Received: 28 April 2022 | Accepted: 26 August 2022

DOI: 10.1111/iej.13829

INTERNATIONAL ENDODONTIC JOURNAL | WILEY

REVIEW ARTICLE

Outcomes reporting in systematic reviews on revitalization: A scoping review for the development of a core outcome set

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Abstract

Background: Revitalization is a type of regenerative endodontic treatment (RET) that offers the exciting prospect of revitalizing damaged tissue, therefore improving outcomes for non-vital immature teeth. To evaluate its potential, there needs to be consistency in outcome reporting of clinical studies investigating revitalization to allow for evidence synthesis and inform clinical decision making.

Objectives: The aim of this scoping review was to identify outcomes that are reported in systematic reviews on revitalization including how and when these outcomes are measured. Additionally, evidence of selective reporting bias in the reviews was assessed.

Methods: A comprehensive electronic search of healthcare databases and grey literature was conducted to identify systematic reviews published in the English language reporting outcomes of revitalization in permanent immature teeth. There was no restriction on the date of publication. Outcome data was extracted by four reviewers independently and mapped with a healthcare taxonomy into five core areas: survival, clinical/physiological changes, life impact, resource use and adverse events. Selective reporting bias and how it was measured was assessed independently by two reviewers.

Results: Twenty-six systematic reviews were included in this scoping review. There was lack of standardization in reporting and significant heterogeneity across reviews in outcome endpoints. The outcomes reported could be aligned within the five core areas of the taxonomy including tooth survival which was reported in nine reviews. Patient-reported outcomes were generally limited and no review reported on Oral Health Related Quality of Life. Many of the reviews reporting on randomized control trials were at low risk of selective reporting bias whilst other study designs were at higher risk.

Discussion: Consistency in outcome reporting is necessary to realize the benefits of old but particularly novel therapies. Data from this review confirmed heterogeneity in reporting outcomes of revitalization and the need for development of a core outcome set (COS).

Conclusions: Several important outcomes including survival, root development, tooth discolouration and periapical healing have been identified in this review which could inform the development of a COS in this area.

Registration: Core Outcome Measures in Effectiveness Trials (COMET) database (registration no. 1879).

KEYWORDS

endodontics, immature teeth, outcomes, regenerative endodontic, revitalization

INTRODUCTION

Immature teeth with necrotic pulps have traditionally been managed with calcium hydroxide apexification in which the material is used, over several visits, to induce the formation of a calcific barrier enabling obturation and completion of root canal treatment (Cvek, 1992; Frank, 1966). This approach has been criticized due to the high-level of patient compliance required and the increased risk of tooth fracture observed in the long-term follow up (Andreasen et al., 2006; Cvek, 1992). As a result, management shifted from the apexification technique to the one of two-visit placement of a mechanical barrier/plug using a biocompatible material such as Mineral Trioxide Aggregate (MTA) or other hydraulic calcium silicate material (Simon et al., 2007; Witherspoon, 2008). Many studies have reported high success rates for the apical barrier technique, (Krastl et al., 2021), however, as this approach does not lead to further root development, it is debatable whether this approach completely reduces fracture risk in immature teeth (Bonte et al., 2015).

A biological approach that allows for continued root development in terms of both root length and width could improve long-term success and survival of these teeth. In this regard, revitalization as part of a group of regenerative endodontic treatments (RET) has emerged as biologically based procedures designed to replace damaged structures such as dentine, root structures, and cells of the pulp-dentin complex (Murray et al., 2007). In essence, RETs include cell-homing techniques such as revitalization, which have been developed clinically (Galler et al., 2016) and the largely experimental cell-based techniques in which a stem cell population is placed into the empty root canal accompanied by morphogens/growth factors and a scaffold as part of a tissue engineering design (Brizuela et al., 2020). The cell homing concept is based on an influx of stem cells from the apical papilla into the root canal, however, it remains unlikely that this results in true pulpal regeneration (Jeeruphan et al., 2012) being more likely reparative in nature (Meschi et al., 2016). Following the publication of the first revitalization procedures (initially called revascularization) (Banchs & Trope, 2004; Iwaya et al., 2001), an increasing number of case reports, case-series, retrospective clinical studies, clinical trials and systematic reviews evaluating the outcome of these treatments have been published. However, a lack of consensus in selecting the outcomes to report and how and when the outcome should be measured reflects the current controversy as to how effective these treatments are over existing therapies. For instance, earlier studies evaluating the evidence for root development have used different outcomes including complete root formation (Kontakiotis et al., 2014), apical closure (Rossi-Fedele et al., 2019) and increased root length (Kahler & Rossi-Fedele, 2016). As for other endodontic treatment, the importance of patient-reported outcomes is not clear for revitalization procedures (Duncan et al., 2021a). This lack of standardization in outcome reporting makes it difficult for evidence synthesis and the development of clinical guidelines (Saldanha et al., 2020). Therefore, an urgent need exists to develop a minimum core outcome set (COS) for revitalization procedures which would be used in all future studies of these treatments and other RETs when they are developed for clinical use.

A COS is defined as an agreed, standardized group of outcomes that must be evaluated and reported in all clinical trials and clinical outcome studies in a particular discipline (Williamson et al., 2012). Adopting a COS strategy in clinical research is critical for assuring study validity, ensuring that essential outcomes are measured, and improving evidence synthesis by minimizing heterogeneity and outcome-reporting bias (Clarke, 2008). The COS development process starts with a systematic review of the literature, followed by a structured consensus process to identify the most relevant outcomes and how and when these outcomes should be measured (Kirkham et al., 2016, 2017). Using this methodology, a project for establishing COS for different endodontic treatment modalities is currently ongoing (El Karim et al., 2021). The initial phase of this process involves a thorough scoping review of the literature to determine existing knowledge on outcomes reported for all endodontic treatment including vital pulp treatment (VPT), surgical and non-surgical endodontics and revitalization procedures. The aim of the systematic review process is to identify outcomes reported in all clinical studies in humans in order to generate list of outcomes that are to be categorized according to health intervention taxonomy (Dodd et al., 2018) for validation via a subsequent Delphi process and consensus meeting. The process has been completed for VPT (Cushley et al., 2022), surgical endodontics (Shah et al., 2022) and non-surgical root

canal treatment (Kirkevang et al., 2022). A recent expert review provided critical analysis of research methods on revitalization procedure (Galler et al., 2022) and covered a range of aspects including subject recruitment, study design, diagnosis, treatment parameters and outcomes. Although the review provided useful insights into the outcomes of revitalization procedure, it was not planned as part of the development of a validated COS project. Therefore to complete the process for COSET in regenerative aspects of endodontics a scoping review was conducted with the aims to: (1) Identify what outcome domains are assessed in published systematic reviews evaluating revitalization (2) Report on how the outcomes are measured and the follow up time for reporting these outcomes and (3) Assess any selective reporting bias in the included reviews.

METHODS

This scoping review is reported in line with the PRISMA-ScR guidance (Tricco et al., 2018). The protocol for this review and the COSET project has previously been published (El Karim et al., 2021). The project is registered in the Core Outcome Measures in Effectiveness Trials (COMET) database (registration No. 1879).

Inclusion criteria

Humans undergoing clinically established revitalization procedures in an immature permanent tooth.

No restriction on follow-up period.
Systematic reviews reporting clinical and or radiographic outcomes or other clinician or patient-reported outcomes of revitalization procedures.
Systematic reviews published in the English language.

Information sources

A comprehensive structured literature search was performed using PubMed/MEDLINE, Ovid EMBASE, Scopus, Cochrane Database of Systematic Reviews, Web of Science databases and Open Grey to identify systematic reviews published in English covering the outcomes of revitalization procedures. No year of publication restriction was applied.

Search process

A detailed search strategy was developed in MEDLINE and adapted for other bibliographic databases (Table S1). An electronic library of all references was uploaded to EndNote 20 and duplicates were removed. Four reviewers working in pairs (SC, MH, CMcL, ML) independently assessed the title and abstracts of all systematic reviews identified. Any disagreement about inclusion of article was resolved by arbitration from two further reviewers (HD, IEK) if required.

Outcome measures

The main outcomes of this scoping review were: (1) Identification and list all outcomes reported in the reviews (clinician and patient-reported outcomes), (2) Methods used to measure these outcomes and (3) Duration of follow up of the reported outcomes.

Date extraction

Data extraction from the full text of eligible reviews was completed independently by four reviewers (SC, MH, ML, CMcL). Extracted data included all clinician and patient-reported outcomes. Data were also collected on the range of instruments for example, (planar radiographs, Cone Beam Computed Tomography [CBCT] and pulp sensibility testers) used for outcome measurement and the duration of the follow-up. In addition, demographic, and other data to facilitate description of the included reviews were collected including, country of study and the method of data synthesis. Data on selective outcome reporting and how it was measured was recorded when available.

Categorization into domains

Outcomes data collected were aligned with a healthcare taxonomy (Dodd et al., 2018). The taxonomy involves grouping outcomes into five core areas: survival, clinical/physiological changes, life impact, resource use and adverse events. The outcomes in each domain were collated and presented in tabular format.

RESULTS

Literature search

A total of 126 records were identified from the electronic search strategy. Seventeen duplicate records were removed leaving 109 for full text screening of which 77 were excluded for reasons summarized in Figure 1. The

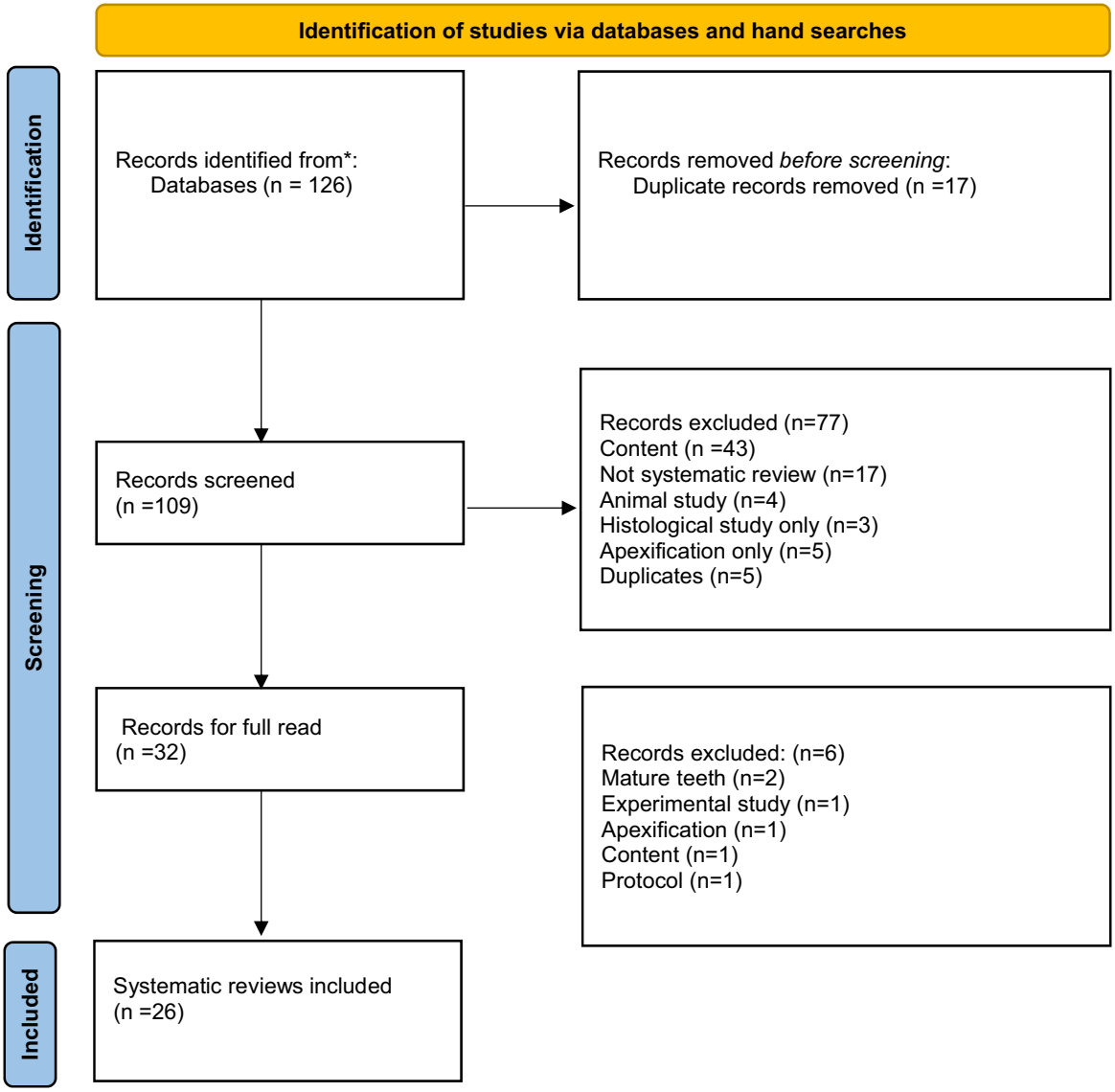

FIGURE 1 PRISMA diagram illustrating studies selection process.

remaining 32 articles were assessed against the inclusion criteria and the six further records not meeting inclusion criteria were excluded (Table S2). Finally, 26 systematic reviews were included in this scoping review.

Characteristics of included reviews

The characteristics of the included systematic reviews reporting are summarized in Table 1. Reviews were reported from different countries across Europe, Asia, Australia, North and South America. Many of the reviews ($n = 13$) were published during or post 2020. All included reviews reported on revitalization of immature permanent teeth. For any review which included studies of both mature and immature teeth ($n = 3$), data was extracted only from those studies where there was a high degree of certainty that the tooth was immature based on the participant's age.

The full range of study types was observed with a total high number of case reports and case series ($n = 334$) included in comparison to randomized controlled trials ($n = 124$) across the 26 reviews. Meta-analysis was conducted in 11 of the included reviews.

Synthesis of results

Outcome domains for revitalization were shown in Table 2 and described in detail below:

Survival

In the survival core area, the outcome domain was tooth survival which was reported in nine of the 26 reviews. Survival was defined as tooth present at the endpoint of follow-up.

TABLE 1 Characteristics of included systematic reviews

Author	Year published	Country	Journal name	Outcomes reported	Number and type of study in review						Meta-analysis performed Y/N	Follow-up min/max
					No.	RCT	CCT	Pro	Ret	CSR		
Alghamdi & Alsulaimani, 2021	2021	Saudi Arabia	*Dental and Medical Problems*	Success of RET[a].	18[a]	3	—	3	5	7	N	2 months–8 years
Alghamdi & Alqurashi, 2020	2020	Saudi Arabia	*The Scientific World Journal*	Effectiveness of RET in immature necrotic permanent teeth.	46	3	2	18	3	20	N	2 months–4 years
Almutairi et al., 2022	2022	Saudi Arabia	*Clinical Oral Investigations*	Prevalence of intra-canal calcification following RET and association with intracanal medicaments.	8	3	—	2	3	—	Y	12–34.3 months
Antunes et al., 2016	2016	Brazil	*Acta Odontologica Scandinavica*	Efficacy of pulp revascularization in root formation in necrotic immature permanent teeth and level of evidence supporting treatment.	11	2	—	1	1	7	N	6 months-5 years
Báez et al., 2022	2022	Argentina	*Journal of Oral Biology and Craniofacial Research*	Predictability of RET with antibiotic pastes and calcium hydroxide in terms of root lengthening, root dentine wall thickening, apical closure, periapical repair.	32	12	—	6	5	9	Y	1–72 months
Castro-Gutierrez et al., 2021	2021	Mexico	*Applied Sciences*	Effectiveness (measured as increase of root length, changes of apical diameter or clinical success) of regenerative endodontic procedures with scaffolds compared to apexification or procedures using only a blood clot.	10	10	—	—	—	—	Y	1–29 months
Chisini et al., 2018	2018	Brazil	*Societa Italianan di Endodonzia*	Clinical success of therapies (revascularization vs. apexification with MTA plug) deposition and thickening of dentinal walls and continuation of root development.	5	1	—	1	3	—	N	14–49 months
do Couto et al., 2019	2019	Brazil	*Paediatric Dentistry*	Clinical and radiographic results of pulp revascularization employing triple antibiotic paste in teeth with incomplete root formation.	8	8	—	—	—	—	N	1–19 months
Duggal et al., 2017	2017	UK	*European Archives of Paediatric Dentistry*	Relative effectiveness of apexification, apical plug technique and RET for treating traumatized non-vital immature permanent anterior teeth and any intermediate/long-term side-effects/limitations of materials or techniques.	8	8	—	—	—	—	N	0–>36 months
Iqbal et al., 2021[f]	2021	Pakistan	*Journal of Pakistan Medical Association*	Pulp tissue engineering cell and autograft and adjuvant alloplastic material to bridge defects and the protocols relative to presence or absence of apex closure, age of patient and technique employed.	14	6	—	2	—	6	N	3 months–4 years
Kahler & Rossi-Fedele, 2016[f]	2016	Australia	*Journal of Endodontics*	Tooth discolouration post regenerative endodontic procedures and association with specific materials.	80	—	—	—	2	78	N	6 months–5 years

(Continues)

TABLE 1 (Continued)

Author	Year published	Country	Journal name	Outcomes reported	Number and type of study in review						Meta-analysis performed Y/N	Follow-up min/max
					No.	RCT	CCT	Pro	Ret	CSR		
Kahler et al., 2017	2017	Australia	*Journal of Endodontics*	Root maturation of immature teeth with pulp necrosis after regenerative endodontic procedures. Comparison of clinician and patient-based criteria following apexification, apical barrier techniques, and regenerative endodontic procedures.	6	1	—	2	3	—	N	6–>36 months
Kharchi et al., 2020	2020	UK	*Primary Dental Journal*	Clinical and radiographic outcomes of regenerative endodontic procedures involving any disinfectant irrigant with a non-antibiotic intra-canal medicament.	5	1	—	—	4	—	N	9–108 months
Koc & Del Fabbro, 2020	2020	Turkey	*Journal of Evidence-Based Dental Practice*	Success of RET for necrotic pulps based on aetiology of pulpal necrosis[c].	18	8	—	—	5	—	Y	8–46 months
Kontakiotis et al., 2014	2014	Greece	*Journal of Endodontics*	Assign levels of evidence for the outcome of regenerative endodontic therapy, clinical signs, symptoms, apical radiolucency, root length, root wall thickness, apical closure for clinical and radiographic outcomes of regenerative endodontic therapy.	51	—	—	—	2	49	N	6–108 months
Lolato et al., 2016	2016	Italy	*Platelets*	Do immature necrotic teeth treated with platelet concentrates achieve radicular development, remaining asymptomatic with positive response to cold and electric tests and in the presence of a periapical lesion, does a platelet concentrate resolve the condition achieving satisfactory regeneration of the apical defect in the absence of signs and symptoms?	4	3	—	—	—	1	N	12–18 months
Metlerska et al., 2019[f]	2018	Poland	*Journal of Endodontics*	Effectiveness of autologous platelet concentrates in RET.	26	5	—	—	—	21	N	1 week–50 months
Nicoloso et al., 2017	2016	Brazil	*International Journal of Paediatric Dentistry*	Clinical and radiographic success and formation of apical barrier of endodontic treatments in management of necrotic immature permanent teeth[d].	7	7	—	—	—	—	Y	6–18 months
Ong et al., 2020	2020	USA	*Journal of Endodontics*	Survival, apical healing and root development of immature necrotic permanent teeth treated with RET[e].	11	3	—	6	2	—	Y	12–93 months

TABLE 1 (Continued)

Author	Year published	Country	Journal name	Outcomes reported	Number and type of study in review						Meta-analysis performed Y/N	Follow-up min/max
					No.	RCT	CCT	Pro	Ret	CSR		
Panda et al., 2020	2020	India	*Cells*	Effectiveness of autologous platelet concentrates compared to traditional blood clot regeneration in management of young immature necrotic permanent teeth: Dentinal wall thickness, increase in root length, calcific barrier formation, apical closure, vitality response, and success rate.	10	10	—	—	—	—	Y	10–49 months
Rossi-Fedele et al., 2019	2019	Australia	*Brazilian Dental Journal*	Clinical and/or radiographic and/or histological outcomes of revascularization endodontic procedures in non-vital immature permanent teeth.	7	1	1 animal	—	—	5	N	2 weeks–24 months
Shaik et al., 2021	2021	USA	*Journal of Pharmacy and Bioallied Sciences*	Survival, clinical and radiographic signs periapical healing, continued root formation as judged by decreased apical foramen, root lengthening and root dentine formation for infected immature permanent teeth treated by RET.	22	6	—	1	6	9	Y	12–96 months
Tong et al., 2017	2017	Singapore	*Journal of Endodontics*	Survival, clinical and radiographic signs and symptoms of periapical healing and continued root development for non-vital immature permanent teeth treated using RET.	14	5	3	6	—	—	Y	0–36 months
Torabinejad et al., 2017	2017	USA	*Journal of Endodontics*	Comparison of survival and success of necrotic immature teeth treated with RET and MAP[b].	146	11	—	10	8	117	Y	1.6–120 months
Wikstrom et al., 2021	2021	Sweden	*European Archives of Paediatric Dent*	Clinical and radiographic symptoms, periapical healing, dentine wall thickening, apex closure, continued root development, discoloration in immature necrotic permanent teeth treated with regenerative endodontic procedures and apexification techniques.	7	2	—	1	4	—	N	12–128 months
Xie et al., 2021	2021	China	*European Archives of Paediatric Dent*	Clinical and radiographic, including periapical periodontitis, changes in root length, root thickness and apex closure after revascularization or apexification in immature necrotic teeth.	5	5	—	—	—	—	Y	3–18 months

Abbreviations: CCT, controlled clinical trial; CSR, case series and case reports; MAP, mineral trioxide aggregate plug; No, number of studies included in the review analysis, Pros, prospective clinical study; RCT, randomized controlled trial; RET, regenerative endodontic treatment; Ret, retrospective clinical study.

[a]Success defined as significant root development maturation as well as healing/absence of periapical pathology and no further treatment required.

[b]Survival defined as a retained tooth in the oral cavity at follow-up. Success was defined as a lack of clinical symptoms (i.e., pain on percussion/palpation/function or sinus tract) and complete radiographic healing of the periapical lesion.

[c]Success defined as asymptomatic teeth examined both clinically and radiographically during the follow-up period and teeth not requiring any other endodontic treatment after RET protocol.

[d]The success or failure was considered in a dichotomous way, based on the author's criteria previously defined in each study.

[e]Survival defined as the tooth being retained after the treatment at follow-up. Healing was defined as the absence of clinical symptoms with resolution of the periapical radiolucency.

[f]Review included both mature and immature teeth.

TABLE 2 Outcomes reported in included systematic reviews

Core area	Outcome domain	Cited by	Outcome assessed at: (Min–Max)	How it is measured
Survival	Tooth	Kahler 2017	6–33 months	Tooth present
		Kharchi 2020	6–108 months	
		Antunes 2016	27.32 ± 30.47 months	
		Ong	12–93 months	
		Shaik 2021	NS	
		Tong 2017	1–33 months	
		Torabinejad 2017	12–21 months	
		Kontakiotis 2014	6 months	
		Wikstrom 2020	18–42 months	
Physiological/ clinical changes	Pain	Antunes 2016	10–60 months	Patient report
		Do Couto 2019	1–19 months	
		Kharchi 2020	6–108 months	
		Alghamdi 2021	2–6 years	
		Castro-Gutierrez 2021	1–18 months	
		Kahler 2017	12 months	
		Tong 2017	6–23 months	
	Mobility	Castro-Gutierrez 2021	1–18 months	Clinical assessment
		Rossi-Fedele 2019	2 weeks-19 months	
	Clinically asymptomatic	Do Couto 2019	1–18 months	Clinical assessment
		Duggal 2017	NS	
		Kharchi 2020	6–108 months	
		Alghmadi 2020	1.5 years	
		Antunes 2016	10–60 months	
		Lolato 2016	12–18 months	
		Metlerska 2019	1–50 months	
		Ong 2020	12–93 months	
		Rossi-Fedele 2019	6 weeks–18 months	
		Xie 2021	3–18 months	
	TTP/palpation	Do Couto 2019	5–18 months	Clinical assessment
		Kharchi 2020	9–58 months	
		Metlerska 2019	5.5–50 months	
		Rossi-Fedele 2019	2 weeks–19 months	
	Infection-swelling sinus fistula abscess resolution	Antunes 2016	10–60 months	Clinical assessment
		Do Couto 2019	5–12 months	
		Kharchi 2020	6–108 months	
		Alghamdi 2021	2–6 years	
		Castro-Gutierrez 2021	1–18 months	
		Kahler 2017	12 months	
		Tong 2017	12 months	

TABLE 2 (Continued)

Core area	Outcome domain	Cited by	Outcome assessed at: (Min–Max)	How it is measured
	Vitality/Sensibility	Antunes 2016	6–15 months	NS
		Do Couto 2019	5–12 months	Cold and EPT
		Iqbal 2021	12–48 months	EPT, Cold test
		Kharchi 2020	9–19 months	Cold test or EPT
		Castro-Gutierrez 2021	6–29 months	Cold test and/or EPT
		Lolato 2016	12–18 months	Cold test and EPT
		Metlerska 2019	3–36 months	
		Panda 2020	12–49 months	
		Shaik 2021	NS	
		Tong 2017	1–19 months	
	Periodontal probing depths/CAL	Metlerska 2019	1–12 months	Clinical
		Rossi-Fedele 2019	2 weeks–19 months	
	Complete root formation	Alghamdi 2021	2 months–3.5 years	Radiographic
		Alghamdi 2021	24 months	
		Do Couto 2019	12 months	
		Kharchi 2020	6–108 months	
		Kontakiotis 2014	6 months–13 years	
	Continued root development	Duggal 2017	0–36 months	Radiographic
		Torabinejad 2017	12–21 months	
	Apical narrowing/ diameter foramen reduction	Castro-Gutierrez 2021	3–29 months	Radiographic, CBCT
		Kahler 2017	12–18 months	Radiographic
		Ong 2020	12–93 months	
		Shaik 2021	NS	
		Wikstrom 2020	28 months	
		Nicoloso 2017	11–18 months	
		Shaik 2021	NS	
		Tong 2017	9–33 months	
		Xie 2021	3–18 months	
	Apical bridge	Iqbal 2021	12–24 months	Radiographic, CBCT
	Complete apex/closure	Alghamdi 2021	2 months–8 years	Radiographic, CBCT
		Alghamdi 2020	2–36 months	Radiographic
		Antunes 2016	10–60 months	
		Baez 2022	NS	
		Do Couto 2019	3–19 months	
		Duggal 2017	1–19 months	
		Kahler 2017	18 months	
		Kharchi 2020	6–27 months	
		Castro-Gutierrez 2021	3–18 months	Radiographic, CBCT
		Kontakiotis 2014	6–13 years	Radiographic
		Lolato 2016	12–18 months	
		Metlerska 2019	5.5–50 months	
		Nicoloso 2017	11–18 months	
		Panda 2020	12–18 months	

(Continues)

TABLE 2 (Continued)

Core area	Outcome domain	Cited by	Outcome assessed at: (Min–Max)	How it is measured
		Tong 2017	9–33 months	
		Xie 2021	3–18 months	
		Wikstrom 2020	18–42 months	
		Ong 2020	12–93 months	
		Rossi-Fedele 2019	3–18 months	
		Shaik 2021	NS	
	Absence of apical seal	Shaik 2021	NS	
	Apical healing/resolution PAP	Alghamdi 2021	2 months–6 years	Radiographic
		Alghamdi 2020	6–48 months	
		Antunes 2016	6–60 months	
		Baez 2022	NS	
		Do Couto 2019	3–18 months	Radiographic, CBCT
		Duggal 2017	1–57 months	Radiographic, CBCT
		Iqbal 2021	3–12 months	
		Kahler 2017	6-36 months	
		Karchi 2020	3 weeks–108 months	Radiographic
		Kontakiotis 2014	6–13 years	
		Lolato 2016	12–18 months	
		Metlerska 2019	5.5–50 months	
		Ong 2020	12–93 months	
		Shaik 2021	12–96 months	
		Tong 2017	1–33 months	
		Xie 2021	3–18 months	
		Torabinejad 2017	Up to 60 months	
		Wikstrom 2020	30 months	
	Periradicular healing	Rossi-Fedele 2019	2 weeks–19 months	
	Increase bone density	Castro-Gutierrez 2021	3–12 months	Radiographic, CBCT
		Do Couto 2019	12 months	
		Kahler 2017	6–36 months	
	Thickening dentine walls	Alghamdi 2021	6–26 months	Radiographic
		Antunes 2016	10–60 months	
		Baez 2022	NS	Radiographic, CBCT
		Castro-Gutierrez 2021	3–27 months	Radiographic, CBCT
		Chisini 2018	17–35 months	Radiographic
		Duggal 2017	0–36 months	
		Iqbal 2021	3–24 months	Radiographic, CBCT
		Kahler 2017	6–>36 months	Radiographic geometric imaging
		Kharchi 2020	6–108 months	
		Alghamdi 2020	6 months–4 years	
		Do Couto 2019	9–19 months	
		Kontakiotis 2014	6–13 years	
		Lolato 2016	12–18 months	
		Metlerska 2019	5.5–50 months	

TABLE 2 (Continued)

Core area	Outcome domain	Cited by	Outcome assessed at: (Min–Max)	How it is measured
		Ong 2020	12–93 months	
		Panda 2020	12–18 months	
		Shaik 2021	NS	
		Tong 2017	0–36 months	
		Xie 2021	3–18 months	
		Wikstrom 2020	18–42 months	
		Rossi-Fedele 2019	3–18 months	
	Increased root length	Alghamdi 2021	6–26 months	Radiographic
		Antunes 2016	10–60 months	
		Castro-Gutierrez 2021	3–29 months	Radiographic, CBCT
		Chisini 2018	17–35 months	Radiographic
		Iqbal 2021	3–24 months	Radiographic, CBCT
		Kahler 2017	6–>36 months	Radiographic geometric imaging
		Kharchi 2020	6–108 months	
		Alghmadi 2020	6 months–3 years	
		Baez 2022	NS	
		Do Couto 2019	3–19 months	
		Kharchi 2020	6–108	
		Kontakiotis 2014	6–6 years	
		Lolato 2016	12–18 months	
		Metlerska 2019	5.5–50 months	
		Ong 2020	12–93 months	
		Panda 2020	12–18 months	
		Shaik 2021	NS	
		Tong 2017	0–36 months	
		Xie 2021	3–18 months	
		Wikstrom 2020	18–42	
	Hard tissue barrier not at apex	Alghmadi 2020	5.5–14.5 months	Radiographic
		Ong 2020	12–93 months	
		Panda 2020	12–49 months	
		Shaik 2021	NS	
	Unpredictable pattern of deposits in root morphology	Shaik 2021	NS	
	Cervical barrier calcific	Castro Gutierrez 2021	6–12 months	Radiographic
		Iqbal 2021	12–24 months	Radiographic, CBCT
		Nicoloso 2017	11–18 months	Radiographic
		Ong 2020	12–93 months	
		Panda 2020	12 months	
		Tong 2017	6–26 months	
	CVEK classification	Alghamdi 2021	2–8 years	
		Alghmadi 2020	2 months–4 years	

(Continues)

TABLE 2 (Continued)

Core area	Outcome domain	Cited by	Outcome assessed at: (Min–Max)	How it is measured
	Root area dimension change	Castro-Gutierrez 2021	27 months	Radiographic
		Do Couto 2019	3–18 months	
		Ong 2020	12–93 months	
		Lolato 2016	12–18 months	
		Metlerska 2019	3–18 months	
		Tong 2017	NS	
	Blunt root tip	Kharchi 2020	6–108 months	Radiographic
	Tissue regeneration	Alghmadi 2020	1.5 years	NS
Life impact	Success	CastroGuteirrez 2021	3–29 months	Clinical and radiographic
		Chisini 2018	17–35 months	
		Kahler 2017	9–36 months	
		Alghamdi 2021	2 months–8y	
		Antunes 2016	9–19 months	
		Koc 2020	8–46 months	
		Nicoloso 2017	6–18 months	
		Panda 2020	12–18 months	
		Rossi-Fedele 2019	1–24 months	
		Kontakiotis 2014	6 months	
		Metlerska 2019	1–50 months	
		Torabinejad 2017	12–21 months	
		Wikstrom 2020	18–42 months	
	Functional tooth	Antunes 2016	15–18 months	NS
	Discolouration	Antunes 2016	6–36 months	Clinical
		Castro-Gutierrez 2021	6 months	
		Do Couto 2019	18 months	
		Kahler 2016	1 month–13 years	Spectrophotometric analysis
		Kharchi 2020	6–26 months	
		Metlerska 2019	1–18 months	
		Tong 2017	6–26 months	
		Shaik 2021	NS	
		Torabinejad 2017	12–21 months	
		Xie 2021	3–21 months	
Resource use	Need for further intervention/or not	Antunes 2016	15 months	Clinical and radiographic
		Kahler 2017	14.5 ± 8.5 months	
		Alghamdi 2021	2 months–8 years	
	Number visits	Alghamdi 2021	2 months–8 years	NS
		Koc 2020	8–46 months	
Adverse effects	Intracanal calcification	Almutairi 2022	12–34.3 months	Radiographic
		Castro-Gutierrez 2021	6 months	
		Xie 2021	3–12 months	
	Partial or total obliteration	Do Couto 2019	18 months	Radiographic

TABLE 2 (Continued)

Core area	Outcome domain	Cited by	Outcome assessed at: (Min–Max)	How it is measured
		Kharchi 2020	6–108 months	
		Lolato 2016	12–18 months	
		Metlerska 2019	3–12 months	
		Ong 2020	12–93 months	
		Shaik 2021	NS	
		Tong 2017	NS	
	Resorption	Tong 2017	6–23 months	
	Tooth fracture	Tong 2017	6–23 months	
	Reinfection	Tong 2017	6–23 months	

Abbreviations: CAL, clinical attachment loss; CBCT, cone beam computed tomography; EPT, electric pulp test; NS, not specified; TTP, tenderness to percussion.

Clinical and physiological changes

Most outcomes were reported in this core area. Common signs and symptoms of pulpal health were inconsistently reported across reviews with an emphasis on root maturation. Presence or absence of signs of infection, including swelling, sinus or abscess were infrequently reported ($n = 8$). Whilst the reporting of root development was largely homogeneous, with most reviews ($n = 20$) focused on complete apical closure and three simply reporting non-specified evidence of continued root development, several studies also reported changes in root area ($n = 6$) and reduction in the diameter of the apical foramen ($n = 9$). Thickening of the dentine walls was reported in 21 reviews and increased root length ($n = 20$). Evidence of apical healing and resolution of periapical pathology was reported in 18 reviews with one review reporting on wider aspects of peri-radicular healing.

Life impact

The two most reported outcomes in this core area were success ($n = 14$) and tooth discolouration ($n = 10$). Whilst similar, there were some differences in the definition of success across the reviews. No report on OHRQoL was found.

Use of resources

The 'need for further intervention' and 'number of visits to complete the procedure' were the two domains reported in this core area. Neither domain was frequently reported across the reviews ($n = 3$, $n = 2$) respectively.

Adverse effects

Adverse effects were not frequently reported but included intracanal calcification ($n = 4$), canal obliteration ($n = 7$), resorption ($n = 1$), tooth fracture ($n = 1$) and reinfection ($n = 1$).

How were the outcomes measured?

There was commonality across outcome measurement in the reviews. Evidence of healing and resolution of periapical pathology was typically assessed radiographically ($n = 13$) whilst four reviews included combinations of radiographic and CBCT measurements in this domain. Four reviews did not state the method of measurement of tooth vitality/sensibility whilst six adopted traditional thermal and or electric pulp testing.

When are the outcomes measured?

Whilst the timing of measurement was outcome dependent, there was wide variation across the reviews. Clinical signs and symptoms of pulpal disease were typically measured in both the short and longer term (range: 1 month-108 months). Apex closure which would typically require a long- term follow up was reported from 1 month to 8 years.

Outcome reporting bias

A summary of selective reporting bias within the included reviews is provided in Table 3. Five of the reviews did not include an assessment of selective reporting bias. All

TABLE 3 Selective reporting bias in included reviews

Systematic review	Method for assessing risk of bias RCT	Method for assessing risk of bias for other studies	Risk of bias Randomized	Risk of bias Other studies
Alghamdi 2021	Cochrane RoB	ROBINS-1	3 low	11 low, 4 unclear
Alghmadi 2020	Cochrane RoB	ROBINS-1	2 low, 1 unclear	40 low, 3 unclear
Almutari 2020	Cochrane RoB	ROBINS-1	3 low	4 moderate, 1 serious
Baez 2022	Cochrane RoB	Cochrane RoB	11 low, 1 high	20 low
Castro-Gutierrez 2021	Cochrane RoB	N/A	10 some concerns	
Chisni 2018	Cochrane RoB	N/A	1 high	4 high
do Couto 2019	Cochrane RoB	N/A	6 low, 2 unclear	
Duggal 2017	Cochrane RoB		NS	
Kharchi 2020	Cochrane RoB	EPHPP	NS	1 unclear
Koc 2020	Cochrane RoB	ROBINS-1	7 low, 1 unclear	9 low, 1 moderate
Kontakiotis	N/A	NOS		[a]
Lolato 2016	Cochrane RoB	N/A	4 low	
Metlerska 2019[d]	Cochrane RoB		1 low	
Nicoloso 2016	Cochrane RoB		7 low	
Ong 2020	Cochrane RoB	Cochrane RoB	3 low	6 low[b]
		NOS		[c]
Panda 2020	Cochrane RoB	N/A	10 low	
Rossi-Fedele 2019	Cochrane RoB	Joanna Briggs Critical appraisal tool	1 low	[a]
Tong 2017	Cochrane RoB	Cochrane RoB	1 high, 4 low	1 high, 5 low
		NOS		[a]
Torabinejad 2017	Cochrane Rob	Cochrane RoB	[a]	[a]
		QA tool for observational cohort and cross-sectional studies		[a]
Wikstrom 2020	Cochrane RoB 2	ROBINS	1 high, 1 low	2 unclear
Xie 2021	Cochrane RoB	N/A	5 low	

Note: Five reviews did not report on selective reporting bias.

Abbreviations: RCT, randomized controlled trial; RET, regenerative endodontic treatment; RoB, risk of bias.

[a]Cannot be determined from reporting.

[b]Prospective cohort studies measured with Cochrane RoB tool.

[c]Two retrospective studies cannot be determined.

[d]Review included both mature and immature teeth, however, only the 1 immature study included in this analysis.

the reviews which reported on randomized control trials followed Cochrane's Risk of Bias tool. Selective reporting bias within the non- randomized and other study types was assessed using a range of tools including Risk of Bias in Non-Randomized studies of interventions (ROBINS-1) ($n = 5$), Cochrane Risk of Bias tool (RoB) ($n = 4$), Newcastle-Ottawa Scale (NOS) ($n = 3$), Effective Public Health Practice Project Tool (EPHPP) ($n = 1$) and Joanna Briggs Critical Appraisal tool ($n = 1$). Included in the 20 reviews reporting risk of selective reporting bias in randomized trials, 68 studies were at low risk, 4 unclear, 4 high risk and 10 with some concerns. Of the included studies in the 12 reviews reporting RoB in other study designs, 91 were at low risk, 5 moderate, 7 high/serious and 10 unclear risk of selective reporting bias. One review which included both randomized and other study designs reported that RoB was completed but provided no further information (Torabinejad et al., 2017).

DISCUSSION

Summary of evidence

The aim of this scoping review was to identify outcomes of revitalization procedures reported in systematic reviews and

how and when these outcomes were measured. Twenty-six systemic reviews reporting on the outcomes of revitalization were included in the scoping review. The majority of reviews were published after 2019, which is consistent with this growing area of research focus. The included reviews reported only on the clinically established RETs based on cell-homing techniques as described in the ESE position statement (Galler et al., 2016) and excluded any experimental cell-based techniques (Brizuela et al., 2020).

The terminology used varied across the reviews with earlier studies using earlier definitions such as revascularization, while others used the term "Regenerative Endodontic Treatment" (RET) and more recent studies using the term revitalization. The outcomes reported in the systematic reviews comes under the five core areas defined in the taxonomy developed for health interventions (Dodd et al., 2018), with the majority of the outcomes reported in the domain of clinical and physiological changes and only a limited number of outcomes in the life impact and adverse events domains. There was evidence of heterogeneity in the outcome definitions particularly in relation to root development and the optimal timing for reporting these outcomes. Similarity, however, was evident for the instruments used to assess healing/root development, mainly radiographic examination with occasional use of CBCT.

As expected in this area of emerging research, there is a lack of consensus and standardization of reporting outcomes and therefore a need for the development of a COS for revitalization and eventually other RETs (El Karim et al., 2021, 2022). It is clear from the outcome of this review that most of the outcomes reported are clinician-focused with few if any patient-reported outcomes. The oral health-related quality of life (OHRQoL), which is the most important patient-reported outcome and a significant contributor to overall health-related quality of life (John, 2020), was not reported in any of the systematic reviews or their included studies. The development of a COS is important to ensure that patient-reported outcomes are adequately reported in clinical studies and furthermore are placed at the centre of treatment assessment particularly in relation to the cost-effectiveness of such treatment.

The outcomes reported in this review were mostly evaluated via patient history, clinical examination including chairside tests and radiographic examination. It was clear that conventional and digital radiographic examination was universally used for assessment of the outcomes such as root development and periapical healing following revitalization. Another emerging imaging technique, CBCT was used in some studies but whether this provided any added benefit to conventional radiographic examination is not clear (Elsheshtawy et al., 2020; Meschi et al., 2018). It is evident from this review that there is heterogeneity on the optimal timing for reporting outcomes. Whilst there is no clear indication of the optimal time to measure long-term vs short-term outcomes, a recent publication has identified time points appropriate for revitalization and other RET follow-up (Duncan et al., 2021b).

Strengths of review

A strength of this scoping review is the comprehensive literature search that was performed including all systematic reviews published without time restriction. Review selection, data extraction and assessment of risk of selective bias were performed in duplicate and cross referenced to minimize the likelihood of errors. Although a COS for revitalization has been suggested in a recent review (Galler et al., 2022), to our knowledge this is the first review to report on the outcomes of revitalization adopting the heath intervention taxonomy to summarize outcomes into a format compatible with validated COS development for revitalization.

Limitations of review

The outcome data reported in this scoping review was based on high-level systematic review data with no exploration of their included individual studies. As a result, there is a reliance on the review authors' choices and accuracy as well as potential under-reporting of outcome measurement tools as this level of detail is often absent in a systematic review. The included reviews were limited to those published in English language with potential for risk of publication bias.

Future directions

Considering the opportunities that revitalization and RET offer in improving the prognosis of compromised immature teeth, there is a need to build on the current level of evidence through well-designed randomized trials. To support this translational work and enable guideline development, there is a clear need for a COS representing both clinician and patient-reported outcomes. The COS to be developed for the revitalization can also be expanded and further developed to include other forms of RET once these are established in clinical practice.

CONCLUSION

This review suggests that whilst there is some homogeneity in the selected outcomes and methods of measurement

reported in revitalization systematic reviews, reporting of outcomes does not consistently reflect all the aims of revitalization. Developing a COS will support translational research in realizing the opportunities of this biological approach and ensure that patient perspective is captured and informs future direction.

AUTHOR CONTRIBUTIONS

All the authors have made relevant contributions to the manuscript. All the authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

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

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated.

ETHICS STATEMENT

Ethical approval was not necessary as this article is secondary research involving review of the literature.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Cushley, S., McLister, C., Lappin, M.J., Harrington, M., Nagendrababu, V. & Duncan, H.F. et al. (2022) Outcomes reporting in systematic reviews on revitalization: A scoping review for the development of a core outcome set. *International Endodontic Journal*, 55, 1317–1334. Available from: https://doi.org/10.1111/iej.13829