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Review

Clinical studies in restorative dentistry: New directions and new demands

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ABSTRACT

Clinical research of restorative materials is confounded by problems of study designs, length of trials, type of information collected, and costs for trials, despite increasing numbers and considerable development of trials during the past 50 years. This opinion paper aims to discuss advantages and disadvantages of different study designs and outcomes for evaluating survival of dental restorations and to make recommendations for future study designs. Advantages and disadvantages of randomized trials, prospective and retrospective longitudinal studies, practice-based, pragmatic and cohort studies are addressed and discussed. The recommendations of the paper are that clinical trials should have rational control groups, include confounders such as patient risk factors in the data and analysis and should use outcome parameters relevant for profession and patients.

Contents

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1. Introduction

Clinical research of restorative materials is confounded by problems of study designs, length of trials, type of information collected, and costs for trials, despite increasing numbers and considerable development of trials during the past 50 years. In the 1970s the first clinical studies on the performance of direct composites were published at a time when amalgam remained the gold standard material for direct restorations in posterior teeth [1–3]. At that time performance investigations were more about the potential of test materials rather than effectiveness in everyday clinical practice, resulting in highly controlled studies, typically undertaken in academic institutions. Such studies revealed a great deal about the clinical performance of the materials under investigation, but had dubious applicability in the primary care settings. Today, there is an upcoming of so-called practice based studies that attempt to collect data from general practices, but at the same time include the risk to be flawed by untrained practitioners in placement, management, and assessment.

To reduce selection bias and allow restorations of different materials to be evaluated according to standardised and controlled protocols, well defined criteria for evaluating restorations were developed and introduced. For direct restorations, USPHS or Ryge criteria were published, with modified versions still being used today to assess various features of restorations [4,5]. To modernise this method for the evaluation of dental restorations, new criteria were published by the FDI in 2007 [6–8]. These criteria were updated in 2010 [6–9]. Basically, this method for the assessment of the clinical performance of restorations requires that:

- Patients should be recalled for restoration evaluation visit (best within specific timeframes)
- All restorations should be clinically evaluated by calibrated evaluators.
- The evaluators should use prescribed list of criteria to assess qualities of the restorations, based on specific grades varying from excellent to poor in need of replacement [4,5]. The number of used grades depends on the aim of the evaluation.

However, the detailed type of evaluation requires huge, sustained effort and incurs high costs for the recruitment of patients, the placement and baseline evaluation of the required number of restorations, and for the recall of patients at specific time points for the detailed assessment of the qualities of individual restorations, typically including clinical photographs and the recording of impressions. Costs may limit a study's follow-up period, frequency of recall visits, let alone the number of patients included in the trial — factors critical to the viability of the investigations. Moreover, the relevance of such outcome measures to patients, providers and payers needs to be questioned [10].

To avoid selection bias and assessments of the efficacy of restorative materials and different treatment modalities, randomized controlled clinical trials (RCT) have been favoured in the past, being widely considered to be the best design to answer specific questions in clinical research. However, RCTs in dentistry are extremely resource intensive and costly and oftentimes performed under artificial conditions with limited external validity. Furthermore, many RCTs in dentistry suffer from limited sample sizes and relatively high participant attrition rates over, in particular, extended observation times, while materials under investigation are already replaced on the market.

The often proclaimed demand for more randomized clinical trials with longer observation times could be considered to be unhelpful, indeed unrealistic. Consequently, additional alternative designs and outcomes should be considered and accepted by funders and reviewers of research on the clinical performance of dental restorations. For example, retrospective clinical studies have the capacity to provide data over extended observation times on large numbers of restorations placed by general practitioners [10–12]. These trials seek different outcomes (oftentimes less standardised and granular than RCTs), which merit more detailed consideration for their validity, sensitivity and reliability in guiding practitioners in primary care settings [11]. Moreover, other designs like cohort studies should be considered. Cross sectional studies, that are often used to reflect the situation in general practice are unreliable for providing longevity data and should not be used for that purpose [13].

This opinion paper aims to discuss advantages and disadvantages of different study designs and outcomes for evaluating survival of dental restorations and to make recommendations for future study designs. It should serve as a basis for further discussions on the most efficient and effective use of resources available for clinical research in restorative dentistry to better serve both the advancement of

Table 1 – Descriptive analysis on studies evaluating longevity of posterior composite restoration (n = 87) according study characteristic and statistical analysis performed. (Studies published between 2005 and 2015).

Variables	Retrospective studies n (%)	References	Prospective studies n (%)	References
Study characteristic				
Funding of the study				
By dental manufactures	0 (0.0)	–	28 (37.3)	[31,32,51–76]
By private or public institutions	3 (25.0)	[33,42,77]	23 (30.7)	[17,19,27,28,78–96]
Not reported	9 (75.0)	[43,44,97–103]	24 (32.0)	[30,104–126]
Observation time				
Up to 5 years	2 (16.7)	[98,100]	57 (76.0)	[30,32,33,42–44,51–62,64–73,75–80,82,84–87,92,94,95,97–108,110–114,117–126]
5 years or more	10 (83.3)	[33,42–44,77,97,109,101–103]	18 (24.0)	[17,19,27,28,31,63,74,81,83,88–91,93,96,109,115,116]
Restorations included				
Up to 100	2 (16.7)	[97,100]	49 (65.3)	[30–33,42–44,52–54,56–58,61,63,64,66–73,75–80,82–84,86–88,90,96–115,117,122–126]
More than 100	10 (83.3)	[33,42–44,77,98,109,101–103]	26 (34.7)	[17,19,27,28,51,55,59,60,62,65,74,81,85,89,91–95,116,118–121]
Participants included				
Up to 100	5 (41.7)	[42–44,97,109]	67 (89.3)	[30–33,42–44,51–54,56–64,66–115,117,119–126]
More than 100	7 (58.3)	[33,77,98,100–103]	8 (10.7)	[17,19,27,28,55,65,116,118]
Risk Patients excluded				
Yes	4 (33.3)	[33,42,101,102]	45 (60.0)	[19,30–32,51–53,56–64,66–69,72,75,76,82–85,87,104,105,107,108,110–113,117–126]
No	3 (25.0)	[43,98,109]	20 (26.7)	[27,54,55,62,65,70,71,74,81,86,88–96,116]
No reported	5 (41.7)	[44,77,97,100,103]	10 (13.3)	[17,28,73,78–80,106,109,114,115]
Statistical analysis performed				
Survival rate				
No	0 (0.0)	–	36 (48.0)	[17,27,30,51–53,59,61,65,67–69,72,73,75,76,79,80,82,85,87,88,104,107–110,112,114,115,117,120,123,124,126]
Yes	12 (100.0)	[33,42–44,77,97–103]	39 (52.0)	[28,31,32,54–58,60,62–64,66,70,71,74,78,81,83,84,86,89–96,105,106,111,113,116,118,120,122,125]
Multivariable regression model				
No	3 (25.0)	[33,109,100]	71 (94.7)	[17,19,30–33,42–44,51–54,56–105,107–126]
Yes	9 (75.0)	[42–44,77,97,98,101–103]	4 (5.3)	[27,28,55,106]
Reasons for failure reported				
No	1 (8.3)	[103]	3 (4.0)	[59,114,123]
Yes	11 (91.7)	[33,42–44,77,97–102]	57 (76.0)	[17,19,27,28,32,33,42–44,51–59,62–65,68–72,74,77,79–86,88–109,111–113,115,116,118–122,124]
No failures	0 (0.0)	–	15 (20.0)	[30,31,60,61,66,67,75,76,78,87,110,117,125,126]
Total	12 (100.0)		75 (100.0)	

the art and science of dentistry and the consumers of oral healthcare—our patients [12].

2. Clinical studies of different designs

In an attempt to get an overview of different types of studies, research questions, clinical trial methodologies, variables and outcomes, a literature search was performed. An overview of longevity studies on direct posterior composite restorations published over the last 10 years (from January 1st, 2005 to September 30th, 2015) is set out in Table 1. The selection of studies was based on a search of the National Library of Medicine international electronic database — MEDLINE/PubMed (Table 3). The search was restricted to papers written in English. Table 1 divides the 87 selected studies into "prospective" and "retrospective" and includes details on study characteristics and the statistical analyses performed. Detailed information on the assessment of each individual study is presented in Appendix A (Supplementary material). From Table 1, it can be seen that more than 60% of the prospective clinical studies had less than 100 restorations included, observation times of <5 years, and 60% of the studies did not provide information on important patients' risk factors such as caries experience and parafunctional habits. Moreover, only a limited number of the prospective studies assessed the influence of risk factors on the longevity of restorations by means of multivariable statistical analyses. More importantly, given relatively short observation times, 20% of the studies included no data on restoration failures.

From the 10 year look-back review, prospective controlled studies, despite having better quality of design (*e.g.* risk of bias definition — something we admittedly did not assess here), it may be concluded that the considerable effort (and cost) of running the typical prospective trial results in important limitations linked to observation time, low number of retained patients and statistical underpowering. Furthermore, there is evidence that an increasing number of RCTs are being performed to investigate materials that "do not outperform *in vitro*, lack fundamental properties, or do not fulfil the prerequisites required for clinical trials" [14].

3. Relevant research questions

When a clinical study is being planned, one of the main questions should be: will the design and expected outcome contribute to better care in dentistry? Clinical relevance of studies will be improved if problems and questions general practitioners face every day will be addressed by the research. In our opinion, the following questions could have such relevance:

1 Technique comparisons

Studies comparing two fundamentally different restorative techniques for a specific situation, such as indirect versus direct restoration [15], mechanistic, interventive amalgam techniques versus minimum intervention composite resin techniques [16,17], repair versus replacement [18], intervention versus no intervention. The number of prospective clinical studies addressing such issues is limited, possibly given the lack of funding and sponsoring opportunities — manufacturers have limited interest in these types of studies, and only RCT's comparing amalgam and composite have been supported by the American NIH in recent times [17,19]. Another problem is the number of variables involved, especially when fundamentally different techniques and materials are compared, *e.g.* amalgam *vs.* composite. However, these types of comparisons are important for dentists when it comes to effecting a change in behaviour, such as a shift to the use of composite rather than amalgam in the management of primary lesions of caries requiring operative intervention. Behavioural change with many new technologies is highly relevant to the further development of the profession.

2 Materials testing

Research questions testing a new material or technique as an alternative to an existing (gold standard) material or technique that might offer major improvements in longevity, applicability, safety or efficiency [20,21]. Studies comparing a new material with an existing material (*e.g.* a new, supposedly improved formulation vs. the current formulation) might not have high clinical relevance if the existing standard material already performs sufficiently [22,23]. Moreover, one should note that any performance against the gold standard materials may well require high sample sizes to yield statistical significant differences, given the excellent performance of 'gold standard' materials. Considerations of the relevance of differences which are hard to demonstrate should be a focus in future trial reports [24].

3 Assessing patient risk factors

Studies investigating the influence of risk factors on longevity that are related to the human factors in dentistry: patients and dentists. While most clinical studies focus on materials and their properties, it is increasingly recognised that other factors, including caries risk, bruxism, socioeconomic status and operator variables [25–28] play a major, and even dominant role in restoration longevity.

4 High risk testing

Studies aiming to test the performance of restorative work in challenging clinical situations [29] may be considered to be 'high risk testing'. Many clinical studies exclude high risk patients, notably high caries risk patients and patients with bruxism from their study population [30,31]. Moreover, the size of restorations in clinical trials is oftentimes limited, and cases involving deep subgingival margins or cusp replacement are excluded. This is understandable as RCTs aim to remove confounding variables, but might also be linked to sponsors and funders of clinical research wishing to see positive outcomes from expensive studies. Dentists, however, face such challenges on a daily basis, and need meaningful research data

Table 2 – Summary of characteristics of different trial types.

Characteristics	RCTs	Pro- or retrospective non-randomized trials
Risk of selection bias	Low	High
Risk of performance bias	Probably high	Probably high
Risk of detection bias	Possibly high	Possibly high
Risk of selective reporting	Low (if registered)	Higher, registration possible prior conduct (in prospective studies) or analysis
Follow-up	Usually short	Longer
Risk of attrition	High	Low
Sample size and power	Usually low	Possibly high
External validity	Usually low (could be high in practice-based RCTs)	Usually high
Outcome measures	Should be relevant to all stakeholders	Should be relevant to all stakeholders
Costs and administrative efforts	High	Low (especially when using routine data)

to guide them in their adoption, or rejection of new materials and techniques.

5 Long-term longevity studies

Studies planned with less than 2–3 years observation time have limited clinical relevance as most, modern day materials will be able to perform satisfactorily for that length of time in clinical service [21,32]. Moreover, one of the most important reasons for restoration failure, secondary caries, tends to occur after more than 2–3 years in clinical service [28]. Future studies should compare materials or treatments over a relevant timeframe.

4. Outcomes and outcome measures

As described, most clinical trials on restorative materials use standardised criteria, applied by calibrated observers, which yield minute differences between materials or treatments on a range of aspects (colour, margin, surface behaviour *etc.*) [20,26]. Moreover, they often deem specific situations as requiring replacement (the Ryge criteria, for example, include Charlie and Delta ratings, indicating that restorations need immediate replacement or replacement in the near future). In clinical dental practice however, the replacement of a restoration depends not only on the status of the restored tooth but also on the oral and general health of the individual patient, risk assessment outcomes, and, last but not least, informed consent of the patient. Given that restorations nowadays are often monitored, refurbished or repaired, even those rated Charlie or Delta might continue to function (*i.e.* remain in clinical service) for many years. As well defined standardised criteria are the key to compare the clinical status of restorations over time, the FDI criteria might be an alternative, and could even be simplified by merging grade 1–3 to one grade — clinically satisfactory. Similarly, not all FDI criteria need to be used in all studies; in fact, single criteria can be selected for the specific goal of the study and the remaining criteria could be omitted (*e.g.* aesthetics).

Alternative to Ryge or FDI criteria, the functional presence of a restoration may be viewed as critical, indicating that a restoration is still functioning in the mouth (success) or has been replaced or repaired (failure). This method is used in practice based studies, prospective as well as retrospective [27–29,33] but lacks detailed quality assessment of a restoration. It is highly dependent on the treating dentist and the criteria he or she uses to decide whether a restoration needs to be replaced or not. Therefore, the reasons for failure or replacement, and the criteria used for such decision need to be recorded. When it comes to defining what is a success and a failure, Anusavice [34] suggest that a restoration is "successful" if no intervention is indicated, and a "failure", when the entire restoration must be replaced or the tooth extracted. A third category is restorations that are repaired or received endodontic treatment with the restoration remaining in place; these are classified as "survived" [32]. For direct restorations, previously all interventions were considered indicative of failure, including repairs where the original restoration is still (at least in large part) in place. For standardisation reasons, and to be able to compare longevity of direct and indirect restorations, it would be good to use the same definitions of success, survival and failure for all types of restorations:

1. Success: at evaluation, the restoration is still functioning and no intervention (repair or replacement) is indicated. In this regard, refurbishment, recontouring and polishing is not considered to be an intervention.
2. Survival: a restoration requires repair. This category would also include teeth that require endodontic intervention, but with the restoration remaining in place, with the access opening restored following the endodontic therapy.
3. Failure: cases where a restoration must be replaced or the tooth removed for reason related to the restorations, such as tooth fracture, but unrelated to periodontal health or trauma.
4. If a restoration is removed for reasons unrelated to material performance; for example, an abutment tooth for a bridge or a tooth removed for periodontal reasons, the event may

be noted but not recorded as a failure, resulting in censoring in the analysis.

Besides longevity, there is increasing acceptance that other outcomes, including, subjective judgment and material considerations by patients or practitioners are also relevant. As occurs in other disciplines, core outcome sets should be established for restorative trials; these are defined in consensus between patients, practitioners and other stakeholders [22,35]. The resulting sets are minimum standards of outcomes to be assessed; they help to report on the most relevant aspects of trials, but also prevent selective reporting [10,36].

More recently, patient-based outcomes measures (PBOs) have been emerged as an important aspect to complement conventional clinical measures that have been the main focus of oral health research [37]. The assessment of the opinion of patients about their own health is a key point to evaluate the effectiveness of an intervention. In this way, the assessment of the impact that restorations can have on patients' oral health-related quality of life (OHRQoL) should be stimulated.

The present digital revolution provides opportunities for designing new assessment methods that combine the need for standardisation using a well-defined list of criteria and data acquisition from electronic patient files and digital imaging. Intra-oral electronic photography and inspection of digital bitewing radiographs may provide standardised information on the quality of restorative work and provide insight on the application of replacement criteria by practitioners. New intra-oral scanning methods, including colour reproduction capacities have been developed, which might become important tools in future clinical studies. However, patients still have to attend to obtain images, so data acquisition remains dependent on patients being available for recall and sufficient resources to fund recall procedures. Also, images have to be stored securely and evaluated using sophisticated methodologies which are both time consuming and costly. Anyway, dentistry should start to put effort on the establishment of guidelines advising on how dentists should record clinical data and images to allow proper follow up of restorative treatments.

5. What is the ideal study design?

5.1. *RCT*

The randomized clinical trial is most often considered to be the ideal design for comparing different treatments in medicine and as a consequence, procedures and the use of different materials in dentistry. However, as discussed, the RCT approach has several disadvantages when testing restorative materials:

1 Blinding

In RCTs, blinding of patients and researchers for the applied therapy is considered to be most important in the prevention of performance bias (operators perform different therapies differently if they know the group allocation) and detection bias (patients and evaluators being aware of the allocation and being more or less prone to detect or report differently). However, in clinical research in restorative dentistry, *e.g.* in trials comparing crowns and fillings, blinding is impossible and the likelihood of these types of bias is inevitable, albeit that it may be reduced by using more operators and evaluators. The fact that patients are aware of the applied therapy includes the risk for sampling bias, as many patients will not be enrolled because they do not want to have, for example, amalgam restorations, and, as a result, designing a clinical trial to address this still important research question [38] will include the risk of a non-representative sample of the population. It is acknowledged that many of these disadvantages apply also to non-randomized clinical studies.

2 Time of follow-up

Differences in effectiveness of therapies may only be measured after several years, as failure behaviour may vary -and one type of material may be more susceptible to caries and the other to tooth fracture on the long term [33]. As a result, long observation times are required, sometimes exceeding 10 years to record all relevant effects and differences. To maintain a population of trial participants over an extended period is very challenging. Attrition bias is a common phenomenon in clinical research in dentistry, making it very difficult to achieve long observation times in clinical trials (Table 1). Recently, results from two clinical trials with a long observation time were published by a Danish research group, but this is exceptional [39,40].

3 Inclusion bias

If inclusion criteria are not well defined, it may lead to inclusion bias, as the restorations are placed for a variety of different reasons including active caries, fracture due to bruxism and aesthetic considerations. Moreover, it is likely that in some clinical trials highly motivated patients with a good oral hygiene tend to be included, a feature which is seldom mentioned in trial reports. A typical example of this is two randomized clinical trials comparing the longevity of amalgam and composite restorations in young children [17,19]. The inclusion criteria were that children should require one or more restorations, which is likely oftentimes a result of primary caries, indicating high caries experience. Obviously, the inclusion bias is that a high risk population is investigated, but this is not mentioned in any of the relevant reports [11,17,41].

4 Independent evaluation

To avoid reporting bias, dentists that place restorations in a clinical study should not evaluate their own restorations at recall. Therefore, independent evaluation is mandatory, making the process of clinical testing very expensive and, out of necessity often limited to university settings.

In Table 2, characteristics of RCTs in restorative dentistry are summarised. Given the above mentioned issues, alternative trial designs should be considered.

Table 3 – Structured search strategy carried out in MEDLINE/PubMed database.

Search	Topic and terms
#4	Search #1 AND #2 AND #3
#3	Composite resin/dental restoration: (("composite resins" [MeSH Terms] OR "resins, composite" [Title/Abstract] OR ("composite" AND "resins") [Title/Abstract] OR "composite resins" [Title/Abstract] OR ("composite" AND "resin") [Title/Abstract] OR "composite resin" [Title/Abstract] OR "Dental Restoration, Permanent" [Mesh] OR "Dental Restoration, Permanent" [Title/Abstract] OR "Permanent Dental Restoration" [Title/Abstract] OR "Restoration, Permanent Dental" [Title/Abstract] OR "Restorations, Permanent Dental" [Title/Abstract] OR "Dental Restorations, Permanent" [Title/Abstract] OR "Permanent Dental Restorations" [Title/Abstract] OR "Dental Permanent Fillings" [Title/Abstract] OR "Fillings, Permanent Dental" [Title/Abstract] OR "Permanent Dental Fillings" [Title/Abstract] OR "Permanent Fillings, Dental" [Title/Abstract] OR "Permanent Filling, Dental" [Title/Abstract] OR "Dental Filling, Permanent" [Title/Abstract] OR "Dental Permanent Filling" [Title/Abstract] OR "Filling, Dental Permanent" [Title/Abstract] OR "Filling, Permanent Dental" [Title/Abstract] OR "Permanent Dental Filling" [Title/Abstract] OR "Fillings, Dental Permanent" [Title/Abstract] OR "Dental Fillings, Permanent" [Title/Abstract]
#2	Survival analysis: ("Survival" [All Fields] OR "Success" [All Fields] OR "Longevity" [All Fields] OR "Annual failure rate" [All Fields] OR "Clinical evaluation" [All Fields] OR "Survival Analysis"[Mesh] OR "Survival Analysis" [All Fields] OR "Analysis, Survival" [All Fields] OR "Analyses, Survival" [All Fields] OR "Survival Analyses" [All Fields] OR "Failure" [All Fields] OR "Dental Restoration Failure"[Mesh] OR "Dental Restoration Failure"[All Fields] OR "Failure, Dental Restoration" [All Fields] OR "Restoration Failures, Dental" [All Fields] OR" Failures, Dental Restoration" [All Fields] OR" Restoration Failure, Dental" [All Fields] OR" Dental Restoration Failures" [All Fields])
#1	Clinical trial/Longitudinal study/Retrospective study/Cohort study: (("clinical" [Title/Abstract] AND "trial" [Title/Abstract]) OR "clinical trials" [MeSH Terms] OR "clinical trial" [Publication Type] OR random*[Title/Abstract] OR "random allocation" [MeSH Terms] OR "therapeutic use" [MeSH Subheading]) OR "Longitudinal Studies"[MeSH Terms] OR "Longitudinal Studies" [All Fields] OR "Longitudinal Study" [All Fields] OR "Studies, Longitudinal" [All Fields] OR "Study, Longitudinal" [All Fields] OR "Longitudinal Survey" [All Fields] OR "Longitudinal Surveys"[All Fields] OR "Survey, Longitudinal" [All Fields] OR "Surveys, Longitudinal" [All Fields] OR "Prospective Studies" [Mesh] OR "Prospective Studies" [All Fields] OR "Retrospective Studies" [MeSH Terms] OR "Studies, Retrospective" [All Fields] OR "Study, Retrospective" [All Fields] OR "Retrospective Study" [All Fields] OR "Clinical Evaluation" [All Fields] OR "Follow-up" [All Fields] OR "Cohort Studies" [Mesh] OR "Cohort Studies" [All Fields] OR "Cohort Study" [All Fields] OR "Studies, Cohort" [All Fields] OR "Study, Cohort" [All Fields])

6. Retrospective longitudinal studies

For robust longevity analyses of restoration longevity, it is important that for all restorations placed in a certain time period, not only date and reason of failure, but also date of placement, and even more importantly, the assessment date for restorations remaining in clinical service are recorded. Comparing only the number of failed and remaining restorations in the comparator groups leads to erroneous conclusions [13].

When it comes to comparing restorative techniques and dental materials, retrospective studies run considerable risk of selection bias, as dentists invariably choose the restorative technique that is most appropriate for a given indication. Using data on cohorts of restorations placed at a different time for the same indication (*i.e.* composites in situations where amalgams had been placed in the past) might help to overcome this problem [33]. Accounting for recorded confounders as indicators of selection bias and considering them during statistical evaluation is another way of reducing the impact of selection bias. The reliability of patient records used for retrospective studies is highly dependent upon the number of individuals who remain patients and receive all their dental treatment in the practice(s) over extended periods of time. In situations where patients often change dentists, or where it is common practice to refer patients for certain treatments to specialists, patient files have limited value in retrospective studies.

Moreover, in retrospective studies, quality of patient files is dependent on the practice investigated. If the dentist who placed the restoration also decided when a restoration should be replaced, there is significant risk of detection — and probably also reporting bias. In certain studies, this risk and the risk that certain restorations may be replaced in another practice is overcome by independent evaluators visiting the practice [42–44], but this limits the number of patient records that can be analysed and greatly increases research logistics and costs. Typical characteristics of non-randomized and retrospective studies are summarised in Table 2.

Given the opportunities afforded by intraoral, digital cameras and scanning devices, it is possible in the future that photographs and scans of restored teeth can be obtained and assessed for qualitative analysis by independent investigators, reducing the risk for reporting bias. This would also offer the opportunity to evaluate the influence of operators on the treatment result.

Furthermore, contractual, commissioning and reimbursement systems may highly influence the decisions of dentists and patients, significantly influencing the selection of materials and techniques as well as replacement decisions and, in turn, longevity.

7. Prospective longitudinal studies and pragmatically designed trials

Recently, a number of large prospective clinical studies, based on survival data obtained by the treating dentists from patients records in Scandinavian public health clinics and practices participating in the practice based research network in the USA have been published [27,28,45]. As with retrospective studies based on patient clinical records, reporting bias is a limitation of these prospective study designs. However, when it is possible to access large datasets, pragmatic study designs make it possible to compare the performance of different materials and restorative techniques in the primary care setting, assuming data, including information on all relevant potential risk factors could be obtained from electronic files.

8. Population-based (birth) cohort studies

In cohort studies, a group of individuals is observed for a period of time allowing the investigation of the effects of living life on health outcomes. The use of population-based samples allows extrapolation of data to the target population. Recently, data from the Pelotas 1982 Birth Cohort were used for analysing factors affecting the quality of posterior restorations [25] and the placement of amalgam or composite fillings in posterior teeth [46]. These studies showed that individual characteristics, such as socioeconomic status, type of service provided and individual caries risk, influence the longevity of posterior restorations. The inclusion of restoration assessment in such large multidisciplinary studies creates access to data on a wide range of variables pertaining aspects of dental care and general health and wellbeing. This is especially interesting when investigating patients' risk factors. With this approach, information on events occurring in life is collected. However, the observational nature of cohort studies does not allow researchers to obtain precise data on, for example, the date of restoration placement.

9. Statistical analysis

In the ideal RCT, all variables are standardised, with only the experimental variable differing between the test and control groups. In such cases, the Kaplan Meier statistical model helps generate survival graphs and enables comparisons between experimental groups, for example a log-rank test which shows if survival curves are statistically different. However, in RCTs not all confounding variables are perfectly balanced (accounting for all possible confounders during randomisation is theoretically possible, but practically hard to achieve). Parameters such as caries risk [33,42], bruxism [42], socioeconomic status [25], age [33,42], number of teeth in the dentition [19], as well as tooth type and details of the practitioner(s) who treated the patient [19,45] should thus be recorded during the trial and included in the evaluation using multi-variate analyses. In planning prospective trials, the estimation of the required sample size should take into account the need to undertake such analyses.

Oftentimes, in clinical studies in dentistry, more than one tooth is treated in participating patients. Multilevel statistical models are required to properly account for this clustering of statistical units [25,29]. Similarly, statistical evaluation should make best use of specific designs such as split-mouth studies, which are common in restorative trials [47,48].

10. Recommendations for future clinical studies

To further development restorative dentistry, several specific research questions are of central importance. Clinical trial designs should address these questions:

1 Choose a rational control

Studies comparing new materials to their predecessors are necessary prior to the launch of new products. Such studies are, however, of limited priority in the quest to further develop restorative dentistry. Clinical studies comparing different treatment options are of much greater importance. Direct versus indirect restorations, tooth replacement versus tooth retention, restoration repair versus replacement, bridge versus implant, are all examples of research comparisons which need to be addressed. If trials compare materials, such comparisons should be made against a gold standard, not "straw men" comparators which yield favourable results for the material to be tested [49]. For such material testing trials, clear reporting of all sponsorship should be mandatory [50].

2 Choose relevant outcome parameters

Regardless of what is investigated, the chosen outcomes of trials should reflect what is most relevant to patients, dentists and other stakeholders. The use of an agreed outcome set for future trials would be desirable also to reduce risk of selective reporting.

3 Include data on patient risk and interventions

Major confounders such as caries risk and bruxism should be recorded as part of trial methodologies and appropriately considered during analyses. The time and reasons for any interventions should also be recorded to allow discrimination between success, survival and failure, and to perform statistically valid survival analyses.

Different trial designs should be considered when planning to compare restorative treatments and materials: while randomised clinical trials reduce selection bias, their observation times are usually short and sample sizes limited. Retrospective and prospective practice based studies circumvent these limitations, but have considerable risk of indication bias and confounding which need to be dealt with appropriately. Perhaps the answer lies in coordinated, multicentre studies of different design, no one design being capable of yielding all the required outcomes. Whatever the way forward funders and sponsors of clinical research in restorative dentistry should encourage investigators to come forward with new innovative approaches to answers priority questions.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dental.2017.08.187.

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