

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/142951/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Nagendrababu, V., Duncan, H.F., Pulikkotil, S.J. and Dummer, P.M.H. 2021. Glossary for randomized clinical trials. *International Endodontic Journal* 54 (3) , pp. 354-365. 10.1111/iej.13434

Publishers page: <https://doi.org/10.1111/iej.13434>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Glossary for randomized clinical trials

V Nagendrababu¹, HF Duncan², SJ Pulikkotil³ PMH Dummer⁴

¹Department of Preventive and Restorative Dentistry, College of Dental Medicine, University of Sharjah, Sharjah, UAE, ²Division of Restorative Dentistry, Dublin Dental University Hospital, Trinity College Dublin, Dublin, Ireland, ³Division of Clinical Dentistry, School of Dentistry, International Medical University, Kuala Lumpur, Malaysia, ⁴School of Dentistry, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK.

Corresponding author

Henry F Duncan
Division of Restorative Dentistry,
Dublin Dental University Hospital,
Trinity College Dublin,
Dublin,
Ireland

E mail: Hal.Duncan@dental.tcd.ie

Keywords: Endodontics, glossary, randomized clinical trials.

Running title: Glossary

The authors deny any conflicts of interest related to this study.

Glossary for randomized clinical trials

Randomized clinical trials are positioned at the highest level of primary clinical evidence, as they are designed to be unbiased with a reduced risk of systematic error. The Consolidated Standards of Reporting Trials (CONSORT) statement was first developed in 1996 to improve the reporting quality of randomized clinical trials with updates being published subsequently. Recently, the Preferred Reporting Items for RAndomized Trials in Endodontics (PRIRATE) 2020 guidelines were developed exclusively for the field of Endodontics to address the sub-optimal quality of randomized clinical trials submitted to Endodontic journals, which result in many being rejected. A principal flaw in submissions is the fact that many authors are unclear on the key terms that should be used when developing manuscripts for publication. Clearly, authors should be aware of the most common terms used when conducting and reporting randomized clinical trials. Hence, the aim of the current paper is to present a comprehensive glossary of the terminology used in randomized clinical trials in order to assist authors when designing, executing and writing-up randomized clinical trials.

Glossary for randomized clinical trials

Abstract

Randomized clinical trials are positioned at the highest level of primary clinical evidence, as they are designed to be unbiased with a reduced risk of systematic error. The Consolidated Standards of Reporting Trials (CONSORT) statement was first developed in 1996 to improve the reporting quality of randomized clinical trials with updates being published subsequently. Recently, the Preferred Reporting Items for RAndomized Trials in Endodontics (PRIRATE) 2020 guidelines were developed exclusively for the field of Endodontics to address the sub-optimal quality of randomized clinical trials submitted to Endodontic journals, which result in many being rejected. A principal flaw in submissions is the fact that many authors are unclear on the key terms that should be used when developing manuscripts for publication. Clearly, authors should be aware of the most common terms used when conducting and reporting randomized clinical trials. Hence, the aim of the current paper is to present a comprehensive glossary of the terminology used in randomized clinical trials in order to assist authors when designing, executing and writing-up randomized clinical trials.

Keywords

Endodontics, glossary, randomized clinical trials.

Introduction

In the context of evidence-based Medicine and Dentistry, well-designed, conducted and reported randomized clinical trials provide reliable sources of evidence on the efficacy of interventions (Cioffi & Farella 2011, Hariton & Locascio 2018). On the other hand, poorly conducted and reported clinical trials are associated with bias, which leads to spurious results on the effects of specific treatments that can in turn mislead clinical decision-making at the individual patient-level and potentially have a negative impact on national public health policy (Moher *et al.* 2012).

The number of randomized clinical trials submitted each year to the *International Endodontic journal* in the field of Endodontology has increased over recent years, from approximately 14 in 2017 to 23 in 2019 (Dummer PMH, unpublished data). However, randomized trials in Endodontics often have deficiencies in randomization, blinding, allocation concealment and insufficient power, as well as an absence of funding and *a priori* protocol registration (Duncan *et al.* 2016, Alamri & Alharbi 2018, Yi *et al.* 2020), resulting in many manuscripts being of sub-optimal quality (Lucena *et al.* 2016).

The Consolidated Standards of Reporting Trials (CONSORT) guidelines contain a checklist and flowchart to help authors improve the reporting of randomized clinical trials. The Preferred Reporting Items for Randomized Trials in Endodontics (PRIRATE) 2020 guidelines were developed exclusively for trials in the field of Endodontics using a consensus-based process (Nagendrababu *et al.* 2020) that adapted the CONSORT statement (Moher *et al.* 2012) and the Clinical and Laboratory Images in Publications (CLIP) principles (Lang *et al.* 2012).

A large variety and range of terms are used in reports of randomized clinical trials submitted to journals. A glossary explaining the meaning of these terms in simple language will be helpful for authors when writing manuscripts and also for readers of reports describing randomized clinical trial. A glossary is an explanation (definition) of the terms in a specific subject, field, or area that helps to standardize and establish the correct terminology, thus assisting in dissemination and

implementation within the discipline and associated fields (Rabin *et al.* 2008). The current paper provides a comprehensive list of terms used in randomized controlled trials with a brief and simple explanation for the benefit of readers, researchers and authors. The terms in the paper are accompanied by relevant references for readers who wish to learn more.

Glossary List

1. *Absolute effect sizes* - The absolute difference in the mean outcomes between the intervention and control groups in a clinical trial. In other words, the absolute magnitude of the treatment effect due to the intervention compared with the control. For example, in a clinical trial, 4.5% of subjects had post-obturation pain following intake of Medication A, whereas 7.5% of subjects had pain after taking the placebo. So, the benefit (absolute effect size) of medication A was 3% (7.5 – 4.5 %). Absolute effect sizes are specific to the sub-population/sample under investigation and cannot be generalized to other populations, which are likely to have varying characteristics (e.g. age) (Sullivan & Feinn 2012).
2. *Adjusted analyses* - Analyses that balance variations caused by differences in background variables that occur between the intervention and control groups. For example, if the age of participants is different in the intervention and control groups and age is known to affect the outcome variable, the effect of age on the results can be controlled by an adjusted analysis. Other examples could include gender and medical conditions such as diabetes. All analyses including the adjusted analyses should be pre-specified in the protocol to avoid bias (Moher *et al.* 2012). Pre-specified adjusted analyses are considered stronger evidence than *post hoc* adjustments (Tanniou *et al.* 2016).
3. *Adverse effect* – An untoward or unwanted effect experienced by a few or all the subjects in a trial that appears to be associated with the use of the experimental intervention or drug (Chou *et al.* 2010). For example, in a clinical trial comparing the anaesthetic success of Gow-Gates and inferior alveolar

nerve blocks, several patients who received the inferior alveolar nerve block had prolonged lip numbness and tenderness at the site of injection.

4. *Adverse events* - An untoward or unwanted event occurring during or after completion of a trial that may or may not be attributed to the intervention or drug given to the subjects (Chou *et al.* 2010, Kalenderian *et al.* 2017), e.g. aspiration of endodontic files while performing root canal treatment, extraction of the wrong tooth etc.
5. *Allocation concealment* - The process used to eliminate selection bias (Item 59) which would otherwise occur if the investigators allocated specific subjects (preferred allocation) to respective treatment arms. Allocation of subjects must always be done by an independent person who withholds information on the allocation sequence from investigators and participants until the trial has been completed (Forder *et al.* 2005, Sargeant *et al.* 2014).
6. *Allocation ratio* - The ratio of intended subjects among the treatment/intervention/control arms in a trial, which can be either equal or unequal (Altman 2018), dependent on the study design. An intervention that results in less precision (larger standard deviation) would benefit from recruiting more patients, resulting in an unequal allocation. Unequal allocation may also be of value when one intervention is extremely expensive in comparison to the control or another intervention (Vozdolska *et al.* 2009).
7. *Bias* - A systematic flaw in a trial that leads to errors in the results and the subsequent inferences (conclusions) by favouring a treatment arm more than could occur by chance. The three major classification of bias are: information bias (Item 32), selection bias (Item 59), and confounding bias (Item 14). Bias can occur at various stages of a trial: data collection, data analysis, data interpretation, publication, or data review (Delgado-Rodriguez & Llorca 2004).
8. *Binary outcome* - A variable that has only two possible mutually exclusive outcomes (Petrie & Sabin 2005) such as: present or absent, male or female, alive or dead, vital or non-vital. For example, when comparing the effect of

premedication on the anaesthetic success of inferior alveolar nerve blocks while performing root canal treatment in mandibular molars the outcome could be assessed by presence or absence of pain.

9. *Blinding* – The process by which study participants, investigators, operators/evaluators and outcome assessors are completely unaware of the assigned intervention to make sure they are not influenced (biased) by that information (Schulz & Grimes 2002). It is also sometimes referred to as masking. Blinding plays a vital role in ensuring the validity of randomized clinical trials (Penić *et al.* 2020). Randomized clinical trials can be blinded or non-blinded (Gandhi 2011); a non-blinded trial is also called an open-label study. In general, there are several levels or degrees of blinding: “single” (Item 61), “double” (Item 19) and “triple” (Item 69) (Saltaji *et al.* 2018). For example, in a clinical trial comparing the effectiveness of root canal retreatment and periapical surgery neither intervention is easily blinded and both the subjects and investigators will be fully aware of the intervention. Consequently, trials incorporating sham procedures and inactive devices have become popular in order to reduce the confounding effects associated with a subject’s knowledge of treatment assignment.
10. *Block randomization* – A commonly used technique in trial design that randomizes subjects into groups of equal sample size. It is particularly useful for studies of small size, helping to reduce bias and achieve balance in participant allocation (Efird 2011). For example, 36 patients were recruited into a root canal irrigation study by block randomization with 18 allocated to a sodium hypochlorite and 18 to a chlorhexidine regimen. However, a disadvantage of block randomization is that it can also increase the predictability of subject enrolment near the end of the recruitment phase (Saghaei 2011). A way of countering this predictability is to introduce variable block size for example, including block sizes of 4, 5 and 6 in random order.
11. *Cluster effects* - Clustering may arise when there is a potential for correlation of outcomes among patients in similar groups, which can result in a loss of independence of observations (Oltean & Gagnier 2015). For example, in a

multi-centre study examining the outcome of root canal treatment, if one University dental clinic supplied 20 patients and a general dental practice supplied 100 patients there is a risk of clustering in the analysis when the results are combined. Clustering can also occur within a patient, if more than one tooth is included in the study analysis.

12. *Confidence interval (CI)* – A range of values at the stated confidence level that contains the true value of the unknown parameter, such as the ‘mean’, which is calculated from the dataset. To eliminate bias, the confidence level to be used should be decided before the data is analysed (Goodman *et al.* 1994). For example, a 95% Confidence Interval provides a range of values that contains the true value at a confidence of 95%, in other words, if the experiment was conducted 100 times, 95% of the true values (the respective means) would fall within these intervals (limits).
13. *Conflict of interest* – The presence of individual private or commercial interests that can influence the primary interest in a clinical trial. The primary interest of a clinical trial is to reveal the truth about the effectiveness of a chosen intervention. The presence of a conflicting interest, financial or otherwise, is likely to affect the validity of the trial and should be disclosed for the end-user to understand that a conflict exists and make their own decision on its relevance (Probst *et al.* 2016). For example, a person who developed a new instrument, will inevitably be biased in favour of their own instrument when evaluating its effectiveness.
14. *Confounding bias* - The presence of various factors not considered as independent factors in a trial, but which may have an impact on the outcome of the trial. These factors are called ‘confounders’ and can result in bias if not addressed. A confounding factor is of concern if it is related to the outcome and distributed differentially among the groups being compared in the study (Skelly *et al.* 2012).
15. *Confounding factors* - Factors that are not measured but can influence both dependent and independent variables in a trial and which can lead to spurious

associations between the measured independent variable and the outcome. Many background variables such as age, gender, race, economic status, diet and presence of other disease states can act as confounders (Skelly *et al.* 2012).

16. *CONSORT* statement (CONsolidated Standards Of Reporting Trials) - A checklist of 25 items and a flow diagram that provides detailed advice and guidance on the reporting of randomized trials to ensure all the necessary information is included, i.e. it directs authors to report trials completely and transparently (Moher *et al.* 2012). When a trial is peer-reviewed and later published, the CONSORT statement can be used as a checklist to evaluate its methodological quality.
17. *Continuous outcome* – Numerical measures that can have infinite values that the variable can take (Petrie & Sabin 2005). For example, outcomes such as height, blood pressure, haemoglobin level etc.
18. *Crossover design* – In a two-armed trial, patients are initially allocated to one of two groups; one group is assigned to the intervention and the second group is not assigned to the intervention. After a period of time, during which the outcomes have been assessed, the patients from both groups undergo a period of ‘washout’ so that the effect from the initial group intervention is removed. Once this occurs, the subjects then crossover into the other group and the trial continues. The crossover study design has the benefit of reducing the variability in outcome measures that can be influenced by external confounders, as each individual patient serves as their own control. This is in contrast to a parallel design where different sets of individuals are allocated to the specific intervention(s), or control, before being compared (Nair 2019).
19. *Double blind* - The concealment of important information from participants and investigators/examiners within a clinical trial, including its objectives, hypotheses, expected outcome and group allocation (Misra 2012).
20. *Drop-outs* – The withdrawal, loss, or non-participation of subjects, which for any reason leads them to not complete a trial is referred to as drop-outs.

Participants are expected to complete all phases of a trial as stated in the protocol. Differential drop-out rates among different treatment arms or an overall large number of drop-outs can affect the validity of a trial, its results and conclusions. Authors must describe in detail the number and reason for all drop-outs in reports (Bell *et al.* 2013).

21. *Effect size* – The magnitude of the quantitative measure of an event or phenomenon is referred to as the effect-size, sometimes called the treatment effect or effect estimate. A significant difference between the treatment arms (or ratio of effect sizes) confirms the superiority of one treatment over another (Sullivan & Feinn 2012).
22. *Eligibility criteria* – Eligibility or selection criteria dictate which subjects are selected for a trial based on specific inclusion and/or exclusion criteria (Item 31). This is carried out to ensure that all subjects being allocated to the various treatment arms are similar as a consequence of them being selected using identical criteria (Bhattacharya & Cantor 2013).
23. *Equivalence trial* - A type of randomized controlled trial in which the primary objective states that the experimental treatment is as effective as the standard treatment (gold standard). The hypothesis (Item 30) and power calculation (Item 47) are based on the fact that both groups will have a similar outcome using a two-sided statistical test to determine if the experimental intervention is no better than the standard (Greene *et al.* 2008). The design includes a specification of two equivalence margins and that the two treatments are equivalent if the experimental effect lies between these limits. This design will require a special sample size calculation and statistical analysis, which are distinct from a superiority trial (Item 66). In the statistical analysis, non-equivalence is rejected if the 95% confidence interval for the effect size lies completely within the equivalence margins (Walter & Nowacki 2011). Although, sometimes confused with non-inferiority designs (Item 41), the two types of trial use different statistical tests. For example, it could be hypothesised that pulp capping using material A will be equivalent in efficacy

(not better or worse) to pulp capping using material B as measured clinically and radiographically after 3 years.

24. *Estimated effect size or Relative effect sizes* - The treatment effect of the intervention compared with the control, but adjusted to take into account the variability of the sample tested so that it can be generalized to other populations (Sullivan & Feinn 2012). It is used for variables with no intrinsic meaning (e.g. Likert scale), when the results of multiple studies are combined.
25. *Exaggerated treatment effects* - A reported result or effect that is larger than exists in reality or is shown in subsequent trials. This problem was noted in early clinical trials in Medicine that reported a larger (exaggerated) response (Alahdab *et al.* 2018). This effect has been linked to underpowered studies, reporting bias, lack of blinding and problems with allocation concealment amongst other factors (Page *et al.* 2016).
26. *External validity* - Refers to the extent to which results of a study can be applied (or generalized) to other situations, groups or the 'real world' (Saltaji *et al.* 2017). For example, apical microsurgery on molar teeth by an experienced specialist in one referral practice resulted in a 98% success after one year in 25 patients using MTA as the root-end filling material, while zinc oxide eugenol was only 85% successful; this study is likely to have low external validity compared with a study of 150 patients in general dental practice using five dentists of mixed experience operating on anterior teeth.
27. *Factorial trial design* - An experimental trial that simultaneously tests the effect of more than one intervention at the same time (Frishman *et al.* 1994). It requires a design that permits assessment of potential interactions among the interventions and is colloquially referred to as 'two trials for the price of one'. It necessitates a larger sample size and a design that accounts for potential interactions between treatments (Montgomery *et al.* 2003). For example, a randomized controlled trial could investigate the efficacy of both postoperative videos and leaflets in improving postoperative attendance following root canal treatment.

28. *Feasibility trial* - A study to determine (test) whether a full trial can actually be carried out, and if so, in what manner. Feasibility trials can be stand-alone or be embedded in a randomized controlled trial investigating whether the planned trial is possible to carry out (Eldridge *et al.* 2016). Various factors, including participant recruitment and retention, operator remuneration and unforeseen technical issues, which prevent trials from progressing can be investigated in this design. The progression and funding of the full study may rely on successful completion of a feasibility study using a marker such as a traffic light system. It differs from a pilot study which is a distinct trial on a smaller scale (Eldridge *et al.* 2016).
29. *Generalizability* - The extent to which the results from a study on a specific sample or population can be extrapolated and related to other individuals or populations in different settings/contexts or the 'real world'; it is also referred to as 'external validity'. An assessment of generalizability is important as not all individuals who may benefit from the findings of a study can be investigated in a research setting (Stuart & Bradshaw 2015).
30. *Hypothesis* - A statement derived from the research question predicting the research outcome. Testing of a hypothesis by statistical analysis is the hallmark of quantitative study designs, including randomized controlled trials. A hypothesis is the suggestion of a new explanation for existing facts, which subsequent theoretical and experimental work will develop into something robust enough to be called a theory (Gasparyan *et al.* 2019). Often the 'null' and 'alternate' hypothesis are written together.
31. *Inclusion and Exclusion criteria* - Inclusion criteria are the factors governing the entry or recruitment of subjects onto a clinical trial. The factors preventing the eligibility of subjects into a clinical trial are considered as exclusion criteria (Van Spall *et al.* 2007). For example, a clinical trial aiming to compare the anaesthetic efficacy of lidocaine and articaine during pulpectomy of mandibular molars diagnosed with irreversible pulpitis will include only

mandibular molars with the condition, whereas mandibular premolars, incisors and canine with or without irreversible pulpitis will be excluded.

32. *Information bias* – A systematic difference from the ‘actual truth’ that arises when collecting, recalling, recording and handling patient data. It may include observer, misclassification, recall and reporting bias (Tripepi *et al.* 2010) and often stems from an attempt by the researcher to report what they expect, or indeed want to see. Alternatively, it may occur due to mishandling or reporting of missing data in a clinical trial. An example of misclassification bias would arise if a researcher erroneously classified pulpitis cases as healthy in a vital pulp treatment outcome study, while an example of reporting bias would be if a researcher with established views on the success of pulp capping procedures, may report the results (even sub-consciously) in a manner which conforms with their previous beliefs, hence introducing bias.
33. *Informed consent* – An essential requirement before recruitment of subjects into a trial is their formal written consent (acceptance). This can only be done when they have been fully informed of the purpose of the trial, any expected effects and adverse effects and they understand the risks and benefits of the trial. Informed consent is an ethical and legal requirement for all human research (Nijhawan *et al.* 2013).
34. *Intention-to-treat analysis* – Is the statistical method employed to analyse results of all subjects randomized and enrolled in a trial, irrespective of whether they completed all phases of the trial or not. This is to ensure that the full benefits of randomization are achieved and any differential loss of subjects in the treatment arms that occurs does not affect the validity of the trial. This is in contrast to a ‘*per protocol*’ analysis where only those subjects who completed the trial are included in the analysis and contribute to the results (Hariton & Locascio 2018).
35. *Interim analyses* – Analysis carried out on data collected before the completion of a trial as part of the protocol is important for many reasons including understanding the costs of trial, as well as its validity and integrity. The results

of an interim analysis may affect the logistical, monitoring, and recruitment procedures of an ongoing trial (Kumar & Chakraborty 2016). For example, a randomized controlled trial comparing a new root canal filling material with gutta-percha after 5 years, planned an interim analysis after 2 years, with a view to indicating superiority of the new material or the futility of continuing the trial.

36. *Internal validity* - Refers to how accurately the results represent the actual truth in the population being studying and are not the result of methodological errors (Patino & Ferreira 2018). High internal validity is ensured by rigorous study planning to ensure that all potential confounding factors are accounted for and that the research methodology is detailed and robust.
37. *Logistic regression* - A statistical model used to identify association of all predictors and possible confounders to a binary outcome (Platt 1977).
38. *Minimization* - Randomization, particularly in small groups, can result in significant imbalance with regard to certain patient factors. If the level of some prognostic factors, such as patient age or radiographic size of apical lesion, is unmatched the study results may be misleading or even invalidated. Minimisation is a restricted randomization method, which allocates subjects to treatment groups, while attempting to maintain balance in other prognostic factors (Saghaei 2011). It is distinct from block randomization (Item 10) in which imbalance in numbers is corrected within the study or between sites in a multi-centre trial (Item 39). Minimization generally uses an algorithm (there are several available) which usually non-randomly assigns patients to groups based on predefined patient factors, while ensuring equal numbers. Advocates suggest that the experimental groups display better balance after minimisation, while detractors suggest that it is possible to predict intervention allocation in some cases (Scott *et al.* 2003).
39. *Multi-centre trial* - A clinical trial following a single established *a priori* protocol conducted in several locations by different operators. This allows a trial to include a large sample size in a short time as well as to understand the

effect of the various locations and operators (environments) on the result (Blumenstein *et al.* 1995, Youssef *et al.* 2008).

40. *Nested trial* - A type of randomized controlled trial, which forms part of a larger host trial. In other words, it is 'nested' within the host trial. 'Nesting' can be a cost-effective and efficient way in which to investigate another area of interest using the same group of patients; however, it can be problematic for reasons of ethics, small numbers, randomization related to the primary objective (not the 'nested' objective) and a lack of generalizability (Graffy *et al.* 2010). An example of a nested trial, could be in a study investigating whether selective versus non-selective caries removal was most effective in the management of deep carious lesions in which pulp capping could be compared with partial pulpotomy should the pulp become exposed.
41. *Non-inferiority trial* - A type of randomized controlled trial in which the primary objective states that the experimental treatment is not less effective than the standard treatment (gold standard). The description should explain that a treatment is non-inferior to another treatment if the effect size is larger than the non-inferiority margin. As with an equivalence trial (Item 23), the sample size calculation and the statistical analysis differ from those of a superiority trial (Item 66). The hypothesis and power calculation assume that the outcome in both groups will be similar and uses a one-sided test to determine if the experimental treatment is no worse than the standard treatment (Greene *et al.* 2008). It is similar to an equivalence trial but it differs based on the hypothesis and the statistical test used to determine power.
42. *Outcome* - Is the variable that is measured in a trial to evaluate the effectiveness of an intervention or exposure. Primary outcomes are the most critical into answering the research question, while secondary outcomes assist in the interpretation and understanding of the primary outcomes (Ferreira & Patino 2017).
43. *Outcome measure* - The objective/quantitative measurement of the outcome variable. The outcome measure is used to evaluate the effectiveness of an

- intervention and to compare with the placebo/control (Smith *et al.* 2015). Outcome measures should be measurable, normally using a numerical value.
44. *Parallel design* – A study design where subjects are allocated to the treatment/intervention arms or control. A group of subjects allocated to an arm of the study, remains in that group until the study is completed. This is in contrast to crossover designs (Item 18), where subjects of one group (treatment arm) are reallocated to another group after a period of time (Nair 2019).
45. *Pilot study* – A small scale preliminary study that precedes the definitive trial in order to evaluate its design, power, methodology and feasibility (Hassan *et al.* 2006).
46. *Placebo* – An inert substance with no pharmacological action/properties used to compare and evaluate the therapeutic effect of the experimental drug (Ito 2011).
47. *Power calculation* - A well-designed randomized clinical trial will identify a pre-specified effect of an intervention in a population by testing a suitable number of individuals in a sample derived from a population. The power of a study is the probability of detecting a true effect between the tested groups when there is an actual or real difference. A study with higher power reduces the chance of type II error and detects the difference with a greater probability (Jones *et al.* 2003). A power calculation is carried out before starting the trial in order to establish the sample size and should be based on previous literature or informed by a pilot study (Item 45) (Duncan *et al.* 2020).
48. *Pragmatic trial* - A type of randomized controlled trial in which the study is carried out in a 'real world' situation (e.g. general dental practice), rather than, for example, a specialist clinic in a university. Pragmatic trial designs aid the transferability and impact of the results as they are directly applicable to the research in question. It differs from an explanatory trial, which is carried out under optimal conditions (Patsopoulos 2011).
49. *Preference trial* - In a preference clinical trial, two or more interventions are compared, however, rather than be completely randomized at least some of

the patients are able to choose their intervention. For example, in a trial comparing the outcome of non-surgical and surgical root canal treatment patients could elect to avoid surgery if they wish. The results are pragmatic in that they may reflect the decisions that are made in the real world (Kowalski & Mrdjenovisch 2013); however, patient preference will result in unequal groups and a loss of blinding.

50. *Primary outcome measure* - The outcome measure(s) that directly answer(s) the research question of a trial and forms the basis for the calculation of an appropriate sample size (Ferreira & Patino 2017).
51. *PRIRATE 2020 guidelines* - A checklist with 58 items and a flowchart, to assist authors to produce high quality reports of randomized clinical trials in the field of Endodontics (Nagendrababu *et al.* 2020). The PRIRATE 2020 guidelines were developed by adapting and modifying the CONSORT statement (Moher *et al.* 2012) and the Clinical and Laboratory Images in Publications (CLIP) principles (Lang *et al.* 2012).
52. *Quasi-randomized controlled trials* - Quasi-random methods (quasi = almost, but not completely random) used to allocate subjects to different treatment arms is the principle characteristic of this trial design. In this scenario, there is a greater risk of selection bias as the lack of allocation concealment of the subjects can lead to investigators and participants becoming aware of who is allocated to the experimental and control groups (Kunz *et al.* 2007). For example, in a study investigating root canal file choice on post-operative pain, alternate patients were used to feed both experimental groups in a quasi or pseudo randomized design.
53. *Random allocation sequence* - The generation of an unpredictable random sequence for the allocation of subjects to different treatment arms of a clinical trial in order to avoid selection bias (Dettori 2010).
54. *Randomization* - The process of random allocation of participants or experimental units (e.g. teeth) to the various treatment arms of a trial in order to provide an equal chance of them being selected for each. This is a mandatory

- and important step in a randomized controlled trial and reduces selection bias significantly (Suresh 2011).
55. *Randomized clinical trial* – A robust form of experiment characterized by the random allocation of subjects to the various treatment arms that are being compared for their effectiveness (Hariton & Locascio 2018). Among the primary study designs, randomized clinical trials provide the highest level of clinical evidence (Burns *et al.* 2011, Petrisor *et al.* 2007).
56. *Restricted randomization* – A system of randomization that uses specific restrictions in order to achieve a similar distribution of confounders among the subjects assigned to various treatment arms of a trial that would not occur by random allocation, e.g. blocking (Item 10), stratification (Items 63 and 64) or minimisation (Item 38) (Hewitt & Torgerson 2006).
57. *Sample size* - The appropriate number of participants recruited to a trial in order to detect the presence of a pre-specified effect associated with the intervention(s) under investigation. Sample size should be determined *a priori* and informed by previous literature or a pilot study (Campbell *et al.* 1995, Moher *et al.* 2012, Schulz & Grimes 2005).
58. *Secondary outcome measures* - An additional measure to complement the primary outcome measure in order to help explain the results from the primary outcome or the mechanism of action of a treatment (Ferreira & Patino 2017). For example, a clinical trial to study the effect of occlusal reduction on postoperative pain following root canal treatment in mandibular molars with symptomatic apical periodontitis in which the primary outcome assessed was the incidence of postoperative pain, whereas the secondary outcome was the incidence and number of analgesic tablets (or placebo) taken by the patients.
59. *Selection bias* - Systematic error in a clinical trial in the selection of study participants from factors that could affect the enrolment or participation of subjects. This could lead to differences in the baseline characteristics of the selected subjects within the intervention and control groups, which in turn affects the validity of the trial (Lambert 2011).

60. *Simple randomization* – The random assignment of subjects to groups in a trial using a single sequence. The random sequence can be generated by various methods, flipping of coin, dice, random number table, sealed envelope, computer generated etc. (Suresh 2011).
61. *Single blind* – The concealment of information from the participating subjects of a trial on the group allocation and the materials used in the experiment. However, the experimenters/investigators are aware of the group or material information in a single blind study (Day & Altman 2000).
62. *Split-mouth study design* - An unique type of paired or crossover study design (Item 18) used in oral health-related research. The subjects' mouth is divided into two halves and randomly assigned to test and control interventions. As the test and control groups are in the same subject, there is minimal biological variability compared to that which may occur in a parallel group study design (Lesaffre *et al.* 2009).
63. *Stratification* - The development of strata (subsets) based on prognostic/background variables for each treatment arm, in order to make sure that randomization of subjects will yield a balance of subjects in the different treatment arms based on those variables (Kernan *et al.* 1999). For example, if age is an important confounder in a clinical trial, stratification into <18 years and >18 years will ensure a balance of the two age groups in the respective treatment arms.
64. *Stratified randomization* – The influence of covariates or background variables in the outcome of a trial can be minimized by stratified randomization. For example, if age is a confounding background variable, randomization of subjects stratified into age groups will ensure balanced allocation into the treatment arms (Suresh 2011). Furthermore, stratified randomization also includes restricting randomization to ensure that the treatments are allocated in equal numbers in each designated stratum (Kernan *et al.* 1999).
65. *Subgroup analyses* - Analysis and comparison of subject data on the basis of subgroups defined by identified variables other than the treatment difference. This is done to identify whether the identified variables influenced the

outcome of the clinical trial. For example, a clinical trial aimed to compare the success of pulpotomy materials. Subgroup analyses were performed to consider the influence of confounding factors including age, gender, arch, side of the oral cavity and experience of the operator. Subgroup analyses should be pre-specified in protocols to avoid bias and should be distinguished from analyses that are suggested post hoc (Tanniou *et al.* 2016).

66. *Superiority trial* - The most common design of randomized controlled trial in which the primary objective states that the experimental treatment(s) is superior to the standard treatment (gold standard). The hypothesis and power calculation are based on a superior efficacy of the experimental group(s) (Dunn *et al.* 2018).

67. *Surrogate outcomes* - An indicator or sign used in place of a real outcome measure to judge if an intervention is effective. Surrogate endpoints in endodontics could potentially include, reduced blood biomarker levels after root canal treatment or reduction in radiographic size of an apical lesion. They are often used instead of real outcomes such as disease resolution or general health, as the results are readily measured at an earlier time point hence saving time and money. This may be important in relation to endodontics and general health in which the symptoms may take years to manifest. However, surrogate endpoints have limitations as they may not represent true indicators of how effective a given treatment is over time (Svensson *et al.* 2013).

68. *Trial registry* - A public record of clinical trials including the purpose, methods, materials tested, outcomes evaluated and methods for dissemination that is maintained usually by a government-appointed body. Such information submitted by the investigators *a priori* is available for public view to prevent bias occurring in the conduct of clinical trials or during their publication and is designed to prevent investigators altering the protocol during or after the completion of the study (Aslam *et al.* 2013).

69. *Triple blind* -The masking of information from participants, investigators/examiners and the individuals performing data analyses in a

clinical trial including its objectives, hypotheses, expected outcome and group allocation (Schultz & Grimes 2002).

Conclusion

This article provides a comprehensive glossary containing definitions and explanations for the most commonly used terms when conducting and reporting randomized clinical trials in Endodontics. It is hoped that defining these terms will benefit researchers during the design and reporting stages of a randomized controlled trial in Endodontics and other disciplines. Furthermore, developing an understanding of the terminology and designs features of clinical trials should ultimately improve the quality of research in this area and eventually the quality of evidence supporting clinical decisions in practice.

References

- Alahdab F, Farah W, Almasri J, *et al.* (2018) Treatment effect in earlier trials of patients with chronic medical conditions: A meta-epidemiologic study. *Mayo Clinical Proceedings* **93**, 278-83.
- Alamri HM, Alharbi F (2018) Quality Assessment of randomized clinical trials reporting in endodontic journals: an observational study from 2012 to 2017. *Journal of Endodontics* **44**, 1246-50.
- Altman DG (2018) Avoiding bias in trials in which allocation ratio is varied. *Journal of the Royal Society of Medicine* **111**, 143-4.
- Aslam A, Imanullah S, Asim M, El-Menyar A (2013) Registration of Clinical Trials: Is it Really Needed? *North American Journal of Medical Science* **5**, 713-5.
- Bell ML, Kenward MG, Fairclough DL, Horton NJ (2013) Differential dropout and bias in randomised controlled trials: when it matters and when it may not. *BMJ*. **346**, e8668.
- Bhattacharya S, Cantor MN (2013) Analysis of eligibility criteria representation in industry-standard clinical trial protocols. *Journal of Biomedical Informatics* **46**, 805-13.
- Blumenstein BA, James KE, Lind BK, Mitchell HE (1995) Functions and organization of coordinating centers for multicenter studies. *Controlled Clinical Trials* **16**, 4-29.
- Burns PB, Rohrich RJ, Chung KC (2011) The levels of evidence and their role in evidence-based medicine. *Plastic and Reconstructive Surgery* **128**, 305-10.
- Campbell MJ, Julious SA, Altman DG (1995) Estimating sample sizes for 116 binary, ordered categorical, and continuous outcomes in two group comparisons. *BMJ* **311**, 1145-8.
- Chou R, Aronson N, Atkins D, *et al.* (2010) AHRQ Series Paper 4: Assessing harms when comparing medical interventions: AHRQ and the Effective Health-Care Program. *Journal of Clinical Epidemiology* **63**, 502-12.
- Cioffi I, Farella M (2011) Quality of randomised controlled trials in dentistry. *International Journal of Dentistry* **61**, 37-42.

Day SJ, Altman DG (2000) Statistics notes: blinding in clinical trials and other studies. *BMJ*. **321**, 504.

Delgado-Rodriguez M, Llorca J (2004) Bias. *Journal of Epidemiology and Community Health* **58**, 635-41.

Dettori J (2010) The random allocation process: two things you need to know. *Evidence-Based Spine-Care Journal* **1**, 7-9.

Duncan HF, Kirkevang LL, Ørstavik D, Sequeira-Byron P (2016) Research that matters-clinical studies. *International Endodontic Journal* **49**, 224-6.

Duncan HF, Nagendrababu V, Bjørndal L, Kvist T, Dummer PMH (2020) Improving the quality of randomized trials in Endodontics. *International Endodontic Journal* **53**, 731-2.

Dunn DT, Copas AJ, Brocklehurst P (2018) Superiority and non-inferiority: two sides of the same coin? *Trials* **19**, 499.

Efird J (2011) Blocked randomization with randomly selected block sizes. *International Journal of Environmental Research and Public Health* **8**, 15-20.

Eldridge SM, Lancaster GA, Campbell MJ, *et al.* (2016) Defining feasibility and pilot studies in preparation for randomised controlled trials: Development of a conceptual framework. *PLoS One* **11**, e0150205.

Ferreira JC, Patino CM (2017) Types of outcomes in clinical research. *Jornal Brasileiro de Pneumologia* **43**, 5.

Forder PM, Gebiski VJ, Keech AC (2005). Allocation concealment and blinding: when ignorance is bliss. *Medical Journal of Australia* **182**, 87-9.

Frishman WH, Bryzinski BS, Coulson LR, *et al.* (1994) A multifactorial trial design to assess combination therapy in hypertension: Treatment with bisoprolol and hydrochlorothiazide. *Archives of Internal Medicine* **154**, 1461-8.

Gallis JA, Turner EL (2019) Relative measures of association for binary outcomes: challenges and recommendations for the global health researcher. *Annals of Global Health*. **85**, 137.

Gandhi P (2011) Clinical research methodology. *Indian Journal of Pharmaceutical Education and Research* **45**, 199-209.

Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD (2019) Scientific hypotheses: writing, promoting, and predicting implications. *Journal of Korean medical science* **34**, e300.

Goodman SN, Berlin JA (1994) The use of predicted confidence intervals when 125 planning experiments and the misuse of power when interpreting results. *Annals of Internal Medicine* **121**, 200-6.

Graffy J, Bower P, Ward E *et al.* (2010) Trials within trials? Researcher, funder and ethical perspectives on the practicality and acceptability of nesting trials of recruitment methods in existing primary care trials. *BMC Medical Research Methodology* **10**, 38.

Greene CJ, Morland LA, Durkalski VL, Frueh BC (2008) Noninferiority and equivalence designs: issues and implications for mental health research. *Journal of Traumatic Stress* **21**, 433-9.

Hariton E, Locascio JJ (2018) Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *BJOG* **125**, 1716.

Hassan ZA, Schattner P, Mazza D (2006) Doing a pilot study: why is it essential? *Malaysian Family Physician* **1**, 70 -3.

Hewitt CE, Torgerson DJ (2006) Is restricted randomisation necessary? *BMJ* **332**, 1506-8.

Ito S (2011) Placebo in clinical trials. *Clinical Pharmacology & Therapeutics* **90**, 637-9.

Jones S, Carley S, Harrison M (2003) An introduction to power and sample size estimation. *Emergency Medicine Journal* **20**, 453 -8.

Kalenderian E, Obadan-Udoh E, Maramaldi P, *et al.* (2017) Classifying Adverse Events in the Dental Office. *Journal of Patient Safety* Jun 30.

Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI (1999) Stratified randomization for clinical trials. *Journal of Clinical Epidemiology* **52**, 19-26.

Kowalski CJ, Mrdjenovich AJ (2013) Patient preference clinical trials: why and when they will sometimes be preferred. *Perspectives in Biology and Medicine* **56**, 18-35.

Kumar A, Chakraborty BS (2016) Interim analysis: A rational approach of decision making in clinical trial. *Journal of Advanced Pharmaceutical Technology & Research* **7**, 118.

Kunz R, Vist G, Oxman AD (2007) Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Systematic Reviews* **18**, MR000012.

Lambert J (2011) Statistics in brief: how to assess bias in clinical studies? *Clinical Orthopaedics and Related Research* **469**, 1794-6.

Lang TA, Talerico C, Siontis GCM (2012) Documenting clinical and laboratory images in publications: the CLIP principles. *Chest* **141**, 1626-32.

Lesaffre E, Philstrom B, Needleman I, Worthington H (2009) The design and analysis of split-mouth studies: what statisticians and clinicians should know. *Statistics in Medicine*. **28**, 3470-82.

Lucena C, Souza EM, Voinea GC, Pulgar R, Valderrama MJ, De-Deus G (2017) A quality assessment of randomized controlled trial reports in endodontics. *International Endodontic Journal* **50**, 237-50.

Misra S (2012) Randomized double blind placebo control studies, the “Gold Standard” in intervention-based studies. *Indian Journal of Sexually Transmitted Diseases and AIDS*. **33**, 131.

Moher D, Hopewell S, Schulz KF *et al.* (2012). CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery* **10**, 28-55.

Montgomery AA, Peters TJ, Little P (2003) Design analysis and presentation of factorial randomised controlled trials. *BMC Medical Research Methodology* **3**, 26.

Nagendrababu V, Duncan HF, Bjørndal L *et al.* (2020) PRIRATE 2020 guidelines for reporting randomized trials in Endodontics: a consensus-based development. *International Endodontic Journal* **53**, 764-73.

Nair B (2019) Clinical Trial Designs. *Indian Dermatology online journal* **10**, 193.

- Nijhawan LP, Janodia MD, Muddukrishna BS, *et al.* (2013) Informed consent: Issues and challenges. *Journal of Advanced Pharmaceutical Technology & Research* **4**, 134.
- Oltean H, Gagnier JJ (2015) Use of clustering analysis in randomized controlled trials in orthopaedic surgery. *BMC Medical Research Methodology* **15**, 17.
- Page MJ, Higgins JPT, Clayton G, Sterne JAC, Hróbjartsson A, Savović J (2016) Empirical evidence of study design biases in randomized trials: systematic review of meta-epidemiological studies. *PLoS One* **11**, e0159267.
- Patino C.M, Ferreira JC (2018) Internal and external validity: can you apply research study results to your patients? *Jornal Brasileiro de Pneumologia* **44**, 183.
- Patsopoulos NA (2011) A pragmatic view on pragmatic trials. *Dialogues in Clinical Neuroscience* **13**, 217-4.
- Penić A, Begić D, Balajić K, Kowalski M, Marušić A, Puljak L (2020) Definitions of blinding in randomised controlled trials of interventions published in high-impact anaesthesiology journals: a methodological study and survey of authors. *BMJ open* **10**, e035168.
- Petrie A, Sabin C. (2005) *Medical Statistics at a Glance*. 2nd Edition, Oxford, UK: Blackwell Sciences Ltd.
- Petrisor BA, Bhandari M (2007). The hierarchy of evidence: levels and grades of recommendation. *Indian Journal of Orthopaedics* **41**, 11 -5.
- Platt RW (1997) Logistic regression and odds ratios. *Injury Prevention* **3**, 294.
- Probst P, Grummich K, Klaiber U, *et al.* (2016) Conflicts of interest in randomised controlled surgical trials: systematic review and qualitative and quantitative analysis. *Innovative Surgical Sciences* **1**, 33-9.
- Rabin BA, Brownson RC, Haire-Joshu D, Kreuter MW, Weaver NL (2008) A glossary for dissemination and implementation research in health. *Journal of Public Health Management & Practice* **14**, 117-23.

Saghaei M (2011) An overview of randomization and minimization programs for randomized clinical trials. *Journal of Medical Signals and Sensors* **1**, 55–61.

Saltaji H, Armijo-Olivo S, Cummings GG, Amin M, Da Costa BR, Flores-Mir C (2018) Influence of blinding on treatment effect size estimate in randomized controlled trials of oral health interventions. *BMC Medical Research Methodology*, **18**, 42.

Saltaji H, Armijo-Olivo S, Cummings GG, Amin M, Flores-Mir C (2017) Randomized clinical trials in dentistry: Risks of bias, risks of random errors, reporting quality, and methodologic quality over the years 1955-2013. *PLoS One* **12**, e0190089.

Sargeant JM, Kelton DF, O'Connor AM (2014) Randomized controlled trials and challenge trials: design and criterion for validity. *Zoonoses and Public Health* **61**, 18-27.

Schulz KF, Grimes DA (2002) Blinding in randomised trials: hiding who got what. *Lancet* **359**, 696-700.

Schulz KF, Grimes DA (2005) Sample size calculations in randomised trials: 118 mandatory and mystical. *Lancet* **365**, 1348-53.

Scott NW, McPherson GC, Ramsay CR, Campbell MK (2002) The method of minimization for allocation to clinical trials. a review. *Control Clinical Trials* **23**, 662-74.

Skelly AC, Dettori JR, Brodt ED (2012) Assessing bias: the importance of considering confounding. *Evidence Based Spine Care Journal* **3**, 9-12.

Smith PG, Morrow RH, Ross DA (2015) Outcome measures and case definition. In *Field Trials of Health Interventions: A Toolbox. 3rd edition*. OUP Oxford.

Stuart EA, Bradshaw CP, Leaf PJ (2015) Assessing the generalizability of randomized trial results to target populations. *Prevention Science* **16**, 475-85.

Sullivan GM, Feinn R (2012) Using Effect Size-or Why the P Value Is Not Enough. *Journal of Graduate Medical Education* **4**, 279-82.

Suresh KP (2011) An overview of randomization techniques: an unbiased assessment of outcome in clinical research. *Journal of Human Reproductive Sciences* **4**, 8 -11.

svensson S, Menkes DB, Lexchin J (2013) Surrogate outcomes in clinical trials: A cautionary tale. *JAMA Internal Medicine* **173**, 611-2.

Tanniou J, van der Tweel I, Teerenstra S, Roes KC (2016) Subgroup analyses in confirmatory clinical trials: time to be specific about their purposes. *BMC Medical Research Methodology* **16**, 20.

Tripepi G, Jager KJ, Dekker FW, Zoccali C (2010) Selection bias and information bias in clinical research. *Nephron Clinical Practice* **115**, c94-c99.

Van Spall HG, Toren A, Kiss A, Fowler RA (2007) Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA* **297**, 1233-40.

Vozdolska R, Sano M, Aisen P, Edland SD (2009) The net effect of alternative allocation ratios on recruitment time and trial cost. *Clinical Trials* **6**, 126-32.

Walker E, Nowacki AS (2011) Understanding equivalence and noninferiority testing. *Journal of General Internal Medicine* **26**, 192-6.

Yi J, Li H, Li Y, Li X, Zheng W, Zhao Z (2020) Risk of bias and its impact on intervention effect estimates of randomized controlled trials in endodontics. *Journal of Endodontics* **46**, 12-8.

Youssef N, Reinhart K, Sakr Y (2008) The pros and cons of multicentre studies. *Netherlands Journal of Critical Care* **12**, 120 -2.