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REVIEW

Outcome measures to assess the effectiveness of endodontic treatment for pulpitis and apical periodontitis for use in the development of European Society of Endodontology (ESE) S3 level clinical practice guidelines: a protocol

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Abstract

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The European Society of Endodontology (ESE) is in the process of developing S3Level Clinical Practice Guidelines for the treatment of pulpal and apical disease for the benefit of clinicians and patients. In order to ensure a homogenous review process in the development of the clinical practice guidelines, it is essential that the core outcomes for all endodontic treatments are standardized and recommendations are made regarding minimum follow-up time specific to each outcome measure. In the absence of a recognized core outcome set in Endodontics, the current project aimed to follow an established consensus process to define the most appropriate clinician and patient-reported outcomes. As part of the project, recommendations will also be agreed regarding an acceptable minimum follow-up period for studies by literature review and group discussion. The selected outcome measures and follow-up periods will be used in subsequent systematic analyses of the literature to investigate the effectiveness of endodontic treatment to alleviate pulpitis and apical periodontitis. In this paper, previous reviews, ESE Guidelines and Position Statements were searched in order to compile a list of potentially important outcome measures for the treatment of pulpitis (working group 1), the nonsurgical treatment of apical periodontitis (working group 2), the surgical treatment of apical periodontitis (working group 3) and the regenerative treatment of apical periodontitis (working group 4). Initially, the two S3 guideline leads selected two independent senior clinical academics with experience of evidence-based dentistry to lead each of the four working groups forming a 10-member steering group. The working group leads in turn selected 32 academics with experience of evidence-based dentistry to lead the individual systematic reviews contained within the respective working groups. These 42 individuals make up the Guideline Development Group (GDG). Prior to the selected systematic reviewers commencing writing and submitting the review protocol, the complete list of outcome variables identified in this document will be ranked by the 42 members of the GDG in their importance to the individual patient using a 9-point Likert scale. A summary of the survey scores will thereafter be shared with the members of the group and the final list of clinician and patient-reported outcome

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measures rated as critical for decision making (7-9 on Likert scale by majority of survey participants) to guide systematic reviews will be consented and confirmed during an online meeting of the steering group. In this online meeting, another aspect with regard to meaningfulness of clinical trial results to be addressed in systematic reviews will be consented: length of follow-up. In order to develop high quality guidelines, it is suggested that the follow-up period after treatment should be related to the specific outcome measure being addressed; however, a minimum of one year for assessing the effectiveness of treatments for pulpitis and apical periodontitis should be considered. It is accepted, that selected research questions that focus on pain, swelling, medication taken or investigating diagnostic accuracy are likely to have shorter follow-up periods. As a result of the GDG consensus process, the outcome measures and length of follow-up will, alongside the use of standard instruments to assess the methodological quality of clinical trials and other comparative studies, be applied to all the commissioned systematic reviews that will inform the subsequent process when developing the ESE S3 Level Clinical Practice Guidelines.

Keywords: clinical outcome measure, clinician-reported outcomes, effectiveness, endodontic treatment, follow-up, guidelines, patient-reported outcomes.

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Description of outcome-related terms used in ESE S3 level guidelines

Outcome measures

Objective or subjective measurement used to evaluate the effectiveness of an intervention compared with the control (Smith *et al.* 2015). Outcome measures should be measurable, often using a numerical value (Nagendrababu *et al.* 2020). Endodontic outcome measures are specifically the measurements or analyses of pulpal and apical disease that are observed in a study or clinical trial that reflect the effectiveness of a therapy.

Clinical outcome

Measurable changes in disease, health, function or quality of life that evaluate the effectiveness of an intervention or exposure. Primary outcomes represent the most critical measures addressing the research question, whilst secondary outcomes assist in the interpretation and understanding of the primary outcome (Nagendrababu *et al.* 2021).

Clinician-reported outcomes
Assess the effectiveness of endodontic treatments using diagnostic tools and tests applied by clinicians, which measure the outcome of the disease (e.g. pulp sensibility test, periapical radiograph, cone-bean computed tomography).

Patient-reported outcomes
Assess the status of endodontically treated teeth from the patient's perspective without interpretation of the patient's response by a clinician or other individual (e.g. pain incidence, pain severity) (John 2018). Within Endodontics retaining a functional and asymptomatic tooth in the long term and a feeling of well-being are important patient-reported outcomes. Understanding the patient's perspective should facilitate the development of, patient-centred outcomes, which are the development of a set of outcome measures that are important to the patient during the treatment of pulpal and apical disease.

Clinical end-point

The primary or secondary outcome measure that is being measured by a clinical trial. Often used interchangeably with outcome measure. The true clinical measure of a treatment outcome assesses the prevention and resolution of disease.

Surrogate end-point
A measure of the effect of a specific treatment that may correlate with a real clinical end-point, but does not have a guaranteed relationship (e.g. reduced biomarker expression in blood samples or alterations in bacterial levels in canals after root canal instrumentation). These end-points are often used when the observation of clinical outcomes requires a long-term follow-up period (Bergenholtz & Kvist 2014).

Validated surrogate end-point
Surrogate measures that have been shown convincingly to relate the outcome of a patient's disease. For example, the radiographic reduction (but not resolution) of an apical radiolucency relates to other

outcomes, such as decreased pain, increased tooth retention and resolution of disease.

Real clinical end-point
A direct end-point that is a true measure of disease prevention or resolution. For example, within Endodontics this may relate to the complete resolution of an apical radiolucency and re-establishment of a 'normal' periodontal ligament space, tooth retention or absence of symptoms. A primary/secondary outcome measure should be important to the patient.

Efficacy and Effectiveness

Efficacy is the performance of an endodontic intervention under ideal and controlled conditions, whereas effectiveness refers to performance in 'real-world' pragmatic conditions. Effectiveness will be used rather than efficacy during the development of the ESE S3 level clinical practice guidelines.

Introduction

A recent focus on the development of patient-reported or centred-outcomes (Neelakantan *et al.* 2020), allied with new diagnostic modalities such as cone-beam computed tomography (CBCT) have highlighted the need to consider appropriate outcome measures to assess the effectiveness of endodontic treatment (Patel *et al.* 2020). Relevant outcomes are particularly pertinent when writing recommendations or undertaking systematic analysis of the literature in order to assist clinical guideline development using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework (Guyatt *et al.* 2008, Guyatt *et al.* 2011, Loos & Needleman 2020, Sanz *et al.* 2020).

Clinical guidelines contribute to an improvement in the quality of dental care for the general population by providing evidenced-based recommendations relevant to patients and clinicians, which later assist decision-making for treatment of specific diseases. The methodological characteristics of guideline development are defined in stages, with the first stage (S1) being guidelines that are based on 'recommendations by a selected group of experts'; the second stage (S2e and S2k) defining higher quality guidelines, which use formalized methodological techniques, and the third stage representing the highest quality and level of guidelines (S3) (Nothacker *et al.* 2014). S3 level guidelines are developed by a comprehensive formalized, systematic guideline development process.

Traditionally, the outcome of root canal treatment has been judged by clinician-reported measures using planar radiography, with less attention paid to patient-reported outcomes such as function, pain, tooth survival or quality of life (ESE 2006, Ng *et al.* 2007). As a result, there is a limited volume of evidence relating endodontic treatment outcomes to these patient-related factors in the literature (Bergenholtz & Kvist 2014). Additionally, there are a range of outcomes after endodontic treatment, with the response of the disease to therapy being most commonly measured by a combination of clinician (radiographic, clinical healing) and patient-reported measures (symptoms, function and adverse effects). Other relevant outcomes may examine the longevity of tooth retention after therapy analysing whether endodontic treatment increases the probability of tooth survival, an important outcome measure for patients, which will take many more years to adequately assess (Tickle *et al.* 2008, Ng *et al.* 2010). Other less explored outcomes after endodontic therapy relate to the feeling of patient well-being or Oral Health Related Quality of Life (OHRQoL) (Neelakantan *et al.* 2020). Finally, the impact of persistent or emerging disease, retreatment or further treatment on the cost-effectiveness of treatment should also be considered an outcome measure relevant to both clinicians and patients, respectively (Schwendicke & Göstemeyer 2016).

Recently several disciplines have developed core outcome sets (COS), which represent a standardized list of outcomes that are measured and reported in clinical studies within a specific discipline (Williamson *et al.* 2012). Currently, a COS is not available within Endodontics. The lack of such standardized outcomes is reflected in the conclusions and quality of several systematic reviews reporting outcomes after root canal treatment (Ng *et al.* 2007) and vital pulp treatment (VPT) (Cushley *et al.* 2020) and is acknowledged in the recent ESE position statement addressing the management of deep caries and the exposed pulp (ESE 2019).

In the absence of a COS for Endodontics, the aim of this project was to select relevant and appropriate outcome measures using a consensus process that are evidenced-based and can help to standardize the outputs of the commissioned systematic reviews within the ESE S3 level guidelines for pulpal and apical disease. Recommendations and agreement will also be reached regarding the minimum follow-up period for comparative studies to be included in the S3 level

guideline process specific to each outcome measure selected in the consensus process.

Methodology

A complete list of outcome measures related to pulpitis and apical periodontitis will be generated in this document. Thereafter, the selection of a subgroup of appropriate outcome measures will be carried out by anonymized online voting by the members of the ESE S3 level guidelines steering committee (10 individuals) and by all of the invited systematic reviewers (32 individuals) involved in the guideline project. The 42 members represent the guideline development group (GDG). A complete list of outcome measures for the treatment of pulpitis and apical periodontitis are summarized in Table 1, which will be used for online assessment and prioritization by all 42 members of the GDG.

ESE S3 Level Guideline Development Group

The ESE S3 level guideline process will consist of 42 global experts, who have previously agreed to take part in the guideline development process. All members will fulfil the following criteria for eligibility: (i) working within the discipline of Endodontics or a related dental science; (ii) have previously published in the area of evidenced-based dentistry; (iii) have a minimum of 5 years academic experience post-qualification (iv) have no conflict of interest in developing ESE S3 level clinical guidelines or that the (COI) is managed within the process. The group will be invited to participate in the identification and prioritization of outcome measures outlined in this document.

Initial steps

A literature search of secondary evidence (and selected primary evidence) as well as relevant ESE position statements and guideline documents (ESE 2006, ESE 2016, ESE 2019) identified a range of clinician and patient-reported outcome measures for the treatment of pulpitis and apical periodontitis (see section 'Clinical outcome measures to be ranked for importance'). The range of surrogate and real outcome measures used within these documents are summarized and separated into clinician and patient-reported outcomes for four working groups, related to the treatment of pulpitis as well as the non-surgical, surgical and regenerative treatment of apical periodontitis (Table 2). Also at this stage, the list of outcome measures was shared with the eight-working group leads and comments were received about the completeness of the list with additional outcome measures added if necessary. In the next stage, the group of outcome measures will be ranked in importance by all members of the GDG using an online link sent directly to the GDG.

Online survey process

An online survey will be conducted amongst the ESE S3 GDG to reach consensus on which measures should be included. The GDG members, independently and confidentially, will be asked to evaluate the items in the survey based on the suitability and importance of each outcome measure for inclusion in all four working groups (WG).

The online survey will be carried out using the 9-point Likert scale recommended for assessing the importance of outcomes for GRADE (Guyatt *et al.* 2011): 1–3 Limited importance; 4–6 important; 7–9 critical importance. This will be related primarily to the relevance of the outcome measure to the patient. For example – a clinician-reported outcome measure (such as radiographic healing of an apical radiolucency) may be rated as, 6 or 7 – importance, as it has been shown scientifically to reflect patient-reported outcome measures such as symptoms, pain and tooth function and survival.

The anonymous responses will be analysed and items with a score of 7–9 by more than 70% and items with a score of 1–3 by less than 30% of members will be included as outcome measures in the guidelines. Alternatively, items with a score of 1–3 by more than 70% and items with a score of 7–9 by less than 30% will be excluded. In round one, all members will be asked to add further outcome measures if they deem them important. If necessary, the process will be continued with further rounds until a final set of clear and suitable items are developed for the guidelines. A final list of outcome measures rated as critical for decision making (7–9 on Likert scale) by majority of survey participants will be included. At the end of the consensus process, members will receive a summary of the results and any revised items.

Clinical outcome measures to be ranked for importance

In clinical medicine, there are broadly two types of clinical end-points, patient or clinician-reported (see 'descriptions of outcome related terms') with the US Food Drug Administration (FDA) (https://www.fda.

Table 1 Proposed outcome measures for use in the development of European Society of Endodontology S3 level clinical practice guidelines

Treatment of pulpitis		Nonsurgical treatment of apical periodontitis		Surgical treatment of apical periodontitis		Regenerative treatment of apical periodontitis	
CROM	PROM	CROM	PROM	CROM	PROM	CROM	PROM
Tenderness to percussion	Pain	Tenderness to percussion	Pain	Tenderness to percussion	Pain	Tenderness to percussion	Pain
Tenderness to Palpation	Tenderness	Tenderness to Palpation	Tenderness	Tenderness to Palpation	Tenderness	Tenderness to Palpation	Tissue Tenderness
Sinus tract	Swelling	Sinus tract	Swelling	Sinus tract	Swelling	Sinus tract	Swelling
Response to pulp sensibility test (not full pulpotomy or pulpectomy)	Foul taste	Mobility	Tooth function (Fracture, restoration longevity)	Mobility	Tooth function (Fracture, restoration longevity)	Mobility	Tooth function (Fracture, restoration longevity)
Radiographic evidence of resorption	Tooth function	Periodontal pocket	Mobility	Periodontal pocket	Mobility	Swelling	Mobility
Radiographic evidence of emerging apical radiolucency	Tooth survival	Fracture/restoration integrity	Tooth survival	Satisfactory soft tissue healing	Tooth survival	Discolouration	Tooth survival
Radiographic evidence of hard tissue dentine bridge formation following pulp capping/ pulpotomy	QHRQoL	Bacterial reduction	QHRQoL	Radiographic evidence of apical lesion size (loose criteria)	QHRQoL	Response to pulp sensibility test (not full pulpotomy or pulpectomy)	QHRQoL
Radiographic evidence of continued root formation	Adverse effects (exacerbation, restoration integrity)	Intracanal or periapical biomarker expression	Adverse effects (exacerbation, restoration integrity)	Radiographic evidence of apical radiolucency and normal periodontal ligament space (strict criteria)	Adverse effects (exacerbation, discharge)	Radiographic evidence of external resorption	Possible adverse effects
Cost-effectiveness of procedure	Need for further intervention	Radiographic evidence of apical lesion size (loose criteria)	Need for further intervention	Cost-effectiveness of procedure	Post-surgical gingival aesthetics	Radiographic evidence of apical lesion size	Discolouration
	Need for medication (analgesics)	Radiographic evidence of apical radiolucency and normal periodontal ligament space (strict criteria)	Need for medication (analgesics, antibiotics)		Need for further intervention	Radiographic evidence of apical radiolucency and normal periodontal ligament space	Need for further intervention
	Need for sick leave	Radiographic signs of continuing resorption	Need for sick leave		Need for medication (analgesics, antibiotics)	Radiographic evidence of periodontal ligament on inner root canal wall	Need for medication (analgesics, antibiotics)

Table 1 Continued

Treatment of pulpitis		Nonsurgical treatment of apical periodontitis		Surgical treatment of apical periodontitis		Regenerative treatment of apical periodontitis	
CROM	PROM	CROM	PROM	CROM	PROM	CROM	PROM
	Cost-effectiveness of procedure	Cost-effectiveness of procedure	Cost-effectiveness of procedure		Need for sick leave Cost-effectiveness of procedure	Radiographic evidence of root thickness and length Cost-effectiveness of procedure	Need for sick leave Cost-effectiveness of procedure

CROM, Clinician-reported outcome measures; PCOM, Patient-reported outcome measures, QHRQoL, Oral Health-Related Quality of Life

gov/home) and the European Medicines Agency (EMA) (https://www.ema.europa.eu/en) both strongly requesting that data from patient-reported outcomes be considered in the assessment of clinical trial end-points. Patient-reported outcomes classically include pain, swelling, function, survival, but may also include OHRQoL and cost-effectiveness analyses and should measure how the treated tooth feels, functions, or survives from the patient's perspective. These outcomes can be objective, such as tooth survival, disease exacerbation, or an adverse clinical event, or subjective including symptom score (e.g. visual analogue scale) or validated OHRQoL. The development of clinical guidelines using GRADE also insists that the outcomes at least consider the patient and are patient-centred; however, clinician-reported end-points are the focus of the bulk of existing studies (Ng *et al.* 2007, 2010) and previous ESE guidelines (ESE 2006). Examples of clinician-reported outcomes are prevention of apical lesion development or resolution of an apical area on radiograph or alternatively response to pulp sensibility testing.

Endodontic research has also classically used surrogate measures to analyse outcome, such as negative bacterial culture (Sathorn *et al.* 2007), bacterial reduction assessed by molecular methods (Rôças & Siqueira 2011) or biomarker expression (Maia *et al.* 2020), however, such markers may or may not convincingly relate to resolution or exacerbation of the patient's disease. Validated surrogate end-points, which have been shown convincingly to relate the patients' disease, such as reduction of an apical radiolucency on radiograph, are considered more relevant (Schuster Bruce *et al.* 2019). These were traditionally categorized as being a 'loose' criteria for healing (Ng *et al.* 2007), with 'strict' criteria (real clinical end-points) requiring complete resolution of the apical radiolucency on planar film. Outcome has traditionally been assessed using 2-D planar radiography; however, with the advent of new imaging modalities such as CBCT possessing increased sensitivity (Kruse *et al.* 2019) compared with conventional radiography the likelihood of attaining complete healing has reduced particularly at early time-points (Patel *et al.* 2012). This may highlight that a surrogate measure of reduction of apical radiolucency (loose criteria) may be more relevant moving forward (Patel *et al.* 2020). It is important that outcome measures relate to resolution of disease rather than the technology (e.g. CBCT or planar film) as the bulk of available comparative studies investigating effectiveness will report using older techniques.

Table 2 Working groups involved in developing European Society of Endodontology S3 level clinical practice guidelines

Working group	Themes
1	The Treatment of Pulpitis
2	The Non-Surgical Treatment of Apical Periodontitis
3	The Surgical Treatment of Apical Periodontitis
4	The Regenerative Treatment of Apical Periodontitis

WG 1: Outcome measures for treatment for pulpitis and prevention of apical periodontitis

The assessment of VPT (and by extension pulpectomy) was described by the ESE (2006, 2019) as 'teeth should be carefully monitored by history and clinical examination at 6 months, supplemented by periapical radiograph at 1 year (Table 1). If symptoms persist or there is uncertainty regarding healing, the tooth should continue to be assessed at regular intervals. Cold and electric pulp sensibility testing should be carried out to monitor pulpal response, noting that teeth with full pulpotomy or after pulpectomy will be unresponsive'. The classic outcome measures relevant for VPT and pulpectomy are generally the prevention of apical periodontitis (as viewed by lack of emerging radiolucency on periapical radiograph) after at least one year. Therefore, for the S3 level guideline process a minimum follow-up of one year is likely to be acceptable to assess these features. Assessment of outcome measures related to the absence of pain, medication, swelling and other patient-related measures may be completed at shorter follow-up periods of one to two weeks; however, these should if possible be supplemented by analysis at longer-term time points. When considering the overall effectiveness other patient-related factors (e.g. OHR-QoL) and cost-effectiveness may be considered again ideally at short and long-term time points. Firm recommendations of the appropriate length of follow-up will be made by steering group discussion after the appropriate outcome measures are selected.

WG2: Outcome measures for non-surgical treatment of apical periodontitis

The outcome measures for nonsurgical root canal treatment and retreatment were described by the ESE (2006) as 'The following findings indicate a favourable outcome: absence of pain, swelling and other symptoms, no sinus tract, no loss of function and radiological evidence of a normal periodontal ligament space around the root' (Table 1). It was suggested that root canal treatment should be assessed at least after one year and subsequently as required (ESE 2006). Reduction of an apical radiolucency on radiograph was described by the ESE as uncertain healing, but has also been referred to as healing by loose criteria (Ng *et al.* 2007, Ng *et al.* 2008). For the purposes of systematic review, it is proposed that a minimum follow-up of one year is acceptable (Ørstavik 1996), with specific exceptions made for outcomes relating to studies addressing pain, swelling and other patient-related measures, as well as diagnostic accuracy studies.

WG3: Outcome measures for the surgical treatment of apical periodontitis

The outcome measures for healing following surgical endodontics (ESE 2006) were defined as 'absence of pain, swelling and other symptoms, satisfactory healing of soft tissue, no sinus tract, no loss of function and radiological evidence of repair of apical periodontitis including reformation of the periodontal ligament space' (Table 1). This represents a combination of patient and clinician-reported end-points, however, both are required as solely using a clinician-reported description of success as the percentage of apical radiolucency resolving in time, hold little or no significance to patients (e.g. 80% successful does not necessarily mean that the other 20% will give pain or the tooth will be lost).

As with nonsurgical root canal treatment, surgical endodontics should be assessed after one year and subsequently as required. Therefore, similarly to WG1 and 2, a minimum follow-up of one year seems reasonable for systematic analysis of the literature with selected exceptions.

WG4: Outcome measures for the regenerative treatment of apical periodontitis

The effectiveness of tissue regeneration in treatment of apical periodontitis will be assessed by outcome measures similar to the outcome measures used after apical surgery (see WG3; Table 1). The outcome of revitalization procedures, however, will be different to tissue regeneration during surgery and have been described in the ESE position statement (ESE 2016) as

a favourable outcome being 'No pain, no signs and symptoms of inflammation, healing of pre-existing bony periapical lesion, increase of root thickness and length, absence of (continued) external root resorption, positive response to sensibility testing, patient acceptance, no unacceptable colour changes; radiographic detection of a new PDL along the inner wall of the root canal'. It appears reasonable that the follow-up of revitalization procedures should be at a minimum of one year postoperatively, with longer follow-up times preferable. Selected outcome measures such as discoloration and pain may be followed up at shorter timepoints; however, specific recommendations regarding appropriate minimum follow-up for each outcome measure will be made at the end of the process.

Online – meeting to finalise the outcome measures and follow-up period

Following the online survey process, the list of outcome measures for the treatment of pulpitis, nonsurgical, surgical and regenerative treatment of apical periodontitis will be presented for further discussion and agreement with the 10 members of the steering group. The ESE S3 level project leader (HD) will share the final results of the online consensus process, agenda of the meeting and the Zoom meeting link to the steering group seven days before the meeting. A final decision on follow-up will also be made at this meeting. The project leader will chair the session. It is expected that a composite of patient and clinician-reported outcome measures will be finalized into the most important patient-centred outcomes during the meeting. Also, the minimum length of follow-up will be confirmed for the subsequent systematic reviews after the completion of the consensus process.

Future plans

The project lead (HD) will share the final list of outcome measures and follow-up period(s) with the GDG, which can then be used to develop the ESE S3 level clinical practice guidelines by systematic analysis of the literature and formal guideline process. The GDG anticipates it will be in a position to release the ESE S3 level clinical practice guideline in 2022/23.

Conclusions

In the systematic assessment of the effectiveness of an intervention in treating pulpitis or apical periodontitis, an appropriate combination of patient and clinician-reported outcome measures should be applied. The proposed consensus process outlined in this document will identify a set of patient-centred core outcome measures for subsequent systematic review. An appropriate follow-up should also be identified for each outcome measure, generally being as long as possible with a minimum of one year appropriate for assessment the effectiveness of treatments for pulpitis and apical periodontitis. There will be selected exceptions to this in terms of studies examining the relief of symptoms, swelling or investigating diagnostic accuracy, which may be concluded after shorter timeframes. A second document demonstrating the results of the online consensus exercise after the appropriate outcome measures are finalized will be published.

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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