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 consensus-based development

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Keywords: Guidelines, Clinical outcome measure, Clinician-reported outcomes, Delphi Effectiveness, Endodontic treatment, Follow-up, Patient-reported outcomes,

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ABSTRACT

Introduction: The European Society of Endodontology (ESE) is in process of developing S3-Level Clinical Practice Guidelines for the treatment of pulpal and apical disease. In order to support robust systematic literature review, appropriate outcome measures (OMs) with minimum follow-up time must first be identified. Hence, the current project aimed to identify the appropriate OMs with minimum/maximum follow-up time to assess the effectiveness of endodontic treatment for pulpitis and apical periodontitis for use in the development of ESE S3-level guidelines by consensus-based methodology.

Methodology: After a literature search, lists of relevant OMs were identified by the Guideline-Development-Group (GDG) for the treatment of pulpitis (working group [WG] 1), the non-surgical treatment of apical periodontitis (WG 2), the surgical treatment of apical periodontitis (WG 3) and the regenerative treatment of apical periodontitis (WG 4). OM relevant to each WG were ranked by the 43 members of the GDG in their importance to the patient using a 9-point Likert scale. Items with a score of 7-9 (critical-importance) by more than 70% and items with a score of 1-3 (limited-importance) by less than 30% of members were included whereas the items with a score of 1-3 by more than 70% and items with a score of 7-9 by less than 30% were excluded. Several online Delphi meetings established an edited list of only important OMs. The ranked OMs were discussed by the GDG and harmonised to produce 'most critical', 'critical' and 'important' measures. After establishing final ranked measures, the minimum and maximum length of follow-up related to each OM was decided. By the Guideline Steering Group.

Results: The Delphi survey was over two rounds. The patient-reported outcome-measure (PROM) 'tooth survival' was rated the 'most critical measure' in all 4 WGs, while other PROMs including 'pain', 'need for medication' were considered 'critical', alongside the clinician-reported outcome measures (CROM), 'radiographic assessment'. The PROMs 'The need for further intervention' and 'oral-health-related-quality-of-life' (OHRQoL) were included, but as 'important' not 'critical' measures. Differences occurred between WGs with 'vitality testing' critical in WG1 and 'increased length and width of the' 'critical' in WG4. A minimum of 1-year and maximum of as long as possible for all OM was deemed necessary, except 'pain', 'swelling', 'medication' and 'OHRQoL' which where shorter follow was accepted.

Conclusions: The GDG consensus process established the patient-reported 'tooth survival' as the 'most-critical' OM. The identified OMs and length of follow-up will be applied to all the commissioned systematic reviews that will inform the subsequent process when developing the ESE S3-Level Clinical Practice Guidelines.

INTRODUCTION

The European Society of Endodontology (ESE) is currently engaged in a process of developing new practice guidelines for the treatment of pulpitis and apical periodontitis for the benefit of both clinicians and patients (Duncan *et al.* 2021a). The process will create S3-level guidelines, which represent the highest quality of guideline and includes exhaustive systematic review of the literature and a formalised methodological guideline development procedure (Nothacker *et al*. 2014). As part of the ESE S3 process, it was previously agreed that in the absence of a recognised core outcome set (COS) for Endodontics (Williamson *et al*. 2012), a list of core outcomes for the treatment of pulpal and apical would need to be agreed by consensus as well as recommendations made regarding minimum follow-up times specific to each outcome measure (Duncan *et al*. 2021b). A protocol for this process was previously published (Duncan *et al*. 2021b), with the focus on patient-reported as well as clinician-reported outcome measures, which is at the core of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework (Guyatt *et al*. 2008, Sanz *et al.* 2020). The agreed outcome measures and associated 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 the previously published protocol a list of clinician and patient reported outcome measures were selected from the literature, prior to comment from the ten members of the ESE S3-Guideline Steering Group (Duncan *et al*. 2021b). The aim of the current study, was to identify and rank the most important clinician and patient outcome measures via several rounds of an online Delphi consensus process and followed by online meeting. After ranking the outcome measures the aim was to select the most critical outcome measure as well as other important and additional measures, before matching the outcome measures to acceptable minimum and maximum follow-up periods for outcome studies to be included in the review process.

METHODOLOGY

Protocol

An *a priori* protocol with detailed methodology of the current study has previously been published (Duncan *et al.* 2021b).

Initial steps

A comprehensive literature search was performed to identify potential clinician and patient-reported outcome measures, based on primary and secondary-evidence as well as relevant ESE position statements (ESE 2016, ESE 2019) and ESE-treatment guideline documents (ESE 2006). A set of surrogate and real outcome measures were identified and categorized into clinician and patient-reported outcomes for four thematic working groups (WG) (WG1: The treatment of pulpitis, WG2: The non-surgical treatment of apical periodontitis, WG3: The surgical treatment of apical periodontitis and WG4: The regenerative treatment of apical periodontitis). Afterwards, the list of outcome measures was shared with the eight WG leads (two leads for each group), in order to provide their feedback about the completeness of the list and if necessary add new outcome measures. Thereafter, the outcome measures were sent to the members of each WG within the Guideline Development Group (GDG) via a google link.

Formation of Guideline Development Group

The GDG were selected from suitable individuals across the globe to participate in the online Delphi process to identify and prioritise the outcome measures, which will be used by reviewers in systematic literature assessment during the development of the ESE S3 level clinical practice guidelines. The GDG includes ESE S3 level guidelines steering committee (10 members [including 2 project leads and 8 WG leads]) and by all the invited systematic reviewers (34 members) working on the 14 systematic reviews commissioned within the guideline project. The eligibility criteria to be member of the GDG were: i) working within the speciality of Endodontology or a related to dental science; ii) have published articles in the area of evidenced-based dentistry; iii) have a minimum of five-years academic experience post-qualification; and iv) have no conflict of interest in developing ESE S3-level clinical guidelines.

Online Delphi Survey

The project leader (HD) shared the information sheet with GDG which explains the process involved in Delphi process and google survey link. The GDG members, independently and confidentially, were asked to score the items within their own WG based on the suitability and importance of each outcome measure for inclusion in all four thematic WGs. The online survey was conducted 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. The 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 has been included whereas the items with a score of 1-3 by more than 70% and items with a score of 7-9 by less than 30% were excluded. Additionally, members have an option to add further outcome measures if they deem them important. The Delphi process continued with further rounds until a final set of final outcome measures were developed.

Online meeting

The list of outcome measures finalised in online Delphi process were presented in online meeting for further discussion and agreement with steering group (10 members). The ESE S3-level project leader (HD) shared the results of the online Delphi process, agenda of the meeting and the Zoom meeting link to the steering group seven days before the online meeting. The online meeting was conducted on 29th January 2021 using the Zoom online platform (San Jose, CA, USA), which was chaired by HD and the principle methodologist involved in the guideline process (Ina Kopp). At the end of online meeting the outcome measures and the minimum length of follow-up for four themes were confirmed.

RESULTS

Online Delphi survey

The online Delphi survey was conducted over two rounds. The response rate for four themes of round 1 and 2 were presented in Table 1. The results of round 1 and 2 are presented in Supplementary Table 1 and 2 respectively.

Online meeting

The attendees discussed the suitability of the outcome measures, adjustments to provide consistency between WGs to ensure homogeneity and the minimum length of follow-up for inclusion in the ESE S3 level guidelines project. The finalised outcome measures for four WGs are presented in Tables 2, 3, 4 and 5.

Outcome measures WG1 – The Treatment of Pulpitis (Table 2)

Main outcome(s): The most critical outcome was decided as the patient reported outcome measure 'tooth survival', whereas the other critical outcomes were 'pain, tenderness, swelling, need for medication (analgesics)', as well as the clinician reported outcome measure 'evidence of emerging apical radiolucency' and 'response to pulp sensibility test (not for full pulpotomy or pulpectomy)'.

Additional outcome(s): Other important outcomes were as follows 'tooth Function (fracture, restoration longevity), 'need for further intervention', 'adverse effects (including exacerbation, restoration integrity, allergy)', 'oral health-related quality of life (OHRQoL)', 'presence of sinus tract' and 'radiological evidence of continued root formation'.

Duration of data collection: A minimum of 1 year and maximum of as long as possible for all outcome measures, except 'pain, tenderness, swelling, need for medication (analgesics)', which will be a minimum of 7 days and maximum of 3 months and OHRQoL which is a minimum of 6 months and a maximum of as long as possible.

Outcome measures WG2- The Non-Surgical Treatment of Apical Periodontitis (Table 3)

Main outcome(s): The most critical outcome was 'tooth survival' whereas, other critical outcomes are 'pain, tenderness, swelling, need for medication (analgesics, antibiotics)', 'radiographic evidence of reduction of apical lesion size (loose criteria)' and 'radiographic evidence of normal periodontal ligament space (strict criteria)'.

Additional outcome(s): Important outcomes were as follows 'tooth function (fracture, restoration longevity), 'need for further intervention', 'adverse effects (including

exacerbation, restoration integrity, allergy)', 'oral health-related quality of life (OHRQoL)' and 'presence of sinus tract'.

Duration of data collection: A minimum of 1 year and maximum of as long as possible for all outcome measures, except 'pain, tenderness, swelling, need for medication (analgesics)', which is a minimum of 7 days and maximum of 3 months and OHRQoL, which is a minimum of 6 months and a maximum of as long as possible.

Outcome measures WG3 - The Surgical Treatment of Apical Periodontitis (Table 4)

Main outcome(s): The most critical outcome was considered 'tooth survival', whereas other critical outcomes are 'pain, tenderness, swelling, need for medication (analgesics, antibiotics)', 'presence of sinus tract, satisfactory soft tissue healing', 'radiographic evidence of reduction of apical lesion size (loose criteria)' and 'radiographic evidence of normal periodontal ligament space (strict criteria)'.

Additional outcome(s): Important outcomes were 'tooth function (fracture, restoration longevity), 'need for further intervention', 'adverse effects (including exacerbation, restoration integrity, allergy)', 'oral health-related quality of life (OHRQoL)' and 'mobility'.

Duration of data collection: A minimum of 1 year and maximum of as long as possible for all outcome measures, except 'pain, tenderness, swelling, need for medication (analgesics)', which is a minimum of 14 days and maximum of 3 months and OHRQoL, which is minimum of 6 months and a maximum of as long as possible.

Outcome measures WG4 - The Regenerative Treatment of Apical Periodontitis (Table 5)

Main outcome(s): The most critical outcome was 'tooth survival', whereas the other critical outcomes are 'pain, tenderness, swelling, need for medication (analgesics, antibiotics)', 'radiographic evidence of reduction of apical lesion size (loose criteria)', 'radiographic evidence of normal periodontal ligament space (strict criteria)' and 'radiographic evidence of increased root thickness and length'.

Additional outcome(s): Important outcomes were considered as 'tooth function (fracture, restoration longevity), 'need for further intervention', 'adverse effects (including exacerbation, restoration integrity, allergy, discolouration)', oral health-related quality of life (OHRQoL), 'presence of sinus tract' and 'response to sensibility testing'.

Duration of data collection: Defined as a minimum of 1 year and maximum of as long as possible for all outcome measures, except 'pain, tenderness, swelling, need for medication (analgesics)', which is a minimum of 7 days and maximum of 3 months and OHRQoL which is minimum of 6 months and a maximum of as long as possible.

FUTURE PLANS

In the next phase of the ESE S3-level guideline process the consensus outcome measures and duration of data assessment detailed in this document will be used to form a specific PICOTS (P=population, I = Intervention, C = Comparison, O = Outcome(s), T = Duration of data collection, S = Included study types) questions for each of the 14 commissioned systematic reviews, which will thereafter be agreed upon by the S3 Steering Group. After minor modification and harmonisation, the final PICOTS will be returned to the reviewers and a review protocol written. The protocol will be checked by the ESE S3 -level clinical practice guideline lead (HD) and the respective WG leads, before submission to PROSPERO for *a priori* registration, before starting the review proper.

After completion of the systematic review, they will first be submitted to the Steering Group to check that the PICOTS are adequately covered and the agreed tools have been used, before an assessment of the quality of the systemic review using AMSTAR 2 (https://amstar.ca/Amstar-2.php). The paper may be sent back for amendment at this stage, prior to formal submission to the *International Endodontic Journal* and a process of rigorous independent peer review. After the completion of the review process the resulting evidence will be compiled using GRADE and initial evidenced-based clinical recommendations prepared, prior to circulation for comment by the Steering Group during a series of moderated Zoom sessions. At this stage conflict of interest will be analysed and discussed, including issues such as reviewer's abstention from voting. The Steering Group will discuss the clinical recommendations and reach informal agreement, before organising a formal moderated consensus conference in order to agree the

recommendations. Finally, after guideline text agreement, the guidelines will be approved at the ESE executive board and thereafter disseminated by publication in the *International Endodontic Journal,* on the ESE website (https://www.e-s-e.eu/) and electronically via local societies and other stakeholders.

CONCLUSION

The identified patient and clinician OMs as well as length of follow-up will be used in all commissioned systematic reviews that will inform the subsequent process when developing the ESE S3 -Level Clinical Practice Guidelines. In the future, while planning and conducting clinical trials, researchers can employ the identified patient and clinician-reported outcomes in combination with long follow-up times, which will ultimately standardise the outcomes of trials and improve patient care.

Table1: Round 1 and 2 response rate for four themes

WGs	Themes	Round 1 - Response rate (%)	Round 2 - Response rate (%)
1	The treatment of pulpitis	86	100
2	The non-surgical treatment of apical periodontitis	85	100
3	The surgical treatment of apical periodontitis	100	75
4	The regenerative treatment of apical periodontitis	100	100

Table 2: Outcome measures for the working group 1: Treatment of pulpitis

Specific outcome measure	**Ranked Importance of Outcome Measure from Likert scale**	**Patient (PROM) or Clinician-Reported (CROM) outcome**	**Minimum and Maximum Follow-up Period**	**Tools necessary to measure**
Tooth Survival	Most Critical	PROM	Minimum: 1 year Maximum: long as possible	Clinical history examination
Pain, tenderness, swelling, need for medication (analgesics)	Critical	PROM	Minimum: 7 days Maximum: 3 months	Clinical examination and pain scale
Evidence of emerging apical radiolucency	Critical	CROM	Minimum: 1 year Maximum: long as possible	Intraoral periapical radiograph, limited FOV CBCT scan
Response to pulp sensibility test (not full pulpotomy or pulpectomy)	Critical	CROM	Minimum: 1 year Maximum: long as possible	Thermal and /or electric pulp test
Tooth Function (fracture, restoration longevity)	Important	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
Need for further intervention	Important	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
Adverse effects (exacerbation, restoration integrity, allergy)	Important	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
OHRQoL	Important	PROM	Minimum: 6 months Maximum: long as possible	Validated OHRQoL questionnaire
Sinus tract	Important	CROM	Minimum: 1 year Maximum: long as possible	Examination
Radiological Evidence of continued root formation	Important	CROM	Minimum: 1 year Maximum: long as possible	Intraoral periapical radiograph, limited FOV CBCT scan

Table 3: Outcome measures for the working group 2: Nonsurgical treatment of apical periodontitis

Specific outcome measure	**Ranked Importance of Outcome Measure from Likert scale**	**Patient (PROM) or Clinician-Reported (CROM) outcome**	**Minimum and Maximum Follow-up Period**	**Tools used to measure**
Tooth Survival	Most Critical	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
Pain, tenderness, swelling, need for medication (analgesics, antibiotics)	Critical	PROM/CROM	Minimum: 7 days Maximum: 3 months	Clinical examination and pain scale
Radiographic evidence of reduction of apical lesion size (loose criteria)	Critical	CROM	Minimum: 1 year Maximum: long as possible	Intraoral periapical radiograph, limited FOV CBCT scan
Radiographic evidence of normal periodontal ligament space (strict criteria)	Critical	CROM	Minimum: 1 year Maximum: long as possible	Intraoral periapical radiograph, limited FOV CBCT scan
Tooth Function (fracture, restoration longevity)	Important	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
Need for further intervention	Important	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
Adverse effects (exacerbation, restoration integrity, allergy)	Important	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
QHRQoL	Important	PROM	Minimum: 6 months Maximum: long as possible	Validated OHRQoL questionnaire
Sinus tract	Important	CROM	Minimum: 1 year Maximum: long as possible	Examination

Table 4: Outcome measures for the working group 3: Surgical treatment of apical periodontitis

Specific outcome measure	Ranked Importance of Outcome Measure from Likert scale	Patient (PROM) or Clinician-Reported (CROM) outcome	Minimum and Maximum Follow-up Period	Tools necessary to measure
Tooth Survival	Most Critical	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
Pain, tenderness, need for medication (analgesics, antibiotics)	Critical	PROM/CROM	Minimum: 14 days Maximum: 3 months	Clinical examination and pain scale
Sinus tract, satisfactory soft tissue healing	Critical	CROM	Minimum: 1 year Maximum: long as possible	Examination
Radiographic evidence of reduction of apical lesion size (loose criteria)	Critical	CROM	Minimum: 1 year Maximum: long as possible	Intraoral periapical radiograph, limited FOV CBCT scan
Radiographic evidence of normal periodontal ligament space (strict criteria)	Critical	CROM	Minimum: 1 year Maximum: long as possible	Intraoral periapical radiograph, limited FOV CBCT scan
Tooth Function (fracture, restoration longevity)	Important	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
Need for further intervention	Important	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
Adverse effects (exacerbation discharge, allergy)	Important	PROM	Minimum: 1 year Maximum: long as possible	Clinical History
QHRQoL	Important	PROM	Minimum: 6 months Maximum: long as possible	Validated OHRQoL questionnaire
Mobility	Important	PROM/CROM	Minimum: 1 year Maximum: long as possible	Examination

Table 5: Outcome measures for the working group 4: Regenerative treatment of apical periodontitis

Specific outcome measure	**Ranked Importance of Outcome Measure from Likert scale**	**Patient (PROM) or Clinician-Reported (CROM) outcome**	**Minimum and Maximum Follow-up Period**	**Tools necessary to measure**
Tooth Survival	Most Critical	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
Pain, tenderness, swelling, need for medication	Critical	PROM/CROM	Minimum: 7 days Maximum: 3 months	Clinical examination and pain scale
Radiographic evidence of reduction of apical lesion size (loose criteria)	Critical	CROM	Minimum: 1 year Maximum: long as possible	Intraoral periapical radiograph, limited FOV CBCT scan
Radiographic evidence of normal periodontal ligament space (strict criteria)	Critical	CROM	Minimum: 1 year Maximum: long as possible	Intraoral periapical radiograph, limited FOV CBCT scan
Radiographic evidence of increased root thickness and length	Critical	CROM	Minimum: 1 year Maximum: long as possible	Intraoral periapical radiograph, limited FOV CBCT scan, validated quantitative measurement software
Tooth Function (fracture, restoration longevity)	Important	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
Adverse effects (exacerbation, restoration integrity, discolouration)	Important	PROM/CROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
Need for further intervention	Important	PROM	Minimum: 1 year Maximum: long as possible	Clinical history and examination
QHRQoL	Important	PROM	Minimum: 6 months Maximum: long as possible	Validated OHRQoL questionnaire
Sinus tract	Important	CROM	Minimum: 1 year Maximum: long as possible	Examination
Response to pulp sensibility test	Important	CROM	Minimum: 1 year Maximum: long as possible	Thermal and /or electric pulp test

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Supplementary Table 1 - Results of Round 1 Delphi survey

No	Outcomes - Treatment of Pulpitis	Inclusion status	Outcomes - Non-Surgical Treatment of Apical Periodontitis	Inclusion status	Outcomes - Surgical Treatment of Apical Periodontitis	Inclusion status	Outcomes - Regenerative Treatment of Apical Periodontitis	Inclusion status
1	Tenderness to percussion	Round 2	Tenderness to percussion	Included	Tenderness to percussion	Included	Tenderness to percussion	Included
2	Tenderness to Palpation	Round 2	Tenderness to Palpation	Round 2	Tenderness to Palpation	Round 2	Tenderness to Palpation	Round 2
3	Sinus tract	Included	Sinus tract	Included	Sinus tract	Included	Sinus tract	Included
4	Response to pulp sensibility test (not full pulpotomy or pulpectomy)	Included	Mobility	Round 2	Mobility	Included	Mobility	Round 2
5	Radiographic evidence of resorption	Round 2	Periodontal pocket	Round 2	Periodontal pocket	Round 2	Swelling	Included
6	Radiographic evidence of emerging apical radiolucency	Included	Fracture/restoration integrity	Round 2	Satisfactory soft tissue healing	Round 2	Discolouration	Round 2
7	Radiographic evidence of hard tissue dentine bridge formation following pulp capping/pulpotomy	Round 2	Bacterial reduction	Round 2	Radiographic evidence of apical lesion size (loose criteria)	Included	Response to pulp sensibility test (not full pulpotomy or pulpectomy)	Included
8	Radiographic evidence of continued root formation	Include d	Intracanal or periapical biomarker expression	Round 2	Radiographic evidence of apical radiolucency and normal periodontal ligament space (strict criteria)	Included	Radiographic evidence of external resorption	Included
9	Cost-effectiveness of procedure	Round 2	Radiographic evidence of apical lesion size (loose criteria)	Included	Cost-effectiveness of procedure	Round 2	Radiographic evidence of apical lesion size	Included
10	Pain	Included	Radiographic evidence of apical radiolucency and normal periodontal ligament space (strict criteria)	Included	Pain	Included	Radiographic evidence of apical radiolucency and normal periodontal ligament space	Included

11	Tenderness	Included	Radiographic signs of continuing resorption	Round 2	Tenderness	Included	Radiographic evidence of periodontal ligament on inner root canal wall	Round 2
12	Swelling	Included	Cost-effectiveness of procedure	Round 2	Swelling	Round 2	Radiographic evidence of root thickness and length	Included
13	Foul taste	Excluded	Pain	Included	Tooth function (Fracture, restoration longevity)	Included	Cost-effectiveness of procedure	Round 2
14	Tooth function	Included	Tenderness	Included	Mobility	Round 2	Pain	Included
15	Tooth survival	Included	Swelling	Included	Tooth survival	Included	Tissue Tenderness	Round 2
16	QHRQoL	Included	Tooth function (Fracture, restoration longevity)	Included	QHRQoL	Included	Swelling	Included
17	Adverse effects (exacerbation, restoration integrity)	Round 2	Mobility	Round 2	Adverse effects (exacerbation, discharge)	Included	Tooth function (Fracture, restoration longevity)	Included
18	Need for further intervention	Included	Tooth survival	Included	Post-surgical gingival aesthetics	Round 2	Mobility	Round 2
19	Need for medication (analgesics)	Included	QHRQoL	Included	Need for further intervention	Included	Tooth survival	Included
20	Need for sick leave	Excluded	Adverse effects (exacerbation, restoration integrity)	Round 2	Need for medication (analgesics, antibiotics)	Round 2	QHRQoL	Included
21	Cost-effectiveness of procedure	Round 2	Need for further intervention	Round 2	Need for sick leave	Round 2	Possible adverse effects	
22			Need for medication (analgesics, antibiotics)	Included	Cost-effectiveness of procedure	Round 2	Discolouration	Included
23			Need for sick leave	Round 2			Need for further intervention	Included
24			Cost-effectiveness of procedure	Included			Need for medication (analgesics, antibiotics)	Round 2
25							Need for sick leave	Round 2
26							Cost-effectiveness of procedure	Round 2

Supplementary Table 2 - Results of Round 2 Delphi survey

No	Outcomes - Treatment of Pulpitis	Inclusion status	Outcomes - Non-Surgical Treatment of Apical Periodontitis	Inclusion status	Outcomes - Surgical Treatment of Apical Periodontitis	Inclusion status	Outcomes - Regenerative Treatment of Apical Periodontitis	Inclusion status
1	Tenderness to percussion	Need to Confirm in meeting	Tenderness to Palpation	Need to Confirm in meeting	Tenderness to Palpation	Need to Confirm in meeting	Tenderness to Palpation	Need to Confirm in meeting
2	Tenderness to Palpation	Need to Confirm in meeting	Mobility	Need to Confirm in meeting	Periodontal pocket	Need to Confirm in meeting	Mobility	Need to Confirm in meeting
3	Radiographic evidence of resorption	Need to Confirm in meeting	Periodontal pocket	Need to Confirm in meeting	Satisfactory soft tissue healing	Included	Discolouration	Included
4	Radiographic evidence of hard tissue dentine bridge formation following pulp capping/pulpotomy	Need to Confirm in meeting	Fracture/restoration integrity	Need to Confirm in meeting	Cost-effectiveness of procedure	Need to Confirm in meeting	Radiographic evidence of periodontal ligament on inner root canal wall	Included
5	Cost-effectiveness of procedure	Need to Confirm in meeting	Bacterial reduction	Need to Confirm in meeting	Swelling	Need to Confirm in meeting	Cost-effectiveness of procedure	Included
6	Adverse effects (exacerbation, restoration integrity)	Need to Confirm in meeting	Intracanal or periapical biomarker expression	Need to Confirm in meeting	Mobility	Need to Confirm in meeting	Tissue Tenderness	Need to Confirm in meeting
7	Cost-effectiveness of procedure	Need to Confirm in meeting	Radiographic signs of continuing resorption	Need to Confirm in meeting	Post-surgical gingival aesthetics	Need to Confirm in meeting	Mobility	Need to Confirm in meeting
8			Cost-effectiveness of procedure	Need to Confirm in meeting	Need for medication (analgesics, antibiotics)	Need to Confirm in meeting	Need for medication (analgesics, antibiotics)	Need to Confirm

								in meeting
9			Mobility	Need to Confirm in meeting	Need for sick leave	Need to Confirm in meeting	Need for sick leave	Included
10			Adverse effects (exacerbation, restoration integrity)	Need to Confirm in meeting	Cost-effectiveness of procedure	Need to Confirm in meeting	Cost-effectiveness of procedure	Included
11			Need for further intervention	Need to Confirm in meeting				
12			Need for sick leave	Need to Confirm in meeting				