randomization are preferred for RCTs. It is recommended to select the most suitable method for the study and have individuals outside of the research team manage this process. Methods such as birthdate, order of application, or registration number are deemed inappropriate for selection. Using sealed opaque envelopes for concealing allocation is recommended.[9,39]

Performance Bias – Detection Bias and Blinding

One of the biases that can arise during the execution of a study and the process of measurements is known as performance bias. If those executing the intervention influence the study outcome, it is termed as the Rosenthal effect; when individuals in the groups knowingly or unknowingly affect the study's outcome, it is referred to as the Hawthorne effect.[40]

Detection bias, on the other hand, involves an effect similar to performance bias, where the individual measuring the outcome anticipates an effect from the group being measured, resulting in biased evaluation.[38] Performance and detection bias can also be collectively termed ascertainment bias.

Blinding or masking stands out as an effective method of preventing these biases. Blinding in RCTs refers to 1 or more individuals involved in the study groups not being aware of whether they are receiving the intervention or the control/comparison.[35,38,39] Maximizing blinding for as many individuals as possible in studies is recommended. During the reporting of the study, details about blinding and reasons for situations where blinding was not feasible should be provided. Studies where only those administering the intervention/measurement or participants are blinded are termed single-blind; those where both administrators/measurements and participants are blinded are double-blind, and studies where administrators, participants, and those conducting statistical analyses are blinded are termed triple/quadruple-blind studies. Studies without any blinding are referred to as open-label studies. While double-blind studies have been perceived as high quality by many researchers and readers when evaluating RCTs, those not designed in this manner should not necessarily be deemed lower quality; examining reported blinding processes is crucial.[31,35,41,42]

Attrition Bias and Resolution Approaches

Throughout a study, certain participants may leave for various reasons, resulting in data loss termed as dropout.[43] Schulz and Grimes[44] recommended that a loss to follow-up of 5% or less is unlikely to introduce bias; a loss of 20% gives concern about the possibility of bias; a loss of between 5% and 20% might be a source of bias. However, when dropout rates exceed this percentage, attrition bias occurs, disrupting the balance established by randomization. The fundamental method for prevention is known as Intention-to-Treat (ITT). Intention-to-Treat analysis entails including every participant in the analysis of the group to which they were assigned post-randomization, regardless of any separations occurring after randomization, without considering any reasons. Its basic principle is known as "randomized so analyzed."[38,45]

Among the significant reasons for considering individuals who did not receive or complete the intervention in assessing the outcomes are the fact that there will always be mismatched individuals in real life and dropout might be due to adverse effects or lack of perceived benefits from the intervention itself. While developing methods to minimize losses during study planning is the primary measure, in long-term studies, these losses are sometimes unavoidable. Alternative methods for ITT analysis include modified ITT and per-protocol analyses.[46]

The pattern and balance of missing data are crucial. Having more dropouts in 1 group is termed uneven attrition and might suggest participant dissatisfaction with the intervention.

All data must be complete for the inclusion of all participants in the analysis. Statistical methods should be employed to address missing data. Some of these methods include Longitudinal Mix Model, Cox Regression, Last Observation Carried Forward, Extreme Case Analysis, Sensitivity Analysis, and Multiple Imputation. Although different statistical strategies are said not to significantly differ in effect estimation, it has been reported that various existing methods for managing missing data may yield different outcomes in effect estimation. Accurate identification of shortcomings is crucial in determining the most suitable method. Researchers are expected to clearly state the losses, their reasons, and the statistical methods used in handling missing or incomplete data.[47]

Reporting Bias and Blinding of the Report Writer

Reporting bias during the writing of the research report is the tendency of the report writer to present the outcomes and interpretations in line with the hypothesis. Selective outcome reporting (SOR) occurs when researchers selectively report findings, presenting only chosen outcomes and analyses, leading to reporting bias. Reporting bias can also stem from the selection of analyses for reporting, resulting in analysis reporting bias.[48] The quality of reporting has been regarded as equivalent to the quality of the study, highlighting the significant threat posed by high SOR prevalence.[49] Göstemeyer et al[50] suggested the mandatory prospective registration in dental journals, proposing that this approach could reduce publication bias and SOR risk while enhancing the design and quality of RCTs. To prevent reporting bias, it is essential for the report writer to remain blinded to the groups until the completion of the report, the protocol should be preregistered, and transparency should be ensured throughout the process.[37]

RANDOMIZED CONTROLLED TRIALS IN DENTISTRY

Randomized controlled trials are considered the most reliable clinical study design for evaluating the effectiveness of an intervention in evidence-based dentistry. Mendes et al[11] have stated that RCTs represent the most appropriate methodology for prospective clinical studies. They emphasized that RCTs provide the strongest evidence for assessing and comparing the effects of treatments and preventive health procedures. However, they also noted that the results of RCTs may still vary, as they are conducted within a specific population. To address this limitation, ensuring transparency in the study and adhering to methodological considerations in study design are essential. Furthermore, they highlighted the necessity of conducting RCTs in dentistry, emphasizing their contribution to the implementation of evidence-based treatments.

The quality of RCTs' design and reporting is critical in terms of evidential value; therefore, it is necessary to examine and improve their quality. Systematic reviews assessing the quality of RCTs conducted in dentistry, based on CONSORT standards, have indicated that the quality of studies has improved over the years.[29] However, many studies still have significant incomplete data. Poor reporting has been equated with poor study quality, as it can lead to unreliable and misleading results. It is not possible to differentiate whether a study is methodologically sound if it is insufficiently reported.[49] It has been suggested that studies with weak quality and internal validity do not contribute any meaningful outcomes to evidence-based dentistry and that these studies represent a waste of existing resources.[34] Improving quality should be a common goal for authors, reviewers, and journal guidelines, and collaborative efforts in this direction are recommended.

CONCLUSION

Randomized controlled trials are considered second-level evidence regarding the clinical implementation of a treatment or intervention and serve as a primary source for studies identified as first-level evidence. To ensure reliable results, careful attention must be given to the planning, design, conduct, data analysis, and reporting of RCTs. At the outset of the study, establishing the research protocol and maintaining records at every stage of the study are fundamental for RCTs. Understanding and controlling various biases, and ensuring internal and external validity are essential. Using appropriate statistical techniques, implementing randomization, and detailing every aspect, whether executed or not, in the research report are highly crucial. Consequently, when approached in this manner, RCTs provide results of evidential value. Despite the evolution of RCTs over time, there are still systematic deficiencies, therefore, researchers should have a good understanding of RCT methodology.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: N/A

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – YK.; Design – DNB.; Supervision – YK.; Resources – DNB, SS, YK; Materials – DNB, SS, YK.; Data Collection and/or Processing – DNB, SS, YK.; Analysis and/or Interpretation – DNB, YK.; Literature Search – DNB, SS.; Writing Manuscript – DNB.; Critical Review – SS, YK; Other – DNB, SS, YK.

Declaration of Interests: The authors declare that they have no competing interests.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Chiappelli F. Evidence-Based Dentistry: two decades and beyond. *J Evid Based Dent Pract*. 2019;19(1):7-16. [CrossRef]
2. Shah HM, Chung KC. Archie Cochrane and his vision for evidence-based medicine. *Plast Reconstr Surg*. 2009;124(3):982-988. [CrossRef]
3. Jiang CM, Lee GHM, Lo ECM, Chu CH, Wong MCM. Randomized controlled trials in dental journals on children and adolescents: a bibliometric analysis. *J Evid Based Dent Pract*. 2021;21(4):101621. [CrossRef]
4. Brocklehurst P, Hoare Z. How to design a randomised controlled trial. *Br Dent J*. 2017;222(9):721-726. [CrossRef]
5. Chow S-C, Liu J-P. *Design and Analysis of Clinical Trials: Concepts and Methodologies*. vol 507. Chichester, UK: John Wiley & Sons; 2008.
6. El Meligy O, Alamoudi NM, Allazzam SM, El-Housseiny AAM. Biodentine(TM) versus formocresol pulpotomy technique in primary molars: a 12-month randomized controlled clinical trial. *BMC Oral Health*. 2019;19(1):3. [CrossRef]
7. Innes NP, Clarkson JE, Douglas GVA, et al. Child caries management: a randomized controlled trial in dental practice. *J Dent Res*. 2020;99(1):36-43. [CrossRef]
8. Hesse D, de Araujo MP, Olegário IC, Innes N, Raggio DP, Bonifácio CC. Atraumatic restorative treatment compared to the Hall Technique for occluso-proximal cavities in primary molars: study protocol for a randomized controlled trial. *Trials*. 2016;17:169. [CrossRef]
9. Akan H. Bilimsel araştırmalarda planlama ve tasarım. *ANKEM Derg*. 2014;28:101-104.
10. Pozos-Guillén A, Chavarría-Bolaños D, Garrocho-Rangel A. Split-mouth design in paediatric dentistry clinical trials. *Eur J Paediatr Dent*. 2017;18(1):61-65. [CrossRef]
11. Mendes FM, Braga MM, Pássaro AL, et al. How researchers should select the best outcomes for randomised clinical trials in paediatric dentistry? *Int J Paediatr Dent*. 2020;31(Suppl 1):23-30. [CrossRef]
12. Lopez-Cazaux S, Aiem E, Velly AM, Muller-Bolla M. Preformed pediatric zirconia crown versus preformed pediatric metal crown: study protocol for a randomized clinical trial. *Trials*. 2019;20(1):530. [CrossRef]
13. Wang X, Ji X. Sample size estimation in clinical research: from randomized controlled trials to observational studies. *Chest*. 2020;158(1s):S12-S20. [CrossRef]
14. Bagiella E, Chang H. Power analysis and sample size calculation. *J Mol Cell Cardiol*. 2019;133:214-216. [CrossRef]
15. Demirel N, Gürler S. Klinik çalışmalarda örneklem genişliğinin belirlenmesine pratik yaklaşımlar. *Kafkas Univ Vet Fak Derg*. 2010;15(2):205-211.
16. Jayaraman J. Guidelines for reporting randomized controlled trials in paediatric dentistry based on the CONSORT statement. *Int J Paediatr Dent*. 2020;31(Suppl 1):38-55. [CrossRef]
17. Zabor EC, Kaizer AM, Hobbs BP. Randomized controlled trials. *Chest*. 2020;158(1S):S79-S87. [CrossRef]
18. Akın B, Koçoğlu-Tanyer D. Randomize kontrollü deneyler. *Hacet Üniv Hemşire Fak Derg*. 2017;4(1):73-92.
19. Lesaffre E. Superiority, equivalence, and non-inferiority trials. *Bull NYU Hosp Jt Dis*. 2008;66(2):150-154.
20. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *Br Med J*. 2013;346:e7586. [CrossRef]
21. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010;63(8):834-840. [CrossRef]
22. Attia A. Bias in RCTs: confounders, selection bias and allocation concealment. *Middle East Fertil Soc J*. 2005;10(3):258.
23. Pannucci CJ, Wilkins EG. Identifying and avoiding bias in research. *Plast Reconstr Surg*. 2010;126(2):619-625. [CrossRef]
24. Song F, Hooper L, Loke Y. Publication bias: what is it? How do we measure it? How do we avoid it? *Open Access J Clin Trials*. 2013;5:51-81.
25. Editors-ICMJE. ICMJ. Clinical Trials Registration. Available at: https://www.icmje.org/about-icmje/faqs/clinical-trials-registration/. Accessed 25 March 2025.
26. Tse T, Williams RJ, Zarin DA. Reporting "basic results" in Clinicaltrials.gov. *Chest*. 2009;136(1):295-303. [CrossRef]
27. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Br Med J*. 2010;340:c869. [CrossRef]
28. Ortiz MIG, Ribeiro MES, Lima D, Silva CM, Loretto SC, da Silva E Souza Júnior MH. Compliance of randomized clinical trials on dental caries prevention methods with the CONSORT statement: a systematic review. *J Evid Based Dent Pract*. 2021;21(2):101542. [CrossRef]
29. Alnamankany A, Ashley P. Assessment of the quality of reporting of randomized clinical trials in paediatric dentistry: a comparative systematic review. *J Taibah Univ Med Sci*. 2020;15(1):1-7. [CrossRef]
30. Lim CY, In J. Randomization in clinical studies. *Korean J Anesthesiol*. 2019;72(3):221-232. [CrossRef]
31. Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. *Lancet*. 2002;359(9307):696-700. [CrossRef]
32. Fernandez A, Sturmberg J, Lukersmith S, et al. Evidence-based medicine: is it a bridge too far? *Health Res Policy Syst*. 2015;13:66. [CrossRef]
33. Avellar SA, Thomas J, Kleinman R, et al. External validity: the next step for systematic reviews? *Eval Rev*. 2017;41(4):283-325. [CrossRef]
34. Lucena C, Souza EM, Voinea GC, Pulgar R, Valderrama MJ, De-Deus G. A quality assessment of randomized controlled trial reports in endodontics. *Int Endod J*. 2017;50(3):237-250. [CrossRef]
35. Turlik M. Evaluating the internal Validity of a randomized controlled trial. *FAOJ*. 2009;3:5. [CrossRef]
36. Godwin M, Ruhland L, Casson I, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and

internal validity. *BMC Med Res Methodol*. 2003;3(1):28. [CrossRef]
37. Armijo-Olivo S, Fuentes J, Ospina M, Saltaji H, Hartling L. Inconsistency in the items included in tools used in general health research and physical therapy to evaluate the methodological quality of randomized controlled trials: a descriptive analysis. *BMC Med Res Methodol*. 2013;13:116. [CrossRef]
38. Higgins J. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. Available at: https://handbook-5-1.cochrane.org/
39. Flecha OD, Douglas de Oliveira DW, Marques LS, Gonçalves PF. A commentary on randomized clinical trials: how to produce them with a good level of evidence. *Perspect Clin Res*. 2016;7(2):75-80. [CrossRef]
40. Mariani LL, Corvol JC. Maximizing placebo response in neurological clinical practice. *Int Rev Neurobiol*. 2020;153:71-101. [CrossRef]
41. Karanicolas PJ, Farrokhyar F, Bhandari M. Practical tips for surgical research: blinding: who, what, when, why, how? *Can J Surg*. 2010;53(5):345-348.
42. Köroğlu G, Çorapçıoğlu A, Kalender B. Kronik böbrek yetmezlikli depresif hastalarda sitalopram tedavisinin yaşam kalitesine etkisi: açık etiketli bir ön çalışma. *Klin Psikiyatr Derg*. 2003;6(3):158-164.
43. Nunan D, Aronson J, Bankhead C. Catalogue of bias: attrition bias. *BMJ Evid Based Med*. 2018;23(1):21-22. [CrossRef]
44. Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *Lancet*. 2002;359(9308):781-785. [CrossRef]
45. Armijo-Olivo S, Warren S, Magee D. Intention to treat analysis, compliance, drop-outs and how to deal with missing data in clinical research: a review. *Phys Ther Rev*. 2009;14(1):36-49. [CrossRef]
46. Gupta SK. Intention-to-treat concept: a review. *Perspect Clin Res*. 2011;2(3):109-112. [CrossRef]
47. Cheema JR. Some general guidelines for choosing missing data handling methods in educational research. *J Mod Appl*. 2014;13(2):3.
48. Norris SL, Holmer HK, Ogden LA, et al. AHRQ methods for effective health care. *Selective Outcome Reporting as a Source of Bias in Reviews of Comparative Effectiveness*. Rockville, MD: Agency for Healthcare Research and Quality (US); 2012.
49. Rajasekharan S, Vandenbulcke J, Martens L. An assessment of the quality of reporting randomised controlled trials published in paediatric dentistry journals. *Eur Arch Paediatr Dent*. 2015;16(2):181-189. [CrossRef]
50. Göstemeyer G, Blunck U, Paris S, Schwendicke F. Design and validity of randomized controlled dental restorative trials. *Materials (Basel)*. 2016;9(5):372. [CrossRef]