A road map for designing and reporting clinical trials in paediatric dentistry.

Short running title: Design of clinical trials in paediatric dentistry

Mariana Pinheiro Araujo[1], Waraf Al-Yaseen[1], Nicola Patricia Innes[2]

[1]Child Dental and Oral Health, School of Dentistry, University of Dundee, Dundee, UK, DD1 4 HR

[2]Applied Clinical Research and Public Health, School of Dentistry, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK, CF14 4XY

All authors had equal contribution to conception, design, drafting and critically revising the manuscript.

Background

Unless clinical trials are well designed, there is a risk that they will not be usable to improve patient care.

Aim

This paper discusses some factors important in designing clinical trials in paediatric dentistry. It uses the prevention and management of dental caries in children as the lens through which to look at these.

Findings

Amongst many other factors to consider are: clear research questions and objectives; appropriate outcomes and outcome measures; sample size calculation and the level of randomisation; methods for random allocation; and operator/ assessor training.

Experts in trial design including statisticians and a trial manager should be consulted early in the design process. The aspects of trial design unique to cariology trials such as “clustering” of data items, mixed dentition issues and those related to trials involving children (communication, consent etc) should be factored in. Comprehensive reporting of the trial’s results is essential.

Conclusion

There are many readily available resources and tools to help the researcher design a trial of good quality that will yield results useful to the research community and beyond, to those who will implement the findings and ultimately those who will benefit from them.

Keywords

Clinical trials, Design, Clinical research, Caries, Prevention

Introduction

In the words of the late Professor Douglas Altman, renowned clinical trial statistician and methodologist “To maximise the benefit to society, you need to not just do research, but do it well”. [1] The activity of research serves two functions; to advance knowledge with and improving care. However, some research does not reach the quality or the appropriate design to be able to fulfil these and may be considered wasteful. Redundant research is a more significant issue that is generally appreciated. Less than 50% of the published biomedical literature is estimated to have been carried out and reported to minimum satisfactory standards. [2] In a study using vitamin supplement research to explore the magnitude of the problem, the vast majority of studies were found to fall below standard and could be considered research waste. [3]

Designing randomised clinical trials involves a number of elements that each have to be designed precisely, to answer the question being asked. These include; randomisation type,

clustering, allocation concealment, blinding of participants, those carrying out treatment and assessors, as well as pre-specifying and complete reporting of outcomes. Each element has to be planned in advance and the correct choices made with regard to subtleties such as the level of randomisation (patient, tooth, practice), the method chosen for allocation concealment and how to maximise blinding. Failure to make the best choices in each situation will affect the carat of each of the remaining uncut gems within the process and compromise results.

This paper will discuss different aspects of clinical trial designs that should be considered to improve their quality. It focuses on trials that investigate the prevention and management of dental caries to illustrate the concepts, although the principles are applicable for most oral health and dentistry related trials. This paper will use the National Institutes for Health definition of a clinical trial, [4] that relates to randomised control trials, where the trial has:

- Human participants who are prospectively allocated to receive an intervention AND
- the purpose of investigating the effects of that intervention on the participants AND
- health-related biomedical or behavioural outcome.

What are clinical trials and why are they so valuable?

Clinical trials are research studies where one intervention (often a dental treatment, a new material or a behavioural intervention) is compared with another, or where it is compared with a placebo or with no treatment. The vast majority of clinical trials investigate the clinical or economic benefits of interventions. However, they are also crucial for detecting harms or side effects. Randomised controlled trials are generally considered to be the “gold-standard” for producing clinical evidence. [5] They are significantly more resource-intensive to undertake compared to studies with other designs such as observational ones. Dental caries clinical trials can particularly require a high level of resource because usually the interventions are designed to reduce the incidence or effects of dental caries but the disease is not quickly progressing and most trials need to be carried out for a number of years to detect any difference in disease experience between the intervention and comparison groups.

Appreciating the value of a highly regulated trial design, requires acknowledging one of the biggest obstacles that interferes with researchers reaching valid findings; bias. Bias is a form of systematic error that can influence a trial's result independent of the intervention. [6] Investigators may consciously or unconsciously fail to remove bias, account for it, or acknowledge it. There are different kinds of bias and they can be grouped, depending on how and where they exert their influence. The more that bias is reduced, the more confident we become in the accuracy of the study findings.

However, it is rare for a single trial's data to be strong enough to culminate in a change in patient care on its own, no matter how robust the trial methodology is. Figure 1 illustrates the stages that data from a clinical trial will generally pass through to reach the stage of having its findings implemented, resulting in a change in patient care. [7]

Figure 1.

Considerations for trial design

The science behind trial design has evolved greatly, although the fundamentals endure. The reader is referred to Friedman et al. textbook "The Fundamentals of Clinical Trial Design" as reference for some of the more complex designs such as crossover, withdrawal, factorial and adaptive designs, together with their indications and pitfalls. One of the most common designs used in dentistry is the parallel group-controlled trial. All aspects of a trial design are linked to its purpose.[8,9] Some of them are discussed in this paper and the journey through them illustrated in Figure 2:

- Research questions and objectives;
- Type of randomised controlled Trails;
- Outcomes and outcome measures;
- Sample size calculation;
- Randomisation and allocation;

- Protocol and registration;
- Training and calibration of operators and outcome assessors; and
- The CONSORT guidelines and other reporting tools.

Figure 2.

Designing and executing high-quality clinical trials is complex. Statisticians and Clinical Trials Units should be consulted very early on in the process of designing a trial to help inform the design.

Research questions and objectives

The trial's specific questions around what the trial team or funder's need to find out drives the trial design. There are two aspects to this. Firstly, is the question being asked important enough to justify the resources that will be required to answer it? The second aspect to asking research questions is around the accuracy of the question being asked and using that to design the trial. [10]

Asking the right question

There is a considerable body of literature advising researchers on how to tailor their research questions. This highlights the importance of identifying the knowledge gap within the area of interest and ensuring it is relevant to patients. A recent scoping review[11] found an over-emphasis on technical and clinician-centred questions and outcomes. Carrying out a thorough literature review is not only good practice but is now considered a fundamental part of a trial design and essential to request funding.[12] However, hand in hand with this, patient and other stakeholder groups should be consulted and the UK's National Institute for Health Research has helpful information to support public involvement in research. [13] Also, the Feasible, Interesting, Novel, Ethical and Relevant framework is a useful tool to guide researchers in not only building a good question but considering other important aspects for designing clinical trials. [10]

Asking the right question in the right way

The research question usually starts as being quite abstract; is material X better than Y? or do children find one treatment more acceptable than another? The next step is refinement to craft

focused and well-directed answerable questions. This stage is the melting pot where the observations, challenges and curiosities that have been part of previous clinical experience and research evidence, are transformed into a highly structured research project with specific outcomes. This process is often iterative. It will involve defining the primary and the secondary questions that the trial will produce data for.

The primary question is the most important query to be answered and the one upon which the sample size calculation is based. The primary outcome should not be changed without explicitly stating why this has happened. This helps to avoid bias with selective reporting of outcomes and reduce the risk of false positive and false negative results if the research produced is not based on the original sample size calculation. Research questions should be related to all elements of that trial. [14] The question should clearly lay out in the trial objectives and comprise; the target population, the intervention(s) being tested or compared, the outcomes and how they are going to be measured. Adopting the PICOT framework for the question (Population, Intervention, Control, Outcomes, and Time guides the investigator not only to define what should be included, but also what will not be part of the study. [15]

An example is shown in Figure 3. for the Primary objectives of the "Seal or Varnish" trial, where the researchers wanted to find out whether fissure sealants or fluoride varnish applications were better for preventing caries in first permanent molars (FPM) in children. [16]

Figure 3

The secondary objectives were to

- "establish the costs and budget impact of FS and FV delivered in a community/school setting and the relative cost-effectiveness of these technologies
- examine the impact of FS and FV on children and their parents/carers in terms of quality of life (QoL) and treatment acceptability measures
- examine the implementation of treatment in a community setting with respect to the experience of children, parents, schools and clinicians."

Type of randomised control trial

One of the fundamental decisions is whether the trial should be designed as a superiority or a non-inferiority trial. Is a new treatment (or a different intervention) being tested expected to be

better than the standard treatment (superiority trial)? The importance of this aspect of trial design (superiority or non-inferiority), is that it will directly influence the sample size necessary to carry out the study. An example of a superiority trial where two different treatments were compared to see which was better is the "Atraumatic Restorative Treatment compared to the Hall Technique for occluso-proximal cavities in primary molars…" trial. [17]

A non-inferiority trial is one where a proposed (potentially new) intervention is expected to be as good as, or not worse than, the standard treatment considering the primary outcome. Non-inferiority trials are considered where the cost of one treatment is lower than another, the treatment is more convenient or perhaps less toxic. Thus, as long as the new treatment is as good as the old one, there is still an advantage in adopting it, compared to the current one. An example is the investigation into whether vital pulp therapy had as good outcomes as root canal treatment in FPMs with irreversible pulpitis. [18]

Other factors to be considered in overall design is whether a parallel group, split mouth, factorial or even cluster design should be included. Clinical Trial Units and other specialists in trial design should be consulted to assist with these fundamental, but sometimes quite complex. [19]

Outcomes and outcome measures

Alongside the trial's objective-setting, determining the most appropriate outcome and outcome measures must be agreed *a priori.* The outcome should align directly to the question being posed. Common outcomes (what is being measured) in cariology clinical trials are "carious lesion progression", "restoration failure", "pulpitis", "tooth loss" or "patient satisfaction". Patient relevant outcomes and patient reported outcomes are becoming more common.

The outcome measure (how the outcome is being measured) has to be chosen with care. It has to be sensitive enough to detect changes, for example when measuring carious lesions, the outcome might be "progression of carious lesion" but that can be measured as a binary "progressed into dentine" or "not progressed into dentine" over time or at a more granular scale such as by using the International Caries Detection and Assessment System[20] criteria which

consists of a seven point scale. [20] The choice of both outcomes and outcome measures will determine whether the findings will be comparable to other research. There is currently no core outcome set for cariology trials. However, even when good outcomes and outcome measures have been chosen, poor reporting compromises their inclusion within systematic reviews, culminating in the loss of their value. [21]

Sample size

Trials have to have the right number of participants for a difference between the groups to be detected. Recruiting too many participants is wasteful and unethical and too few will mean that a difference may not be detected, and an intervention labelled as ineffective when actually it is effective. Determining an appropriate sample size for the trial means calculating the smallest sample number required to attain an accurate result and make valid inferences. In a superiority trial, the sample size is built on the likely numbers of participants needed to show a clinically meaningful difference. Determining the sample size is not always a straightforward procedure. [22]

For trials where the primary objective relates to the tooth, then the tooth should be the level at which the sample size calculation takes place and the data to inform the calculation, is derived from. [17] For trials where the outcome relates to the person, that should be the level the data is taken at as seen, for example, in the Filling Children's Teeth; Indicated or Not. [23] There can be more complex when issues around clustering, for example when more than one data point is gathered within each subject (commonly when more than one tooth is included per subject) are considered and a statistician who understands the particular features of dental trials should be consulted. [24] The Northern Ireland Caries Prevention In Practice trial presents a good example to illustrate the design of clustered-randomised controlled trials in Paediatric Dentistry where randomisation was at the dental practice-level. [25]

Randomisation, stratification, blocking and allocation concealment

Random sequence generation (how the randomisation is constructed) and allocation concealment (how the randomisation is hidden from the allocators) are important steps to ensure that each study group is balanced for key characteristics. These reduce the risk of bias and help ensure that, if any difference is found between the intervention(s) and control, this will likely be due to the intervention and not associated with the participants' characteristics[26]. These take place prior to the participant recruitment stage. Random sequence generation sometimes involves stratification of individual characteristics using "blocking". However, if "blocking" is considered necessary (i.e. key characteristics are forced to balance across arms) it is generally considered best practice to make the blocks of varying (unpredictable) sizes. A clear system has to be put in place, to ensure that recruiters cannot predict to which group the next participants are likely to be allocated. If the principles of allocation concealment are not followed and executed correctly, clinicians involved in the trial may be able to predict which treatment group the next participant will be allocated to. This can lead to conscious or unconscious selection of participants[27].

Randomisation and allocation concealment need to be rigorously designed at the trial planning stage.

Common allocation concealment methods are:

- sequentially numbered opaque sealed envelopes; and
- web based or telephone randomisation.

Web-based randomisation using a bespoke computer programme option is generally considered to be the most secure way of maintaining allocation concealment. The use of envelopes for randomisation must follow a few criteria to have some degree of rigour:

- opaque envelopes;
- sequential numbering;
- sealed envelopes that cannot be opened and resealed; and
- opened in the correct order by the recruiting clinician, only after the participant has been enrolled into the trial.

Maintaining "blinding" to the randomisation sequence and block sizes, for the operators and personnel involved in participants' recruitment will help the veracity of the trial, especially if it is not possible for them to be blinded to the intervention[27].

There are variable degrees of blinding. It can be applied at three levels, that of the participant, the operators and the outcome assessor. If only one is applied, this is known as single blinding, if two; double blind and if all three; triple blind. However, in cariology and restorative research in dentistry is not always possible to have multiple levels of blindness mainly because of the difference in the procedures related to different interventions, the ability of clinicians to distinguish between them and the materials used to restore the tooth, even if assessors are blinded to the allocation. Employing methods to blind other individuals within the research team can offer an acceptable alternative to such issues. For example, blinding methods were used at the radiographic assessment and analysis stages of FiCTION trial[23] since it was not possible for the children and dentists to be blinded to the interventions.

Split mouth Design Trials

Within cariology clinical trials (especially ones of interventions) the split mouth design is relatively common. This is where one treatment is carried out on one tooth and a different one in a different tooth. Randomisation takes place at the tooth level. The advantage is mainly that the patient acts as their own control so gives more certainty that inter-participant differences, such as age, socio-economic conditions, dmft/DMFT, diet etc are matched. However, there are a number of factors that need to be considered when using a split-mouth design. Clinical considerations include avoiding potential carry-over from one treatment to another, so a split mouth study would not be suitable for an intervention of a chemical that could be transmitted across the mouth through saliva and cause contamination, outcome measures carried out at a person level may not be able to be attributed to either treatment and it can be difficult to blind the participant and person carrying out the treatment. Statistical considerations must take into account the site effects and using the correct statistical measurements. [28]

External validity also has to be considered when deciding on a split mouth trial as the correct design. [29] To carry out a split mouth study, the disease being treated, has to be symmetrical across the mouth. By investigating, for example, two different methods for managing dental caries restoratively, we narrow the pool of patients that can be recruited from but also, because each patient must have at least 2 carious lesions, the results are applicable to patients with a DMFT>1.

Protocol

The design elements are put together into the trial protocol; a description of how the proposed clinical trial is going to be conducted. Most major research funding bodies require the use of their protocol template from grant applicants to guarantee participants safety and validity of the findings. [13,30]

Apart from demonstrating trial impact and design robustness, prior registration of the trial protocol promotes transparency in terms of ensuring that all predetermined outcomes are analysed and equally reported and not just the ones that yielded favourable or statistically significant results. The traceable alignment of the planned, assessed and reported outcomes between the trial protocol and final published results reduces the risk of outcome reporting bias and distorting the trial findings.

It is good practice to register the trial with a recognised clinical trial registration website such as International Standard Randomised Controlled Trial Number or ClinicalTrials.gov [31]. This is an important step as most peer reviewed journals require the trial to have been registered before accepting a manuscript for peer review prior to publication. However, there are other significant reasons for registering a clinical trial. It confers benefits to participants, the scientific community, clinicians, stakeholders and funding agencies by demonstrating that the trial has been planned ahead and all the steps and requirements are being filled as initially planned. Trial protocols can be published in journals up until the point that the trial completes recruitment.

Although protocol registration and publication help to ensure the trial is going to be carried out according to them, if changes need to take place once the trial has commenced, these can be addressed in the final write-up or even by altering the protocol with an explanation of why it has changed attached to it.

Resources are available to advise on structuring protocols with several related guidelines to standardise the protocol format and increase the quality of reporting such as the Standard Protocol Items: Recommendations for Interventional Trials. [32]

Assessors; training, calibration and standardisation

Training and calibration of operators (who deliver the intervention) and outcome assessors should be built into the design. Training and standardisation of how operators deliver the intervention will help ensure that all patients receive as close to the same treatment or experience as possible. However, it is important that during the design of the trial, the degree to which this is actually desirable is considered. If a trial shows that something works very well but it has been delivered in a very highly standardised way by trained specialists in a controlled environment, it does not necessarily mean it will be applicable and have the same results in a primary care environment when used by dentists.

Training consists of making the operators or outcome assessors familiar with a technique and capable of replicating them according to the standards. Whether it is to perform a treatment or to use the most appropriate criteria to measure the outcome of interest, training the operators and/or assessors, will ensure that the intervention will be delivered according to previously accepted protocols, reducing the chances of the findings to be associated with this variable (operator/assessor). For example, when performing a restoration, operators need to be trained to perform them in the same way, ensuring that if a failure occurs, it will not be associated with them.

When evaluating an outcome, as for example the presence or absence of carious lesion, the outcome assessor needs to present a consistency according to the criteria chosen (e.g. ICDAS, WHO) at all times the outcome is assessed. For this reason, in addition to being trained and familiar with the criteria selected, the assessor(s) need also to be calibrated, ensuring that they will interpret the outcome with no or very little difference between them (if more than one) at all time-points. Calibration is a peer-review process that involves discussion between the assessors and joint decision-making.

Trials involving children can face additional challenges, especially for longitudinal design as the children (trial participants) are growing rapidly both on mental and physical level. Hence, their perceptions of outcome measures that involve their opinion may change over the time of the trial time or between participants.[33] Also, consideration has to be given to the role of parents in giving opinions on behalf of the child. [34,35]

Reporting according to CONSORT; Improving the quality of reporting clinical trials

The EQUATOR network is described as a "one-stop-shop for writing and publishing high-impact health research" [36] and, amongst a host of other invaluable resources, contains details of The Consolidated Standards of Reporting Trials guidelines[37] which were originally designed as a tool to aid reporting of trials through a checklist of a minimum set of pre-specified information. They aim to ensure that the reader of a journal had adequate information available to interpret it. Many journals require the CONSORT checklist to be completed to allow submission to the journal. However, although this has helped improve reporting to some extent, it is still the case that data from trials has to be excluded from systematic reviews because of missing or imprecise reporting.

Poor reporting of trials affects the ability to synthesise the trials into systematic reviews. Despite the guidelines being developed in the mid-1990s, there is still evidence of "waste" created by poor quality studies. In line with the wider field of biomedical literature[38], there is ongoing evidence of it within paediatric dentistry. Numerous studies have assessed the reporting quality, or completeness of reporting, in trials of Paediatric Dentistry. All have been in general agreement that deficiencies are common. Trials published between 1985-2006 [39] were found to be "poor" in their reporting quality. A substantial gap was found between the CONSORT statement recommendations and what was actually reported. Hence, it was not possible for the readers to assess the trial's validity. In an update of that review, this time including trials published between 2014-2015 [40] for paediatric dentistry clinical trials, they noted tangible improvements in the reporting of the methodology over time especially that titles and abstracts now reflected the research design.

In a report on the quality of systematic reviews related to Paediatric and Preventive Dentistry trials the quality of reporting was found to have improved over the years. [41] A wider review including different specialties within Dentistry (including paediatrics)[42], highlighted the need to differentiate between reporting and methodological quality assessment. The authors suggested that the two concepts were often mistakenly employed within the dental literature interchangeably. CONSORT statements were given as an example for such confusion, as this was developed to assess reporting quality. However, the conclusions regarding the rigour of the trial's methodology would sometimes also be made.

The Reporting stAndards for research in Pediatric Dentistry (RAPID) group are developing a guideline tool for assessing trials within Paediatric Dentistry context [43]. This project will help improve trial reporting, giving guidance for authors, journals editors, and peer reviewers on the elements needed for transparent reporting of Paediatric Dentistry trials. However, like CONSORT, RAPID[44] should be considered as part of the process of design for clinical trials.

Conclusion

Dental care for preventing and managing dental caries is constantly changing. Material sciences are always looking for longer-lasting, easier to use, more biomimetic materials. Our understanding of the biofilm has led to a change from complete carious tissue to understanding that only selective and sometimes no, carious tissue needs to be removed. We are subject to external forces, most notably seen with the influence of the COVID-19 pandemic on our ability to deliver dental care. Finally, our patients' expectations have changed. To continue to apply the best care in this changing landscape, we need to have confidence that the materials we use, treatments we can provide and decisions we make, in partnership with our patients are based on the best evidence. Well-designed clinical trials result in high quality evidence and are a key part of improving patient care. This paper has laid out some of the main considerations in designing cariology trials and signposting to the excellent resources available to support the researcher.

Conflict of Interest Statement

The author(s) declared no potential conflict of interest with the prospect of this article.

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Figure 1. Flow of evidence from preclinical studies whose findings inform primary research (clinical trials), through the synthesis of the primary research findings into secondary research (systematic reviews and data syntheses) and the assimilated information from systematic reviews are then appraised and considered for adoption into guidelines and becoming clinical recommendations tailored to fit with individual or patients' characteristics.

Figure 2. A "roadmap" through the treacherous terrain of clinical trial design.

Figure 3. PICOT applied to the "Seal or Varnish" for first permanent molars (FPM), [16] showing the definition of each component and how the overall trial objective relates to them.

1- Title: I understand the importance of Douglas Altman's phrase; however, the title is not informative to IJPD readers.

Authors' response:

Thank you for your comment. We opted to use the late Professor Douglas Altman's quote to emphasise the value of rigorously designed clinical trials. We acknowledge your point of view that it might not be suitable to IJPD readers.

In this way, we changed the title from: *"'To maximise the benefit to society, you need to not just do research, but do it well'; paediatric dentistry trial design"*

To: *"A roadmap for designing and reporting clinical trials in paediatric dentistry".*

2- Introduction: The introduction should be better explored, showing problems related to RCT designs such as the use of wrong randomization, lack of allocation concealment, and the impact of these in the study.

Authors' response:

Thank you for your comment. The following paragraph has been now added to the introduction.

"Designing randomised clinical trials involves a number of elements that each have to be designed precisely, to answer the question being asked. These include; randomisation type, clustering, allocation concealment, blinding of participants, those carrying out treatment and assessors, as well as pre-specifying and complete reporting of outcomes. Each element has to be planned in advance and the correct choices made with regard to subtleties such as the level of randomisation (patient, tooth, practice), the method chosen for allocation concealment and how to maximise blinding. Failure to make the best choices in each situation will affect the carat of each of the remaining uncut gems within the process and compromise results."

3- "Random allocation, stratification and blocking" section: This section should be better explored. My suggestion is to discuss the importance of allocation concealment.

Authors' response:

Thank you for your suggestion. We edited the section as follows:

Random sequence generation (how the randomisation is constructed) and allocation concealment (how the randomisation is hidden from the allocators) are important steps to ensure that each study group is balanced for key characteristics. These reduce the risk of bias and help ensure that, if any difference is found between the intervention(s) and control, this will likely be due to the intervention and not associated with the participants' characteristics[26]. These take place prior to the participant recruitment stage. Random sequence generation sometimes involves stratification of individual characteristics using "blocking". However, if "blocking" is considered necessary (i.e. key characteristics are forced to balance across arms) it is generally considered best practice to make the blocks of varying (unpredictable) sizes. A clear system has to be put in place, to ensure that recruiters cannot predict to which group the next participants are likely to be allocated. If the principles of allocation concealment are not followed and executed correctly, clinicians involved in the trial may be able to predict which treatment group the next participant will be allocated to. This can lead to conscious or unconscious selection of participants[27].

Randomisation and allocation concealment need to be rigorously designed at the trial planning stage.

Common allocation concealment methods are:

- sequentially numbered opaque sealed envelopes; and
- web based or telephone randomisation.

Web-based randomisation using a bespoke computer programme option is generally considered to be the most secure way of maintaining allocation concealment. The use of envelopes for randomisation must follow a few criteria to have some degree of rigour:

- opaque envelopes;
- sequential numbering;
- sealed envelopes that cannot be opened and resealed; and
- opened in the correct order by the recruiting clinician, only after the participant has been enrolled into the trial.

Maintaining "blinding" to the randomisation sequence and block sizes, for the operators and personnel involved in participants' recruitment will help the veracity of the trial, especially if it is not possible for them to be blinded to the intervention[27].

There are variable degrees of blinding. It can be applied at three levels, that of the participant, the operators and the outcome assessor. If only one is applied, this is known as single blinding, if two; double blind and if all three; triple blind. However, in cariology and restorative research in dentistry is not always possible to have multiple levels of blindness mainly because of the difference in the procedures related to different interventions, the ability of clinicians to distinguish between them and the materials used to restore the tooth, even if assessors are blinded to the allocation. Employing methods to blind other individuals within the research team can offer an acceptable alternative to such issues. For example, blinding methods were used at the radiographic assessment and analysis stages of FiCTION trial[23] since it was not possible for the children and dentists to be blinded to the interventions.

4- "Protocol" section: My suggestion is to discuss the impact of protocol development/register in some bias, such as outcome reporting bias.

Authors' response:

Thank you for your suggestion. A paragraph was added to the "protocol" section.

"Apart from demonstrating trial impact and design robustness, prior registration of the trial protocol promotes transparency in terms of ensuring that all predetermined outcomes are analysed and equally reported and not just the ones that yielded favourable or statistically significant results. The traceable alignment of the planned, assessed and reported outcomes between the trial protocol and final published results reduces the risk of outcome reporting bias and distorting the trial findings."

5- Use of reporting guidelines: Information about reporting guidelines should be revised. There is no relationship between the use of reporting guidelines and the overall quality of clinical trials because the reporting guidelines should not be used as a tool to design clinical trials.

Authors' response:

Thank you, this section has now been removed.

6- Aspects related to blindness could be important to add in the manuscript.

Authors' response:

Thank you for your comment. Blinding as a measure to allocation concealment was also included under the heading "Randomisation, stratification, clocking and allocation concealment" (see point 3).