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Patient-reported Outcomes (PROs) in Clinical Trials in Paediatric Dentistry

Abstract

Patient-reported outcomes (PROs) are reports directly from patients without interpretation by clinicians or others and captured using validated patient-reported outcome measures (PROMs). These measures are increasingly employed in clinical practice and can be incorporated into clinical trials. Benefits of using PROs include reducing observer bias; eliciting unique views on aspects important to patients and increasing public accountability. Despite inclusion in clinical trials PRO data is often under-reported and the results may not be adopted into clinical practice due to concerns about the data generated. This review discusses what PROs are and how to measure them; the benefits of using PROs; how to choose an appropriate PROM to answer the research question; considerations for using PROs in paediatric dentistry and reporting guidelines. Finally, some examples of how PROs have been included in paediatric dentistry trials are given along with discussion of the development of core outcome sets and how these may improve reporting of PROs in the future.

Keywords: Paediatric Dentistry; Patient-reported outcomes; Patient-reported outcome measures; Clinical Trials

Introduction to PROMs

Choosing appropriate outcomes for a clinical trial is crucial for the validity and interpretability of the results. It is increasingly recognised that capturing patient experiences enhances the quality of the results alongside more traditional biomedical indicators. Patient-reported outcome measures (PROs) are "any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else" [1]. Patient-reported outcome measures (PROMs) are the measures used to gain these PROs, usually in self-administered questionnaire form. PROMs may be used to gather data on different aspects of conditions, for example: symptoms arising from the patient's condition or therapy for it; functional outcomes or multidimensional constructs such as (oral) health-related quality of life or health utility [2]. PROMs are increasingly employed in clinical settings to aid clinicians' understanding of how treatment and diseases impact upon those who experience them [3]. There use in clinical trials is also expanding.

In clinical trials in dentistry PROs are usually used to supplement other objective measures such as caries prevalence or measures of treatment success. This allows participants' experiences to be considered alongside these other measures.

Benefits of using PROMs

There are many benefits from including PROMs in clinical trials. These include reduction in observer bias which can be introduced when study personnel attempt to make judgements about what participants are experiencing. Additionally they provide unique information that only those undergoing the intervention can provide [2, 4]. This information enriches our understanding of participant experience and can aid decisions regarding the benefits of a particular treatment. Further benefits are shown in Figure 1.

The recognition of these benefits has led to funders and institutions mandating that PROs should be included in clinical trials [2]. Patient advocacy groups also encourage the inclusion of PROs as they allow participants to communicate their experience, including any unmet needs or areas where care could be improved [5].

How to choose a PROM

The goal of PROM selection should be to achieve a comprehensive evaluation of the participant's experience whilst maximising the relevance to the participant and minimising burden and duplication [6]. Historically, problems have been reported where researchers fail to choose an appropriate PROM. For example, the suitability of PROMs in head and neck cancer trials between 2004-2015 was assessed (n=66) and found that only eight included a hypothesis related to the PRO and therefore it was impossible to assess the appropriateness of the PROM used [7]. In addition, in a number of trials, modifications have been made to the PROM without evaluating what the impact of this would be on the measure's psychometric properties [7]. The US Food and Drug Administration has declined to include PRO data on drug labelling on the basis that the PROM used has not been appropriately developed and validated which suggests this is a problem even within well-resourced drug trials [8].

Luckett and King describe six guiding principles to choosing a PROM in cancer research but these can also be applied to paediatric dentistry [9]. They state that researchers should:

1. Consider which PROM to use early in the study
2. Select a PROM which is likely to evaluate symptoms or direct treatment effects rather than more distant effects
3. Ensure the items are appropriate and consider how these should be combined
4. Appraise evidence of the reliability and validity of the measure
5. Consider the practicalities of administration, participant burden and whether cross-cultural validation and translation are required
6. Try to avoid adding items to validated measures as this may alter their validity and makes comparison with other studies difficult

Trial investigators are being encouraged to consider using proximal PROs (those which assess symptoms etc.) as primary endpoints when evaluating novel therapies in preference to broader or multidimensional constructs like HRQoL. This is because these more distal domains are more likely to be influenced by factors beyond the trial such as social factors or life events [2]. However, in dental research, it may be important to also consider these broader impacts depending on the intervention under investigation. For example, in

paediatric dentistry removal of a carious permanent tooth may relieve pain but might have broader psychosocial impacts. Without the inclusion of an oral health-related quality of life (OHRQOL) measure, these broader impacts may be missed. Therefore it is important to ensure that measures which are chosen to evaluate the outcome cover aspects that are important to those who will undergo the intervention.

The International Society for Quality of Life Research (ISOQOL) published guidance on minimum standards for PROMs in patient-centred research [10]. ISOQOL states eight core properties of PROMs that should be considered. These related to conceptual/measurement model; reliability; content validity; construct validity; responsiveness; interpretability; translation and burden. Definitions for these terms are provide in Table 1. These are similar to those suggested by the COSMIN (Consensus-based Standards for the selection of health Measurement Instruments) initiative who provide a checklist against which PROMs can be assessed [11].

Using such guidelines can help to ensure that the PRO results obtained are robust, although it should be noted that in paediatric dentistry there are other aspects which should be taken into consideration and these will be considered in the next section.

Considerations when choosing PROMs in paediatric dentistry

When choosing a PROM for use with children, it is important to ensure it is appropriate for the age of child who will be asked to complete it. Children in the "intuitive thought" stage which occurs around 4-7 years of age, generally have limited language skills. Therefore questions should be simple and clear and it is advised that the words that children use should be employed to aid understanding [12]. Children at this stage also have short attention spans, which has consequences for the reliability of their answers if they are not engaged by the measure [12]. Around the age of 8 -11 years, children are entering the "concrete operational stage", their language is still developing and therefore simple, unambiguous language should be used. Finally, children in the "formal thought" stage (11-16 years) can start to use measures which are similar to those used in adult surveys, however, they will still need to be engaged and therefore the measure should be interesting to them [12].

There are several complex cognitive stages involved in answering questions [13, 14]:

1. Comprehending the question
2. Retrieving relevant information from memory and formulating an answer
3. Choosing the appropriate response category
4. Evaluation of the chosen answer and editing for social desirability
5. Communicating the final answer

These stages require great effort, especially if there are a large number of questions. Participants are required to put this effort in to "optimise" their responses and produce the high quality responses needed [15]. However, where this effort becomes too hard to sustain, participants may become fatigued and distracted and answer less thoughtfully. This may mean that they choose the middle response option or may choose an answer randomly [16]. This is termed "satisficing" and is more likely to occur where the items are difficult, with participants with lower reading ability and where motivation is low [15]. As it may take a considerable effort for young children to read through a questionnaire, they may be at risk of satisficing and so efforts should be made to reduce participant burden by ensuring only appropriate PROMs are chosen for inclusion.

Gilchrist and colleagues found that children liked paper-based PROMs to be printed on coloured paper to make them more interesting and to have reminders of how to complete the questions at the top of each page [17]. Electronic PROMs, such as those completed on a tablet or mobile device, may use computer-adaptive testing or skip logic meaning fewer questions are asked whilst retaining the instruments validity.

For clinical trials, measures which can be used longitudinally are desirable as these can accurately assess changes which may be experienced by the participants over time [18]. As clinical trials may take several years to complete, it is important to choose a measure which is suitable both at baseline and at the end of treatment. For example, a measure which is validated for 5-8 year-olds may not be suitable for those who were aged eight years at the beginning of the trial and are now 11 years of age at the trial endpoint. A measure which is

validated and can cover a wider age range is therefore more desirable as it may be possible to use it throughout the study period to accurately reflect changes [19].

PROMs in paediatric dentistry

The most commonly used PROMs in paediatric dentistry are based on the construct of OHRQoL. There are generic measures (those which are not specific for one condition) designed for self-report such as the Child Perceptions Questionnaire (CPQ), Child Oral Health Impact Profile (COHIP) or Child-Oral Impact on Daily Performances index [20-22]. Others such as Early Childhood Oral Health Impact Scale (ECOHIS) and Parental-Caregivers Perceptions Questionnaire (P-CPQ) are designed for parents to complete on behalf of their children or the Family Impact Scale which is designed to gather impacts on the family from the child's condition or treatment [23-25]. These generic measures are useful to gain an overview of how disease or intervention may affect various aspect of OHRQoL. In the context of a clinical trial for a specific condition, these may not be sensitive enough to pick up subtle changes which occur as a result of an intervention for a specific condition, e.g. caries. A caries-specific PROM is available, the Caries Impacts and Experiences Questionnaire for Children (CARIES-QC) [17]. The items included in this measure were developed with children with caries experience to ensure that the included items were relevant to those with caries to enable it to pick up subtle changes which might result from different interventions. It has been included in clinical trials in New Zealand and the UK and has been able to demonstrate change from the child's perspective [26, 27].

Another area important to paediatric dentistry, is measuring dental anxiety and the effect that interventions may have on this. Porritt and colleagues conducted a systematic review in 2012 to assess the existing child dental anxiety measures[28] and then went onto develop a new measure called the Children's Experience of Dental Anxiety Measure (CEDAM)[29] which fulfilled many of the properties described in Table 1.

Use of PROMs in clinical trials

PROs are becoming more frequently employed with 27% of trials registered on clinicaltrials.gov including PROs as an outcome between 2004 and 2013 increasing form 14% from 2004-2007 [30, 31]. This may, in part, be due to requirements of funders and agencies which license drugs making PROs mandatory. A scoping review of trials in dentistry published between 2012-2015 found that quality of life and functional outcomes were rarely used as primary endpoints [32]. A systematic review of outcomes considered in caries research found that only 1% reported patient satisfaction or quality of life, 5% reported pain or anxiety and 2% post-operative discomfort [33]. Similarly, a Cochrane systematic review of the use of fluorides to prevent demineralisation during orthodontic treatment found that of the 10 studies included that none had included a PRO [34].

Where PROMs are used in clinical trials there is evidence that there is substantial research waste in relation to PROs, with a recent systematic review identifying that PRO protocol items were frequently omitted, non-reporting of PRO trials results was common and that often data related to PROs was delayed in publication and inadequately reported [35]. A further systematic review identified barriers to maximising the impact of PRO data [36]. It found that authors identified perceived methodological barriers in the following categories: trial design; conduct and analysis; reporting and the use of PRO data in practice.

There are guidelines now available which, if followed, will ensure that PRO data are reported correctly allowing valid conclusions to be drawn. The SPIRIT-PRO (Standard Protocol Items: Recommendations for Interventional Trials) extension is available for reporting trial protocols and the CONSORT-PRO extension (Consolidated Standards of Reporting Trials) contains 14 items and should be considered the minimum reporting standards for manuscripts with PRO data [37, 38]. Details of the CONSORT-PRO extension are shown in Table 2.

Other barriers also reported related to the uptake of PRO trial results in practice [36]. These were attributed to clinicians' lack of familiarity with PROMs and how to interpret the results; concerns about bias due to missing data; failure by researchers to present data in an accessible way and clinicians' concerns about the validity. This highlights the importance of

ensuring that from the outset of the trial that there is a plan for dissemination of the PRO findings, that investigators who are accustomed to collecting and analysing PRO data are included; that PRO data is reported robustly, and presented to those who are likely to use it for the benefit of patients in a way that can be understood. Where these barriers had been overcome, authors had stated that providing training for clinicians and ensuring stakeholder involvement had aided clinical uptake.

Failure to consider these aspects from the outset of the trial risks negating the benefits of including patient-reports. This may mean that outcomes that are important to patients are overlooked, missing valuable insights which could improve patient care.

Examples of use in paediatric dentistry

A systematic review of studies investigating restorative treatment in the primary dentition found that 17 articles included PROs with 79 articles excluded as they did not include these [39]. The outcomes included measured pain, discomfort, OHRQoL, treatment preference, satisfaction, willingness to have treatment again, anxiety and appearance. However, due to studies using different outcome measures only pain, anxiety and OHRQoL were included in the meta-analysis.

A more recent example of a paediatric dentistry clinical trial including PROMs is the FiCTION trial, conducted in the UK of three treatment strategies for the management of caries in children (3 to 7 years old) attending primary dental care services [40]. This trial included child oral health-related quality of life and child dental anxiety as secondary outcomes. In this trial parents completed the 16 item P-CPQ at baseline and final visit with both child and parent measures of child dental anxiety also used [41]. These measures were included to ensure the trial was able to capture whether the treatment strategies addressed the impact of caries on children's lives, albeit from parent's perspectives and whether experiences of the treatment were positive.

Future directions

One way of ensuring robust and consistent reporting of trials is to use core outcome sets (COS). This is important as the results from randomised controlled trials in paediatric dentistry are increasingly being combined in systematic reviews [33]. The ability for meta-analyses to be conducted within these systematic reviews relies on a certain degree of homogeneity of the outcome measures included - both for clinical and patient-reported outcomes measures. To overcome this problem, COS are being developed in different fields of health and dentistry to specify the standardised set of outcomes that should be measured and reported in all clinical trials. The use of COS is intended to improve the robustness of the findings of systematic reviews and ultimately result in better informed decisions about clinical practice.

In dentistry, COS have been developed relating to traumatic dental injuries in children[42], pulp treatment for decayed primary teeth [43], and periodontal treatment [44, 45]. Recently a COS for orthodontic trials has been developed through an approach which involved a scoping review, qualitative interviews with patients, a Delphi process and stakeholder workshop. The resultant COS covers seven core clinical and patient outcomes including: impact of self-perceived aesthetics, alignment and/or occlusion, skeletal relationship and stability, patient-related adherence, breakages, and adverse effects on the teeth or teeth-supporting structures. The use of such a COS in future orthodontic trials will ensure the impact of treatment from the perspective of patients and clinicians is captured in individual trials and when the results of the trials are combined comparison using statistical analyse will be possible. Ongoing work on other dental COS projects, including COS for Molar Incisor Hypomineralisation and dental caries are registered on the Core Outcome Measures in Effectiveness Trials (COMET) Initiative's database (www.comet- initiative.org).

Conclusions

Including PROs in clinical trials has multiple benefits and ultimately will improve patient care by generating unique insights into interventions which cannot be discovered in any other way. It is important that researchers designing trials ensure that they are familiar with guidance on how to choose, analyse and report PRO data with the inclusion of investigators who are experts in this field, thus avoiding tokenistic inclusion of PROs. When choosing PROMs to use with children, the content, length and suitability for the age of the

participants must be considered. The introduction of COS which include PROs should improve the consistency in reporting of outcomes, ensuring that they are robust and clinically useful and reported along with other trial data. It is likely that as in medicine, the inclusion of PROs in paediatric dentistry research will continue to increase.

Why this paper is important to paediatric dentists:

- Discusses what PROs are and how to measure them
- Considerations required when using PROMs with children
- Signposts guidance to ensure adequate reporting of PROs in scientific manuscripts

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Table 1. Patient-reported outcome measure properties and definitions (Reeve et al. 2013)[10]

Table 2. CONSORT-PRO checklist[37]

Figure 1. Benefits of including patient-reported outcomes