Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.intl.elsevierhealth.com/journals/jden

Review

Randomized controlled trials in dentistry: Common pitfalls and how to avoid them

Padhraig S. Fleming [a,*], *Christopher D. Lynch* [b], *Nikolaos Pandis* [c]

[a] *Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AD, United Kingdom*

[b] *Learning & Scholarship, School of Dentistry, Cardiff University, United Kingdom*

[c] *Department of Orthodontics and Dentofacial Orthopedics, Dental School/Medical Faculty, University of Bern, Bern, Switzerland*

ARTICLE INFO

Article history:
Received 12 May 2014
Received in revised form
3 June 2014
Accepted 5 June 2014

Keywords:
Randomized
Clinical trial
Dentistry
Conduct
Reporting

ABSTRACT

Objective: Clinical trials are used to appraise the effectiveness of clinical interventions throughout medicine and dentistry. Randomized controlled trials (RCTs) are established as the optimal primary design and are published with increasing frequency within the biomedical sciences, including dentistry. This review outlines common pitfalls associated with the conduct of randomized controlled trials in dentistry.

Methods: Common failings in RCT design leading to various types of bias including selection, performance, detection and attrition bias are discussed in this review. Moreover, methods of minimizing and eliminating bias are presented to ensure that maximal benefit is derived from RCTs within dentistry.

Conclusions: Well-designed RCTs have both upstream and downstream uses acting as a template for development and populating systematic reviews to permit more precise estimates of treatment efficacy and effectiveness. However, there is increasing awareness of waste in clinical research, whereby resource-intensive studies fail to provide a commensurate level of scientific evidence. Waste may stem either from inappropriate design or from inadequate reporting of RCTs; the importance of robust conduct of RCTs within dentistry is clear.

Clinical significance: Optimal reporting of randomized controlled trials within dentistry is necessary to ensure that trials are reliable and valid. Common shortcomings leading to important forms or bias are discussed and approaches to minimizing these issues are outlined.

* *Corresponding author at*: Department of Oral Growth and Development, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AD, United Kingdom. Tel.: +44 207 3777397.
E-mail address: padhraig.fleming@gmail.com (P.S. Fleming).

http://dx.doi.org/10.1016/j.jdent.2014.06.004
0300-5712/

1. Introduction

Evidence-based care is ingrained within medicine and dentistry; research is now a fundamental pillar underpinning clinical decisions. Clinical research can be categorized into either non-randomized or randomized studies.[1] Non-randomized studies encompass observational designs such as controlled clinical trials, cohort and case–control studies, case series and reports, cross-sectional and ecological studies (Fig. 1). The key distinction between these designs resides in the random and unpredictable allocation of interventions by the investigator in randomized controlled trials (RCTs).[2]

The relative merits of both approaches have been contested[3]; however, RCTs are accepted as the optimal design in the assessment of the efficacy and safety of a clinical intervention.[2] Randomization allows for a ''fair'' comparison, facilitating more assured deduction of causal inferences than is the case with non-randomized designs. For example, a comparison of the efficacy and safety of direct restorative materials may best be undertaken within a randomized design, limiting the potential for selection bias, whereby participants with good hygiene and dietary habits might otherwise subconsciously be allocated to the preferred material in a non-randomized study.

However, while robust RCTs are accepted as having low risk of bias producing highly credible results, lesser quality RCTs may be less trusted and rendered misleading by either inadequate design or poor reporting. Attention has recently been drawn to the preponderance of inadequate research blighting the biomedical literature.[4] It has been estimated that in excess of 50% of research reports may be sufficiently poor or lacking in detail so as to make them unusable, translating into a waste of tens of billions of pounds,[5] notwithstanding risks to patients in recommending delivery of unsafe and unproven treatments.

Similar problems have been exposed in the dental literature with inadequate reporting and conduct of clinical trials a pervasive finding in meta-epidemiological studies in dentistry generally[6–8] and within specialist fields.[9,10] In relation to RCTs specifically, fundamental aspects are often poorly reported with adequate explanation of, for example, random sequence generation (34%), allocation concealment (22%), blinding of participants (21%) and assessors (16%), rarely apparent in trials published in leading dental journals.[6] The aim of this review is, therefore, to highlight some of the most common and fundamental pitfalls in the conduct of clinical trials in dentistry and to raise awareness of best practice in relation to both conduct and reporting of RCTs.

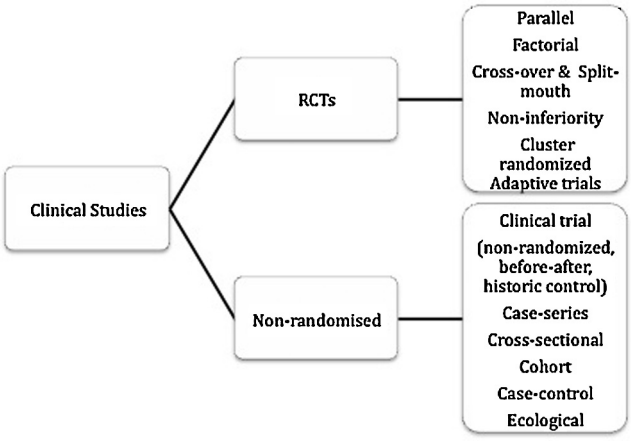

Fig. 1 – Types of clinical studies.

2. Bias and its attenuation in RCTs

RCTs are designed in a manner to deduce an accurate estimate of the expected outcome of a clinical intervention. However, the outcome of a clinical trial may be affected by a range of factors, such as random error, bias or confounding. Random error may arise as a consequence of sampling error manifesting as imprecision of the observed treatment effects. Bias, however, is indicative of systematic error and may distort the estimate of the true treatment effect.

A plethora of subtypes of bias, of varying degrees of significance and prevalence exist[11]; however, the most critical include: selection, performance, detection or observation, attrition, publication and other forms of bias such as those associated with carry-over effects or contamination between treatment groups.[12] While it is difficult to quantify the amount of existing bias, it is possible to mitigate each of these possible forms of bias.

3. Selection bias

Selection bias in clinical trials may lead to confounding or blurring of the effects of an intervention. Specifically, bias may be introduced due to inadequate generation and implementation of an unpredictable, random sequence and subsequent concealment of group assignment. The most pressing concern if non-random allocation occurs is that assignment may be made according to the investigator or operator's preconception. Consequently, baseline differences in respect of influential demographic or treatment-related characteristics may arise.

For example, exploring the aforementioned study of direct restorative materials in more detail, let us assume that this hypothetical study involves comparison of the clinical performance of posterior direct amalgam with direct composite restorations in terms of both the post-placement sensitivity and the longevity of either direct restoration. An operator biased in favour of the use of composite may subconsciously decide to enrol less anxious participants assumed to have higher pain thresholds to the group having composite restorations. Similarly, a subconscious decision to randomize smaller cavities, in participants deemed to have lower caries risk, with better oral hygiene and less parafunctional activity to the composite group may be made. The upshot of biased decisions, irrespective of the intention, is baseline imbalance in important characteristics, which may translate into biased estimates of differences in short- and long-term outcomes erroneously suggesting in the present example that the composite material outperforms amalgam. Random assignment is also critical in controlling unobserved confounders,