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Cariology Clinical Trials: What Are We—and What Should We Be-Looking At?

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Abstract

Randomized control trial (RCT) methodology has compared interventions for the prevention ar management of dental caries since the late 1960s. Despite almost 50 years and evidence of significant wastage within the wider biomedical research field, there has been little investigatio what works well and where weaknesses lie. This paper aims to draw attention to areas for improvement within cariology clinical trial methodology by summarizing systematic reviews on interventions and outcomes, and using examples to illustrate some challenges with interventio delivery fidelity, outcome analyses, and intervention co-production. Trial design stage choices critical to ensure that optimum information is obtained when testing interventions. Intervention choice, outcome choice, and analyses are particularly important, and cariology trials have spe issues associated with them. A systematic search and review of cariology RCTs found 650 RC reports. Social Network Analysis of interventions revealed a high degree of separation betwee prevention and management trials, gaps in clinically important comparisons, and a tendency fo there to be comparisons within groups; e.g., comparison of interventions within the same, rath than different, levels of invasiveness. Outcomes measured for the same trial reports show: a fo on restoration performance and individual/population caries burden; the growing use of cariou lesion activity and economic-related outcomes; and sparse, although an increase in the use of patient-reported/patient-centered outcomes. Fidelity of adherence to complex interventions ca challenging to measure but is important in interpreting trial findings. Involving target populatior intervention design, delivery, and relating it to the planned rollout, are opportunities to ensure intervention relevance and improved uptake. Outcomes analyses should consider the minimur

clinically important differences and outcome relevance measures for the target population. Fac
underlying trialists' comparator and outcome choices need to be identified, and there is a neec
ensure that a minimum dataset of outcomes allow for combination and comparisons of trial da
systematic review.

Keywords

caries, clinical studies, restorative dentistry, preventive dentistry, caries treatment, child denti

Introduction

The first controlled clinical trial, carried out by James Lind in 1747, investigated whether citrus could treat the symptoms of scurvy (Trohler 2005). It took a further 200 years, until 1948, befo first modern, medical, randomized controlled trial (RCT) was conducted (Crofton 2004), which looked at Streptomycin for pulmonary tuberculosis (Yoshioka 1998). The RCT is considered th way to test treatments. However, RCTs are complex, expensive, time-consuming, and difficult carry out to a high standard. The challenges in producing high-quality, relevant, and useful res are manifold (Heneghan et al. 2017). The RCT is often talked about as a single entity; howeve comprises various parts, each of which, at the design, execution, evaluation, and write-up stag subject to choices that can affect the result of the trial or its interpretation. Discussion and recommendations about methods to ensure a trial is successfully conducted have been more limited; for example, which methods within the RCT design are best for which situation (Ioanni al. 2014). It is ironic that there has been so little investigation into how to make trials efficient a high quality, leaving trial design and process lacking in a credible evidence-base. Two key poir where decision making is critical are the areas of intervention choice and outcomes or outcom measures' selection and analyses (Heneghan et al. 2017).

Clinical trials in cariology often do not have well-defined interventions and definite endpoints (Lamont et al. 2015). This paper will present some evidence for caries trials' methodologies re to interventions and outcomes over the last 50 years, and raise awareness of the complexities both intervention design/implementation (Stamm 2004) and outcome choice, using as exampl large-scale UK National Institute for Health Research (NIHR)–funded clinical RCTs (FiCTION a BRIGHT) aimed at the prevention and management of dental caries and carious lesions.

Why Does This Matter?

Ideally, evidence flows seamlessly from novel discovery to evaluation in several primary clinica (Innes et al. 2016), the results of which are synthesized into systematic reviews, which then in practice guidelines, which are then translated, through practitioners' daily care, into improved p outcomes. However, the flow is not always smooth, with significant inefficiencies and wastage business of evidence production (Macleod et al. 2014). Back in 1747, it took 42 years for Jame Lind's work to translate into the British Royal Navy's "Sick and Hurt Board," which introduced c fruits to ships (Trohler 2005). Global life sciences research cost around US$240 billion in 2010 Furthermore, less than half of the biomedical literature that reached the stage of publication is estimated to be of sufficient quality (in conduct and reporting) to be fit for purpose. Overall was within the research system is around US$200 billion; around 85% of the initial investment (Cha and Glasziou 2009). The figure remains unquantified as a whole for oral and dental research b same problem of poor-quality trials and their reporting is well known (Fleming et al. 2014; Pan al. 2014; Rajasekharan et al. 2015; Sandhu et al. 2015; Göstemeyer et al. 2016; Lucena et al. 2017); there is no reason to believe that the relative magnitude of the problem of waste is likel different from the rest of the biomedical field.

Clinical trials have long been categorized as either explanatory or pragmatic (Schwartz and Le 1967). Explanatory trials tend to be undertaken to assess the efficacy of an intervention under optimized conditions, whereas pragmatic trials aim to determine the relative effectiveness of interventions within the environment in which they are going to be applied. In reality, there is a continuum between the 2 extremes (Sedgwick 2014). Pragmatically oriented trials have been increasing, supported by the desire to have evidence more likely to be translated to point of ca Most dentistry is carried out in primary care settings. Primary care networks offer one way of n it easier—and yet still efficient—to carry out clinical trials in the environment where they will eventually apply their results. These networks are trained and prepared for carrying out trials, making the likelihood of the trials' successful completion higher than might be found in practice are not optimized for research. In the US, UK, Germany, Holland, and Japan, successful prima care networks have been set up, with general or other nonacademic practitioners taking a key in the research. This step aside, other efforts to improve the design and efficiency of cariology do not seem to have been taken forward (Blackwelder 2004; Featherstone 2004).

This paper aims to draw attention to areas for improvement within cariology clinical trial methodology. It summarizes the findings of 2 systematic reviews on cariology trial intervention outcomes, and uses examples to illustrate some challenges with intervention delivery fidelity, outcome analyses, and intervention co-production.

Getting the Choice of Intervention and Outcomes Right

To make informed choices between treatment options in the clinical encounter, the clinician mu have a complete picture of how all appropriate and available interventions would perform agai one another. Furthermore, the outcomes that are studied should be relevant to patients, and th must be similar enough across trials to allow synthesis of the data, informing the evidence bas (Heneghan et al. 2017). If interventions are not compared to one another and similar outcome not measured, then it is not possible to synthesize the evidence. To look more closely at these issues within the field of prevention and management of dental caries, we carried out systema reviews of all RCTs over the last 50 years. Interventions and outcomes were categorized and analyzed (Levey et al. 2016; Levey et al. 2017; Schwendicke et al. 2017). Structured searchin elicited 4,774 articles and, after screening titles, abstracts, then full papers, 605 reports of RC were catalogued.

What Do We Investigate in Cariology Clinical Trials? Interventions

The strength of the overall evidence in any area of health care is governed by the extent to wh the full range of relevant comparators have been investigated across the whole network of tria This involves not only the interventions themselves but the relative comparator choice of interv X against intervention Y. However, clinical trial design is often arbitrary, driven by happenstanc individual preferences, or assumed relevance. Within cariology, the changing field has been dr by discoveries of novel remineralizing and biofilm-modulating agents, new materials, and new treatment technologies (sealing in dental caries, for example). However, the overall strength of evidence and the gaps in the field remain difficult to determine. Applying social network analys mathematical modeling tool to evaluate the presence, strength, or absence of relationships an the objects in the network (Rizos et al. 2011), allowed us to identify what has been investigate helped clarify the gaps. This analysis revealed limitations in the evidence on the comparative effectiveness of caries prevention/management strategies (Schwendicke et al. 2017), with comparator choice seemingly driven by clinical indication (as might be expected). However, th findings limit drawing conclusions on the true relative effectiveness of all strategies. There are various comparators that have not been, but should be, compared. For example, there are ver comparisons between invasive caries removal strategies and caries management strategies th not involve invasive removal. It also seems that comparisons within comparator classes (such within various levels of invasiveness for the interventions) are preferred over comparisons bet classes; for example, comparisons between Hall Technique crowns and standard restorations

preferred to comparisons of Hall Technique crowns with the use of silver diamine fluoride. The choices might be clinically driven but they limit an understanding of how interventions perform against one another.

What Do We Measure in Cariology Trials? Choice of Outcomes

Inconsistent outcome reporting is a significant hurdle to combining results from trials into high-quality, systematic reviews (Lamont et al. 2015; Ioannidis et al. 2017). There is also the issue of selective outcome reporting resulting in bias, which is becoming acknowledged as a serious is medicine but has not yet been looked at in the field of dentistry (Ioannidis et al. 2017). The development and use of core outcome sets (COS) can reduce this barrier. A core outcome set agreed minimum set of outcomes included in the design of trials that allow data to be combine compared at the systematic review stage. Our review of outcomes found a total of 1,364 outcc reported in 605 published reports. We mapped outcomes reported in caries prevention and management RCTs as a first step to COS development, using systematic review methodology the last 50 years, outcome reporting for clinical trials on the prevention of caries and managem carious lesions has focused on measuring "caries experience" and "restoration material clinica performance," with measures of "lesion activity" and "cost-effectiveness" increasingly being rep in more recent studies. Patient-reported and patient-focused outcomes are also becoming mo common (as secondary outcomes) but remain low in use. The challenge with developing a CC be anticipating the outcomes relevant for the future based on trends from the past.

Examples of some challenges with intervention delivery fidelity, outcome analysis, and interve co-production are given in the following sections. Using 2 ongoing clinical trials, we explore an illustrate some of the often hidden and unacknowledged complexities with RCTs.

FiCTION (Filling Children's Teeth: Indicated Or Not?) NIHR-HTA-Funde UK-Wide Trial

FiCTION (https://www.journalslibrary.nihr.ac.uk/programmes/hta/074403/#/) is a multicenter, cl level, open RCT concerning primary dental care aimed at determining the most clinically- and effective approach to managing caries in primary dentition in the UK (Innes et al. 2013). The p trial began in 2009 (Marshman et al. 2012) and the main trial began in 2012, involving 72 dent practices and 1,124 children with dentinal caries (3 to 7 y old on enrollment). Children are randomized to receive 1 of 3 caries management strategies (in a 1:1:1 ratio) and are followed

over 3 y (Keightley et al. 2014; Stewart et al. 2015). However, the management strategies use mean that it is not possible to blind the parents, children, or dentists to the arm of the trial.

FiCTION has been commissioned to inform practice, teaching, and funding of children's dentis across the UK, with both quantitative and qualitative data incorporated within the outcomes. Tl primary outcome is incidence of pain or dental infection. Secondary outcomes are the incidenc caries in primary and permanent teeth, quality of life, acceptability of treatment experiences to children and parents, and dentists' treatment preferences. The 3 treatment strategies for mana caries in the primary dentition are as follows:

Arm 1: Conventional Management of Decay, with Best Practice Prevention

Carious lesions are managed based on active treatment of caries by its complete removal. Aft local anesthesia, the caries is mechanically removed using rotary instruments or by hand exca and a restoration is placed. If the dental pulp is exposed during caries removal or there are symptoms of pulpitis, a pulpotomy may be carried out. Best practice prevention is carried out i with current guidelines (see Arm 3).

Arm 2: Biological Management of Decay, with Best Practice Prevention

Carious lesions are sealed into the tooth and separated from the oral cavity by an adhesive fill material over the decay, or by covering the tooth with a preformed crown using the Hall Techni Decay may, on occasion, be partially removed before the tooth is sealed. Injections are rarely needed. Best practice prevention is carried out in line with current guidelines (see Arm 3).

Arm 3: Best Practice Prevention Alone

Control of the biofilm through its frequent removal and low sugar intake can slow down carious lesion progression. For the best practice prevention alone arm, no caries removal, restoration placement, or carious lesion sealing of primary teeth takes place. Treatment plans are based c best practice preventive care according to current UK guidelines. For primary teeth, this involv strands:

- toothbrushing/self-applied topical fluoride use;
- dietary investigation, analysis and intervention; and
- fluoride varnish application.

FiCTION Trial's Intervention Delivery and Adherence to Protocol

Interventions applied over long periods of time in more pragmatically oriented clinical trials ofte suffer from difficulties with adherence to protocol. For FiCTION, monitoring how well practition had applied the 3 different trial arms over the 3-y duration was important to determine where th had been drift or any "blurring" of the trial arms. The direction and extent of deviations is monit quantitatively through data collected from the dentists, which explains which arm the patient w moved to and why. This information will feed into the interpretation of the results by providing a for carrying out the intention to treat and the per protocol analyses.

There is no direct guidance on the thresholds for insufficient adherence to protocol for the arm have been sufficiently implemented as intended. This is further complicated because each arm multiple components. Should all component parts of the arms contribute equally to an episode deviation or should they be weighted? A final complexity is added by the varying levels of treat that are required by the children in the trial. Within trials of medicinal products, the figure of 80 often applied as a cut-off for deciding on adherence if there is no rational basis for choosing a different figure. Because, clinically, this seemed reasonable, this has been taken as our cut-off the FiCTION trial. A child having 21 tooth treatments throughout the trial with 4 teeth treated in different arm will have had 81% adherence to the arm to which they were randomized. Howev child who only has 1 tooth treated in the trial has that single tooth treated away from the arm, t 0% adherence to protocol.

The process evaluation (Moore et al. 2015) has a qualitative component to allow more in-depth analyses of these deviations; this should help to inform the implementation of FiCTION and ex the deviations from treatment that are seen, as these are not uniform across practitioners or a the trial arms.

FiCTION Trial's Primary Outcome: Pain and Infection

One of the biggest hurdles with trying to use clinical studies to underpin clinical decision makir that they often do not include thresholds of direct importance to patient care. The minimal clini important difference is the smallest difference between interventions that a patient or dentist w consider adequate when choosing to use a new intervention (Make 2007).

At the start of the trial, the proposed primary outcome for FiCTION was the proportion of childr with at least 1 episode of dental pain and/or dental sepsis during the planned 3-y follow-up pe

The individual components of this composite outcome were to be considered as having equal importance (Cordoba et al. 2010). The outcome was then to be dichotomized: zero episodes c dental pain/sepsis or at least 1 episode. As the trial progressed, it became clear that the numb episodes experienced by a child was also a clinically relevant outcome and statistically a more sensitive measure. This was directly relevant to the minimal, clinically important differences an the 3 treatment arms. The trial protocol was changed, reappraised by the ethics committee, ar finalized as having co-primary outcomes through 2 analyses for the primary outcome data: 1) t proportion of children with at least 1 episode of dental pain and/or dental sepsis during the foll period (incidence) using logistic regression, and 2) the total number of episodes of dental pain and/or dental sepsis for each child during the follow-up period using negative binomial regress Because the original power calculation for the trial was based on a comparison of proportions, remains the only powered analysis; however, an exploratory hypothesis test for the unpowered comparison of the mean number of episodes will be carried out and reported. The outcome da from FiCTION will be reported and published in September 2018.

BRIGHT (Brushing RemInder 4 Good oral HealTh) NIHR-HTA-Funded UK-Wide Trial

Dental caries affects 1 in 3 12-y-olds in the UK, and is closely linked to deprivation. Brushing w fluoridated toothpaste is a highly effective preventive measure, and early establishment of self operation is associated with improved oral health through life (Broadbent et al. 2016). Mobile h (mHealth) multimedia technologies interface with health care delivery most commonly through mobile phones, making mobile phones a potential vehicle for health behavior change (Head et 2013). Short messaging service (SMS) interventions have shown robust effects on behaviors a outcomes (Fjeldsoe et al. 2009; Head et al. 2013). BRIGHT (https://www.journalslibrary.nihr.ac.uk/programmes/hta/1516608/#/) will evaluate the clinical ar cost-effectiveness of a behavior-change program to improve the oral health of young people li deprived areas across the UK. It is a multicenter, 2-arm, cluster-randomized controlled trial, th school-based and assessor-blinded, with an internal pilot trial involving 5,760 young people (1 y). The BRIGHT intervention is a classroom-based, curriculum-embedded session with co-des follow-up SMS, as compared with routine education and no SMS.

The primary outcome is the incidence of carious lesions in permanent teeth (at 3 y). Secondar outcomes are self-reported frequency of daily tooth brushing, clinical assessment of plaque or gingivitis, cost-effectiveness, and health- and oral health-related quality of life and oral health

behaviors.

BRIGHT Trial's Intervention Design

In the BRIGHT Trial, the intervention was prespecified by the funder as a classroom-based se with a series of follow-up SMSs. The "Keep on Brushing SMS Programme" in New Zealand, o which the funding call was based, had targeted unemployed 18- to 24-y-olds (Schluter et al. 2 Smith and Whaanga 2015); however, the content of those messages was not appropriate for children of 11 to 13 y. We adopted a co-design approach to the content of the SMS by using y people's own words, developed through workshops, to remind and reinforce the messages fro classroom-based session. The assumption before carrying out the workshops had been that y people would be interested in being like their friends, mimicking celebrities, and interested in h These were then presumed to be the factors that would be incorporated into the SMS prompts However, it seemed that the biggest factor that triggered interest in this topic was around avoi disease rather than health and beauty; for example, one of the young people's developed and favored message was, "On a daily basis, 100 million micro-creatures are swimming, eating, reproducing, and depositing waste in your mouth". Designing interventions with the help of the population can help to ensure the relevance of the trial.

Conclusion

Although agreed as being a robust methodology for testing treatments, RCTs are expensive a acknowledged as being one of the most challenging to execute. Nevertheless, little attention h been paid to their design stage, and ensuring that they are appropriate for use. Designing RC complex process that involves multiple stakeholders with multiple agendas. Decisions at the d and analyses stages will have a major impact on the quality and usability of the trial findings downstream. The designs of proposed clinical trials should be informed by evidence from the strengths and weaknesses of previous trials (Richards 2011). In addition, gaps in research evi can only become clear by evaluating what has already been studied. Once identified, gaps in t scope of research and research methodology should be addressed. There must be conversati and coordination among the major funders, researchers, and end users of the research to ens that the right interventions and the right outcomes, with minimal clinically important differences investigated.

Author Contributions

N.P.T. Innes, contributed to conception, design, data acquisition, analysis, and interpretation. T author gave final approval and agrees to be accountable for all aspects of the work.

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