

Interventions for Managing Necrotic Immature Permanent Teeth
Following Traumatic Dental Injury

Thesis submitted in accordance with the requirements of the University of Liverpool for
the degree of Doctor in Philosophy by Laura Margaret Gartshore

26th May 2017

Abstract

Interventions for Managing Necrotic, Immature, Permanent Teeth Following Traumatic Dental Injury

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Background: There is debate in the literature as to whether an optimal intervention exists for the management of necrotic, immature, permanent teeth following traumatic dental injury. There are currently three recognised intervention strategies, including apexification with calcium hydroxide (CaOH), apexification with mineral trioxide aggregate (MTA), and regenerative endodontic procedures (REP). Affected children face unexplored outcomes. Adherence to evidence-based best practice is impeded.

Aim: To address the research question: *Is there an optimal intervention for the management of necrotic, immature, permanent teeth?*

Methods: A survey was designed to determine the clinical decision-making practices of specialists in paediatric dentistry and endodontics. A systematic review was carried out to produce a thorough, explicit and objective description of the relevant literature. A randomised controlled trial was conducted, of participants aged 7-21 years, with a history of traumatic dental injury, and a diagnosis of a non-vital, permanent maxillary central incisor, to compare outcomes of endodontic success for immature teeth, following REP or MTA.

Results:

Some 89% of specialists agree that young people have difficulty accessing good quality management of necrotic, immature teeth. Paediatric dentists are significantly more likely than endodontists to manage this clinical problem ($p < .001$). Some 57% of specialists would choose to carry out MTA as a first line intervention. Some 16% of endodontists and 1% paediatric dentists would plan REP.

No randomised controlled trials have been reported that adequately address the research question in full.

Clinical and radiographic healing was favourable for both intervention groups. Mean increases in root length were 0.5mm for REP (SD 0.44, range 0.10 to 1.50mm), and 0.25mm for MTA (SD 0.36, range -0.10 to 1mm). There was no significant effect of intervention in relation to root length ($p < 0.093$). Mean increases in radiographic root area were 9.03% for REP (SD 5.55, range 2.2 to 21.6), and 0.85% for MTA (SD 2.92%, range -4.6 to 6.8). There was a significant effect of intervention in relation to radiographic root area ($p = < 0.0001$). Effect size and feasibility have been established to facilitate development of the interventions, and the design of future experimental studies.

Conclusions: There is variation in practice between, and within, the specialities, and there are disparities in access to specialist management. There is a lack of quality controlled, comparative randomised controlled trials to support the decision-making practices of clinicians in relation to the optimal management of necrotic, immature teeth. The first randomised controlled trial of its kind has generated reliable evidence to support the clinical and radiographic effectiveness of the interventions, and the occurrence of statistically significant tooth development in regenerative endodontic procedures. Regenerative endodontic procedures may be associated with clinically significant advantages in relation to tooth development.

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3 Preface

This thesis is the original and independent work of the author, L. Gartshore, and is submitted for the degree of Doctor of Philosophy at the University of Liverpool.

A great many people have supported this work. I am particularly indebted to Dr Kathryn Fox, Dr Sondos Albadri, and Dr Fadi Jarad, for their tremendous, and unwavering, guidance, empathy and encouragement. It has been a privilege to work under their supervision.

I am immensely grateful to Professor Rumona Dickson, of the Liverpool Reviews and Implementation Group, for her renowned authority, enthusiasm, and the sharing of her expertise, staff and facilities.

Thank you to Beth Powell for her tireless diligence, and ‘unflappable’ organisational skills, that ensured the smooth running of a randomised controlled trial, and which lifted this work off the ground. Thank you to Sarah McKernon for sharing my passion for optimising response rates, and for believing in teamwork. Thanks to Girvan Burnside for sharing his statistical knowledge, to Claire Newey for her role as second investigator, to Gareth Jones for agreeing to digest large amounts of dental literature, to Jan Atkinson for her warm welcome, to those who have supported my clinical training with patience, to those with the watchful eyes of the keenest proof-readers, and to the administrative staff of the University of Liverpool for their invaluable, and much appreciated, contributions. Thank you all for your time and unwavering conviction.

I am indebted to my much-loved family and friends. I am forever grateful for the skills and compassion that you have shared with me. You have each piloted my willingness to voice a coherent opinion, fortified my endeavour, and have steadfastly supported the paths I have chosen with infinite assurance.

To little Sydney, thank you for being so happy and patient. I am ready to go for that walk now.

4 Setting the Scene

Traumatic dental injuries to the developing dentition frequently impact on a child's oral health, dental appearance and quality of life. If traumatic injury results in pulp necrosis of an immature tooth, a substantial clinical burden is created for children, their families, and for health care providers. The clinical problem of managing non-vital, immature teeth is threefold, in terms of prevalence, complexity and ambiguity. Thus, children who suffer traumatic dental injuries may not have access to endodontic interventions that deliver optimal outcomes. Little is known about how clinicians facing this challenging problem choose to manage necrotic teeth with immature apices. There is a lack of reliable and robust evidence to guide clinical practice in relation to non-vital, immature teeth. Thus, there is little guidance to assist decision-making, and adherence to best practice is impeded. Novel interventions have evolved that may, or may not, offer viable alternatives to traditional approaches. As science advances, the feasibility of introducing a novel intervention into clinical practice appears to be trailing behind. The current situation is ineffectual and inequitable. Affected children face unexplored outcomes in terms of tooth survival and healing. Those with the greatest need may not be presented for continuing care if an inherent and unanswered question presides over prognosis.

This thesis strives to advance dental science, to identify an optimal intervention for necrotic, immature teeth that might be deliverable to all those who present for care, and to raise the profile of children who encounter dental injuries. The specialist management of non-vital, immature teeth is explored to understand what influences the decision-making practices of those trained to guide the profession. The evidence-based literature is systematically reviewed to evaluate the knowledge available, and to establish the need for comparative studies. A randomised controlled trial is conducted that seeks to generate evidence for optimal clinical decision-making, and to establish whether there is a solution for children and their clinicians. Innovative and exploratory steps that have been made towards the creation of a conservative endodontic approach that harnesses the regenerative potential of immature teeth is scrutinised by the testing of a newly defined primary outcome measure of endodontic success for an immature tooth. In doing so, this thesis seeks to change the landscape for children who suffer traumatic dental injuries.

5 Literature Review

5.1 Dental Trauma and the Immature Tooth

5.1.1 Introduction

Traumatic dental injuries to the anterior dentition, which occur during the period of root formation, may have implications for the health and longevity of the affected teeth, and subsequently, for the dental and social experiences of the children affected. Dental injury may result in loss of tooth vitality, rendering a necrotic, immature tooth without a fully formed apex, against which a root canal filling can be placed (Andreasen et al., 2007). Consequently, a root end closure procedure must be carried out prior to completion of endodontic intervention (Hargreaves et al., 2011).

Young patients who present with dental injuries may have little, or no, previous experience of dental care. Clinical outcomes are further compromised by the underdeveloped presentation of the dentinal root walls of the non-vital, immature tooth, increasing the likelihood of cervical or root fracture, coupled with the possibility of tooth loss, in the short to medium term (Andreasen et al., 2002).

Furthermore, the optimal intervention for non-vital, immature permanent teeth requiring root end closure is a matter of debate amongst specialists in paediatric dentistry, endodontics and across the wider field of dentists who provide treatment to children in a primary care setting. Little is known, or agreed, with regards the optimal intervention for affected children.

There is an established relationship between endodontic failure and persistent disease (Kirkevang et al., 2007, Eckerbom et al., 2007). The technical complexities of root end closure, coupled with high material costs, inexperienced dental patients, and limited training of primary care dental practitioners to successfully manage non-vital, immature apices, may result in referral of such cases to specialist care.

Specialist dental services within the UK are limited. The total population of registered specialists in paediatric dentistry and endodontics is circa 500, with similar numbers in each specialty (General Dental Council 2016). The British Society of Paediatric Dentistry estimate that one paediatric dentist is required per 20,000 children. Therefore, at least 650 paediatric dentists are required in the UK; however, as will be discussed later in this thesis, only 227 are currently in active practice.

Approximately 20% of the UK population, or 13 million people, are aged less than 15 years (Office for National Statistics, 2016). Approximately 4% of 15 year old children in England, Wales and Northern Ireland have experienced traumatic damage to their permanent teeth (Steele J et al., 2015). The prevalence of children who might expect to experience dental trauma by the age of 15 is therefore estimated at half a million. Thus, it is likely that the number of specialists required to enable access of young patients to appropriate and timely specialist care is currently insufficient.

5.1.2 Diagnosis of the Pulpal Status of Traumatized and Immature Teeth

Diagnosis of the pulpal status of traumatized, immature teeth is not always straightforward. The prognosis of the pulp's vitality and the likelihood of uninterrupted apexogenesis depend on the nature of the injury and its immediate management (Trope, 2008a).

Children may be unreliable historians. Young patients exhibiting dental anxiety may be reluctant to share presenting symptoms of pulpal inflammation (Krikken et al., 2013). The blood supply of an immature, luxated tooth may be interrupted at the time of traumatic dental injury, yet recovery in terms of revascularisation through the open apex may occur, thus maintaining pulp vitality (Hargreaves et al., 2011).

It is widely accepted that efforts should be made to preserve the vitality of a traumatized, maturing tooth in order to allow completion of the process of apexogenesis (Andreasen, 2011). Caution is thus required in determining pulpal status prior to commencing irreversible pulp extirpation. Conversely, inappropriate postponement of extirpation of an irreversibly damaged pulp may result in commencement of an inflammatory resorption process that will further compromise the dental hard tissues of the affected tooth, and may lead to a deterioration in tooth colour (Hargreaves et al., 2011).

Diagnosis of a traumatised, non-vital, immature tooth, requires careful assimilation of a given history of the traumatic dental injury, the presence and absence of signs and symptoms of pulpal inflammation, a record of any previous interventions, and a clinical and radiographic assessment (Bakland and Andreasen, 2004, Andreasen, 2011). Clinical indicators of pulpal inflammation or periapical infection include the presence of pain, soft tissue pathology, tooth mobility, tenderness to percussion, a lack of response to sensibility testing, and tooth discolouration.

Immaturity of a permanent central incisor can be expected following an injury that results in pulp death when the affected child is aged between six and ten years. On occasion, teeth may remain asymptomatic following loss of pulp vitality.

If no treatment is sought, diagnosis of a non-vital, immature tooth may be made in adolescence or adulthood as an incidental finding following routine radiographic examination of the dentition, or during orthodontic assessment. Intervention for a non-vital tooth is indicated in the case of asymptomatic presentation in order to avoid the sequelae of periapical inflammation that may arise (Hargreaves et al., 2011).

It is noted that sensibility testing may be unreliable in immature, traumatised teeth. Pulp testing with thermal (cold) rather than electrical agents may be more reliable for immature teeth (Fulling and Andreasen, 1976, Klein, 1978, Fuss et al., 1986), particularly following traumatic dental injury (Andreasen, 2011). Application of a cold stimulus to a vital tooth induces a pulpal response that indicates innervation. Roeko Endo-Frost Spray (Coltene), is an odourless stimulus with a temperature of -50 °C that is suitable for chairside application of a cold stimulus for the purposes of sensibility testing.

Loss of pulp vitality may be established radiographically by the presence of a non-transient periapical radiolucency, periapical bone loss, root resorption and loss of the lamina dura (Torabinejad, 2016). Radiographic comparison of the apical maturation of traumatised, immature teeth with that of the contralateral, non-traumatised teeth in similar stages of maturation may provide evidence of failure of continued root development.

Furthermore, following establishment of loss of pulp vitality, the subsequent diagnosis of an open apex may be determined by subjective review of a plain film intraoral radiograph on which the development of the apex of the tooth in question is compared with that of a healthy contralateral tooth that continues to develop.

Following diagnosis of a non-vital, immature incisor, endodontic therapy is commenced that aims to extirpate necrotic pulp tissues, whilst avoiding damage to Hertwig's epithelial root sheath, and to control the presence of infection by placing an antimicrobial root canal dressing material (Torabinejad, 2016). Endodontic interventions, intended to induce apexification, or apexogenesis, can then commence.

5.1.3 Training the Workforce to Deliver Appropriate Care

Paediatric dentistry is the practice and teaching of, and research into, the comprehensive therapeutic oral health care for children from birth to adolescence, including care for children who demonstrate intellectual, medical, physical, psychological and/or emotional problems (Specialty Advisory Committee for Paediatric Dentistry, 2009, Gartshore, 2009). Endodontology is concerned with the study of the form, function and health of, injuries to and diseases of the dental pulp and periradicular region, their prevention and treatment (Claus, 2006).

The paediatric dentistry specialty training curriculum stipulates that trainees must be able to select, and deliver, appropriate interventions for immature permanent teeth, and that they should be able to describe the selection, application, delivery and limitations of contemporary endodontics (Specialty Advisory Committee for Paediatric Dentistry, 2009).

Endodontic specialists in training must acquire, and demonstrate, the knowledge, and skills, required to optimally manage traumatised teeth using appropriate clinical techniques (General Dental Council, 2010). The endodontic specialty curriculum also specifies that successful trainees must be able to manage young patients with confidence and efficiency. The nature of the two specialties determines that they are distinct from one another in relation to their target patient population, clinical environment and typical remuneration structure. Yet, the management of non-vital, immature teeth is within the remit, and teaching, of both specialities.

Young patients referred for the specialist management of non-vital, immature teeth might also continue to access routine dentistry in primary care in an appropriate shared manner. It is, therefore, imperative that both paediatric dentistry and endodontic specialists develop the ability to communicate effectively and professionally with referring clinicians and interdisciplinary colleagues, in order to coordinate the efficient delivery of care.

The vast proportion of all endodontic procedures are undertaken by general dental practitioners. It is recognised that standards of root canal treatment across the UK and Europe are suboptimal and this may be related to the variable quality and quantity of education, and experience, received during undergraduate training (Qualtrough et al., 1997, Eriksen et al., 2002, Segura-Egea et al., 2004, Tavares et al., 2009, Gencoglu et al., 2010, Peters et al., 2011, Woodmansey et al., 2015).

It is recognised that undergraduate clinical experience in relation to traumatised, and non-vital, immature teeth, is particularly limited, and that collaborative, interdisciplinary teams are required in order to provide students with a suitable breadth of knowledge of appropriate intervention options (De Moor et al., 2013). The costs of materials and equipment associated with mineral trioxide aggregate may restrict dental educators in providing undergraduates with clinical or simulated experience of the material (Tanalp et al., 2012, Walker et al., 2013).

European undergraduate endodontic curricula have been subject to change over the course of recent decades (European Society of Endodontology, 1992, European Society of Endodontology, 2001). Previously undergraduates were required to 'be familiar with the indications and availability of apexification'. Recent curricula are less prescriptive, specifying that graduates should be competent at negotiating uncomplicated root canals, whilst having knowledge of the principles and practice of managing dentoalveolar trauma. These curricula are not exhaustive and continued learning for all graduates is encouraged (De Moor et al., 2013).

5.2 The Clinical Problem of Non-Vital Immature Teeth: Prevalence, Complexity, and Ambiguity

The management of non-vital, immature teeth in children presents an endodontic challenge. This challenge can be regarded as threefold as follows:

5.2.1 Prevalence

Traumatic dental injuries are a common childhood experience. As previously stated, the reported prevalence of severe traumatic damage to the permanent anterior teeth of children prior to 15 years of age in England, Wales and Northern Ireland is approximately 4% (Steele J et al., 2015). This rate of injury is coincident with the estimated annual incidence of dental trauma globally of 4.5%, although prevalence studies have reported rates ranging from 1 to 44 new cases per 1000 persons in a year (Lam, 2016).

There has been an apparent decline in the prevalence of traumatic dental injuries over the course of the previous decade. In 2003, the rate of 15 year old children suffering crown fractures of the upper central incisors that involved enamel, with and without dentine, was 34.1 per 1,000 children (Murray et al., 2015). By 2013, children of the same age were experiencing the same traumatic dental injury at a reduced rate of 31.3 per 1,000. Improved primary prevention of traumatic dental injuries, and the changing activity levels of children, may have contributed towards this decline (Andreasen et al., 2007).

Unfortunately, surveys of child dental health appear to confirm that the majority of fracture injuries of permanent teeth remain untreated (Steele J et al., 2015). It is not clear whether dentists choose not to treat such injuries, or lack awareness of the importance of providing care, or whether parents fail to seek treatment for their children following dental trauma. It is also possible that restorations are placed, then subsequently lost and not replaced.

5.2.2 Complexity

Crown fractures account for the majority of traumatic dental injuries sustained to the permanent dentition (Andreasen et al., 2007). Failure to protect exposed dentine following a traumatic crown fracture may predispose to pulp death in approximately 6% of cases, according to a large retrospective study of almost 3000 teeth (Ravn, 1981).

Furthermore, it is thought that 9-77% of teeth diagnosed with luxation injuries may develop pulp necrosis (Andreasen, Andreasen, and Andersson 2007). Similarly, dental caries or developmental anomalies may render immature, permanent teeth non-vital if the pulp becomes irreversibly inflamed (Hargreaves et al., 2011).

Apexogenesis arrests in teeth that are rendered non-vital during the period of root development, yet only pulpal tissue has the ability to form true dentine (Goldman, 1974). Non-vital, immature incisors have thin dentinal root walls that are prone to fracture and a diminished crown to root ratio due to their relatively short root length. Furthermore, the open, and often divergent, apical morphology of immature teeth complicates endodontic intervention. A root end closure procedure is indicated to facilitate obturation of the root canal, against an apical barrier.

Apexification procedures aim to form a compensatory apical, hard tissue barrier in lieu of the apical constriction that would be present in a mature tooth, in order that gutta percha can be condensed without extruding material through the open apex into the periapical tissues. Extrusion of non-biocompatible gutta percha into the soft connective tissues may result in an inflammatory foreign body reaction, further compromising the prognosis of the traumatised tooth and resulting in discomfort for the affected child (Ritchie et al., 1988).

Young patients who have experienced traumatic injury may have little, or no, previous dental experience and may exhibit anxiety as a result of their subjective experience of pain associated with sustaining the injury (Townend et al., 2000). Hence, the endodontic management of non-vital, immature incisors in young children can be challenging.

5.2.3 Ambiguity

There are currently three, distinct management approaches for managing necrotic, immature, permanent teeth. Traditionally, clinicians carried out apexification with calcium hydroxide. More recently, mineral trioxide aggregate established a recognised role in the management of the open apex. Advances in endodontic therapy and material science have challenged this restorative approach, so that that necrotic, uninfected pulps might be regenerated to re-establish apexogenesis.

Regenerative endodontic procedures have rapidly evolved to propose the possibility of a more conservative approach to apexification techniques, by harnessing the therapeutic potential of stem cells of the apical papilla. Clinicians are faced with a lack of high quality evidence to support their decision-making in respect of optimal outcomes for the children in their care (Lam, 2016).

5.3 Options for Intervention of Non-Vital, Immature, Permanent Teeth

In the past, the ability to achieve an effective root filling of an immature tooth was restricted by the need to either adapt gutta percha to fit the size of the open apex (Stewart, 1963, Friend, 1966), or to carry out retrograde apical closure with a surgical technique (Ingle, 1965), which many children might find difficult to tolerate. Techniques for apical barrier formation began to develop in the 1960s (Frank, 1966).

The three recognised intervention strategies for the management of necrotic, immature, permanent teeth are summarised in table 1. It is likely that each, and all, of these interventions has a place in the management of non-vital, immature teeth, yet each intervention also has recognised limitations. Hence, a research question arose with regards the optimal management of the common, complex, clinical problem, of non-vital, immature teeth.

The UK National Clinical Guideline for the management and root canal treatment of non-vital, immature, permanent incisor teeth relays that prolonged dressing of non-vital, immature teeth with calcium hydroxide results in a reduction in the fracture strength of root dentine and that an alternative approach of apical barrier formation with mineral trioxide aggregate may improve the outcome (Vaidyanathan et al., 2010).

The American Academy of Pediatric Dentistry endorses both apexification with calcium hydroxide, and with mineral trioxide aggregate (American Academy of Pediatric Dentistry, 2014). The European Society of Endodontology (ESE) have advised that a dressing material that promotes healing and repair of the root end, or that an apical plug of a suitable material should be utilised (Claus, 2006). More recently, ESE have produced a position statement in relation to regenerative endodontic procedures with the aim of guiding clinicians towards a standardised protocol for the intervention, in addition to enabling an informed consent process (Galler et al., 2016).

5.3.1 Apexification with Calcium Hydroxide

Calcium hydroxide apexification was previously recognised as the gold standard intervention for the management of non-vital, immature incisors (Mackie, 1998). Apexification of non-vital, immature permanent teeth has traditionally involved placement of a non-setting calcium hydroxide root canal dressing, with replacement and apical barrier assessment at regular intervals (Frank, 1966, Heithersay, 1970, Ghose et al., 1987, Yates, 1988).

A number of authors have reported that a single dressing of calcium hydroxide may suffice (Chosack et al., 1997), or that the dressing material should be changed only when signs or symptoms of infection recur (Cvek, 1972). However it is generally accepted that dressing changes enable the clinical assessment of apical barrier formation and may increase the rate of apexification (Abbott, 1998). Apexification is achieved via the formation of a hard barrier at the open apex, against which a root canal filling material can be condensed.

The mechanism by which calcium hydroxide induces apexification is debated in the literature (Rafter, 2005). Suggestions include that calcium hydroxide has osteogenic potential to form heterotopic bone, that repair is induced following collagen synthesis, that osteodentine is formed, and that mineralisation occurs of a necrotic layer of the periapical tissues, that may or may not include the generation of a low-grade irritation of the tissues that accelerates hard tissue formation.

Calcium hydroxide has an effective bacteriostatic effect via its ability to release hydroxyl ions that inhibit bacterial replication with little resistance (Cvek, 1972, Byström et al., 1985). The basic pH of calcium hydroxide has been reported to aid apical barrier formation (Javelet et al., 1985).

Calcium hydroxide apexification has a long-standing record of clinical success and predictability, and delivery of the intervention is well-tolerated by young patients (Mackie et al., 1994, Andreasen et al., 2007). Clinical success rates at 12 months for calcium hydroxide apexification in comparative studies with mineral trioxide aggregate have been reported of 86.7% (El-Meligy and Avery, 2006), and 73.3% (Bonte et al., 2015).

Table 1 Options for intervention of non-vital, immature, permanent teeth

| | Calcium Hydroxide Apexification | Mineral Trioxide Aggregate Apexification | Regenerative Endodontic Procedure |
|---|---|--|---|
| Predictability of apical closure | High | High | Uncertain |
| Initial material and equipment cost | Low | High | Moderate |
| No. of treatment visits required to complete delivery of the intervention | Multiple (3 monthly visits for up to 18 months) | 1-2 | 1-2 |
| Degree of patient cooperation required | Low initially for short chairside procedure Compliance may wane over multiple visits | Moderate – High Prolonged chairside procedure | Moderate Prolonged chairside procedure |
| Practitioner training, experience & skill required | Low Undergraduate education | Moderate – High Postgraduate education | Moderate – High Postgraduate education |
| Summary advantages | Bacteriostatic material Predictable apical closure Well reported technique Previous gold standard intervention | Good apical sealing ability Biocompatible material Predictable apical closure Immediate apical barrier possible Current gold standard intervention | May promote continued root development with associated improved outcomes for tooth survival Good coronal sealing ability |
| Summary disadvantages | No increase in root length or root thickness Negative effect on root dentine strength Repeated radiography may be required to assess apical closure Prolonged temporary restoration Prolonged requirement for patient cooperation and attendance Time and finance intense over a period of repeated visits | No increase in root length or root thickness Tooth discolouration No solvent for removal Requires postgraduate training High initial equipment costs (particularly with the aid of an endodontic operating microscope) | Technique sensitive Tooth discolouration Unpredictable outcomes Lack of universally agreed protocol May require postgraduate training Lack of evidence to support Lack of universally available and consistent root canal dressing material |

Success rates for apical barrier formation have been reported as 43.8% at 6 months (Bonte et al., 2015), 78% at 6 months (Ghose et al., 1987), 93.3% (with tooth loss of 6.7%) at 12 months, (Damle et al., 2012), and 100% at 12 months (Pradhan et al., 2006). Interestingly, randomised studies that compare the success of calcium hydroxide apexification and mineral trioxide aggregate apexification have estimated sample size of 30 participants for 80% power with a hypothesis that apical barrier formation would take place in 5% of cases managed with calcium hydroxide apexification at 6 months (Bonte et al., 2015).

Mean time taken for apical closure with calcium hydroxide is variable, as is the reporting of this outcome. Time taken for apical barrier formation has been reported as 7 months (SD 2.5) (Pradhan et al., 2006), 7.9 months (SD 2.53) (Damle et al., 2012), 5-20 months (Sheehy and Roberts, 1997), 12.2 weeks (SD 1.6) (Lee et al., 2015), and 34.2 weeks (range 13-67 weeks) (Finucane and Kinirons, 1999).

Systematic reviews that sought to compare calcium hydroxide apexification with mineral trioxide aggregate apexification have concluded that there are no statistically significant differences between the interventions in relation to the success or apical barrier formation rates (Chala et al., 2011, Lin et al., 2016b).

However, calcium hydroxide apexification is not without significant limitations in relation to the apparent benefits of repeat root canal dressing, which may conversely present a treatment burden for patients and their families. The material cost of calcium hydroxide is relatively low; however, prolonged treatment time necessitates multiple dental visits that are associated with repeated patient journeys, possible loss of patient motivation for attendance over a prolonged treatment period, and the repeated utilisation of clinical resources.

Interestingly, there is little evidence reported in relation to failed attendance for children undergoing apexification procedures. Repeat exposure to dental radiation may be required for the detection of apical barrier formation unless only clinical assessment methods are used.

Repeated access of the immature root is associated with the risk of over preparation of the root canal, and reinfection, as a result of prolonged temporisation of the coronal access cavity (Swanson and Madison, 1987, Saunders and Saunders, 1994, Heling et al., 2002, Koagel et al., 2008).

A considerable evidence base suggests that prolonged root canal dressing with calcium hydroxide may have a negative effect on root strength (Andreason et al., 2002). There is also some suggestion that the compressive strength of dentine of mature teeth is reduced by short term dressings with calcium hydroxide (Sahebi et al., 2010). Therefore, teeth managed with calcium hydroxide apexification may be at increased risk of cervical root fracture during, or following, root canal treatment, hence short term clinical success may not persist, and may be abruptly discontinued in the event of tooth loss (Rosenberg et al., 2007).

Failure of calcium hydroxide apexification attributed to clinically significant tooth loss due to cervical root fracture has been reported at a rate of approximately 25% within 12 months (Jeeruphan et al., 2012, Bonte et al., 2015). Cervical root fracture may be more likely to occur in immature than mature teeth, and it has been reported that the incidence of fracture may increase up to 77% over a four year period for immature teeth with particularly under-developed roots (Cvek, 1992).

A retrospective study of 93 non-vital immature permanent incisors treated with calcium hydroxide apexification, followed by obturation with gutta percha, reported that the survival rate was 86% at 5 years post-intervention (Mackie et al., 1993). Moreover, that calcium hydroxide apexification is not expected to induce positive dimensional root changes in relation to thickening, or lengthening, of the immature, dentinal root walls.

Variable patient- and clinician-based outcomes may be recorded as a result of the limitations of calcium hydroxide apexification. Despite these drawbacks, apexification with calcium hydroxide remains the treatment of choice for many primary care dental clinicians (Rafter, 2005), most probably because it is currently the intervention of choice for inclusion on many UK undergraduate dental curricula (De Moor et al., 2013).

5.3.2 Apexification with Mineral Trioxide Aggregate (MTA)

Mineral trioxide aggregate was first described in the dental scientific literature in 1993 (Lee et al., 1993). MTA mineral powder (ProRoot MTA Dentsply, USA) was first available in 1997 as a grey cement, with a white variety introduced in 2002. MTA is composed of tricalcium silicate, dicalcium silicate, tricalcium aluminate, tetracalcium aluminoferrite, and radiopaque bismuth oxide (United States Patent #5,769,638). The powder is mixed with sterile water in a 3:1 powder to liquid ratio, and sets in approximately 4 hours.

MTA is a material of low solubility, which has a basic pH, similar to that of calcium hydroxide, of approximately 12, that rises during its setting period, and which appears to be maintained in long-term studies (Torabinejad and Parirokh, 2010, Torabinejad, 2016). The material has been recommended as an alternative to prolonged apexification with calcium hydroxide, due to its ability to provide an immediate apical plug and to induce cemental, hard tissue healing (Shabahang et al., 1999, Torabinejad and Chivian, 1999). The biocompatible, hydraulic material releases calcium ions and expands slightly on setting, providing this excellent sealing ability (Linsuwanont, 2003). Compressive strength is initially low, but appears to improve over time (Hwang et al., 2011).

Mineral trioxide aggregate has been demonstrated to have less apical leakage than other restorative materials such as amalgam, Intermediate Restorative Material (IRM), and gutta percha (Torabinejad et al., 1993).

Immature teeth managed with MTA routinely undergo root canal dressing with calcium hydroxide, following extirpation of the necrotic pulp, to allow the bacteriostatic effect of the dressing material to render the root canal free from bacteria, whilst clinical healing commences, prior to placement of the definitive root filling. It is thought that any detrimental effects that calcium hydroxide may have on the mechanical properties of dentinal root walls will be minimised if the dressing period is less than five weeks duration (Yassen and Platt, 2013).

It has been suggested that root canal dressing with calcium hydroxide prior to MTA apexification may be associated with post-obturation apical leakage (Adel et al., 2014), and with extrusion of MTA, resulting in the formation of a hard tissue barrier beyond the limits of the root canal (Felippe et al., 2006).

Conversely, root canal dressing with calcium hydroxide may improve the marginal adaptation of mineral trioxide aggregate to the dentinal root walls of the apex (Bidar et al., 2010). It has also been suggested that leakage and treatment outcomes are dependent upon the delivery technique and thickness of the apical plug of mineral trioxide aggregate (>4mm thickness being optimal), rather than the material itself, supporting the benefits of clinician training and experience in delivery of the intervention (Hachmeister et al., 2002).

One of the key clinical advantages of mineral trioxide aggregate apexification is the ability of the clinician to achieve an immediate apical barrier in a single visit (Torabinejad, 2016). There is a corresponding reduction in the duration of the root canal dressing period employed during calcium hydroxide apexification, and a reduction in the duration of temporary restoration of the access cavity. Thus, there is a consequent reduction in the number of treatment visits required for young patients and their caregivers.

However, although MTA apexification addresses many of the limitations of calcium hydroxide apexification, the intervention does not address the compromised dimensions of the immature tooth. MTA does not appear to have any ability to promote continued development of the immature root, and therefore an immature tooth will continue to have a poor crown: root ratio, and thin dentinal walls that render it prone to fracture. *In-vitro* studies demonstrate that extension of composite resin restorations into the root canal of root filled teeth can substantially enhance the strength of MTA-filled immature teeth (Desai and Chandler, 2009). Thus, it is thought that definitive resin restorations, placed to seal the access cavity to the coronal third of the root canal following obturation with gutta percha, may have a role in reducing the risk of root fracture (Hachmeister et al., 2002, Lawley et al., 2004).

MTA is associated with tooth discolouration, thought to be attributable to the release of salts of iron and manganese (Asgary et al., 2005). Thus, caution is advised when using MTA in aesthetically critical areas, such as the permanent upper anterior dentition. The use of an endodontic operating microscope, that allows direct visualisation of remnants of the material that may have adhered to intracoronary hard tissues, facilitates its optimal removal from such sites prior to its setting.

Additional drawbacks of MTA include high material cost, prolonged setting time, and the absence of a known solvent to aid its removal (Parirokh and Torabinejad, 2010). As previously discussed, MTA apexification is not yet routinely taught at undergraduate level in dental schools across the UK. The material's application in non-vital immature teeth was fully recognised 20 years ago, and thus primary care clinicians who qualified prior to then may have limited experience of handling it. Therefore, this method of achieving apical closure may not be accessible for clinicians working in the primary care setting.

Placement may be technique sensitive in immature root canals that have a wider, more divergent apical anatomy due to the difficulty of condensing MTA at the open apex where there is little resistance against displacement forces (Hargreaves et al., 2011). Positioning of MTA at an immature apex may be facilitated by the use of endodontic operating microscope, which clinicians working in primary care practice may have limited access to. Manipulation of the material through the root canal to the apex requires practice, and can be problematic, particularly in the anxious child (Torabinejad, 2016).

Early comparative studies of calcium hydroxide apexification versus tricalcium phosphate (employed for apical closure prior to the commercial availability of MTA), either reported no difference between the interventions, or favoured the use of calcium hydroxide apexification (Roberts and Brilliant, 1975, Bal et al., 1993).

Following developments in material science, and with recognition of the applications of MTA, its role in apexification has superseded that of calcium hydroxide. Guidance produced by the British Society of Paediatric Dentistry recognises that several prospective studies favour MTA over calcium hydroxide for managing immature teeth (Felippe et al., 2006, Vaidyanathan et al., 2010).

Observational studies of MTA apexification have demonstrated comparable healing outcomes to calcium hydroxide apexification (Simon et al., 2007, Witherspoon et al., 2008), and acknowledge the previously discussed benefits of achieving an immediate apical plug.

Pseudo-randomised studies comparing MTA with calcium hydroxide reported that MTA apexification was superior in terms of clinical and radiographic periapical healing, and in providing an apical barrier, and proposed that it replace calcium hydroxide apexification (El-Meligy and Avery, 2006, Pradhan et al., 2006). A further study that allocated participants to one of two intervention groups via a random draw of lots carried out by one of the young participants, also reported preferable outcomes for MTA, and supported its role in the management of the open apex (Damle et al., 2012).

A call for randomised controlled trials comparing the interventions for apexification has been made (Bakland and Andreasen, 2012). In response, a randomised study designed to compare the effectiveness of apical closure for the interventions, supported the use of MTA rather than calcium hydroxide in relation to apical healing, and the time taken to complete treatment (Bonte et al., 2015). This study also supported MTA rather than calcium hydroxide in relation to tooth survival, although it was acknowledged by the investigators that tooth loss on the MTA group may have occurred following completion of the 12-month outcome observation period.

A further later study, which was pseudo-randomised, concluded that immature incisors managed with MTA outperformed those managed with calcium hydroxide apexification in relation to apical barrier formation, and that calcium hydroxide apexification is preferable to MTA for increasing root length (which was measured on plain film intraoral radiographs that were not standardised, nor digitally aligned) (Lee et al., 2015). Interestingly, this study also reported that in order to guarantee tooth development, MTA placement should be restricted to the coronal root canal, preserving viable pulp tissue that might remain close to the apical papilla.

A recently published retrospective study of MTA versus REP reported tooth loss for MTA at a rate of 17.2% over a 28 to 96-month period, which was greater than that for REP (Silujjai and Linsuwanont, 2017). The cause of failure, and thus tooth loss, in every MTA case was root fracture. The success rate for MTA, as defined by clinical and radiographic healing, was 80.8%, and superior to that of REP.

Success rates for MTA apical closure at 12 months have previously been reported as 100% (Damle et al., 2012), 76.5% (Bonte et al., 2015), 70% (Pradhan et al., 2006). Mean time taken for apical closure with MTA has been reported as 4.5 months (SD 1.56) (Damle et al., 2012), 3 months (SD 2.9) (Pradhan et al., 2006), 6.6 weeks (SD 1.9) (Lee et al., 2015).

Two systematic reviews have been published that compare MTA and calcium hydroxide apexification (Chala et al., 2011, Lin et al., 2016b). These studies are not without limitations, and both were designed to determine success in relation to apical barrier formation. The majority of studies record apical barrier formation as a primary outcome, yet it is debatable whether this clinician-based outcome is of relevance to intervention success, or of interest to young patients (Torabinejad, 2016). Both systematic reviews concluded that there were no statistically significant differences between the interventions. These reviews will be discussed later in this chapter.

Review of the literature confirms the suitability of MTA in its role for management of non-vital, immature teeth prior to obturation. However, the evidence for the intervention arises mainly from observational and pseudo-randomised studies.

Likewise, a number of queries have been raised in relation to long-term tooth survival following MTA apexification, and the suitability of calcium hydroxide as a root canal dressing material prior to apical plug placement.

Material science continues to advance, and as a result, novel materials have emerged on the commercial market that might also be suitable for achieving apical, or coronal, seal in immature root canals, providing an alternative to MTA. These materials remain largely untested and will be discussed later in this thesis.

It is perhaps not surprising that there is ambiguity in relation to the optimal intervention for immature apices, particularly with the materialisation of regenerative endodontic procedures as a viable third option.

5.3.3 Regenerative Endodontic Procedures (REP)

The dental pulp is a non-mineralised, loose connective tissue consisting of a complex of fibroblasts, undifferentiated mesenchymal cells, macrophages, lymphocytes, type I and II collagen fibres, in a ground substance rich in proteoglycans, glycoproteins, large amounts of water, lymphatic, nervous, and vascular tissues (Andreasen et al., 2007). Complete root development, or apexogenesis, requires a viable pulp containing undifferentiated mesenchymal cells that can differentiate into odontoblasts. Odontoblasts secrete dentine and are responsible for the formation of dentinal tubules within a root. Formation of root dentine, during root development, contributes to increased root strength. Following a traumatic dental injury with consequent loss of vitality, the condition of the necrotic pulp, and the infective status of the root canal, may impact on the ability of a traumatised tooth to undergo endodontic therapy aimed at regenerating vital tissues and enabling continued apexogenesis.

It is accepted that pulp revascularisation of traumatically avulsed, immature teeth may occur following rapid replantation. This was first demonstrated experimentally in the 1970s, with the revascularisation of replanted, avulsed, immature, and infected teeth of dogs (Skoglund, 1978). Pulpal revascularisation began immediately following replantation, and was complete at approximately 45 days. It was reported that the ischaemically necrotic, yet uninfected, pulp tissue of the avulsion injuries, acted as a scaffold for the ingrowth of new vital tissue into the immature root canal space.

The crown of an avulsed tooth usually remains intact, thus restricting bacterial penetration to the pulp. If a traumatised tooth sustains a crown fracture injury that exposes the dentinal tubules, the tooth may develop pulpal necrosis with concomitant infection of the root canal space. If a bacterial-free, avulsion-like environment is necessary for pulp revascularisation, endodontic intervention may be indicated to remove bacteria from the root canal space (Andreasen et al., 2007).

Iatrogenic revascularisation of the necrotic pulps of infected teeth with apical periodontitis was attempted in the 1960s, but was mostly unsuccessful (Nygaard-Ostby and Hjortdal, 1971).

This is most likely because the materials available at that time were not sufficient to render the root canal space free from the presence of bacteria, or to provide sufficient apical or coronal seal to resist post-endodontic bacterial penetration.

Three decades later, case reports began to appear in the dental literature, describing the resolution of periapical inflammation, accompanied by apparent apexogenesis, following extirpation and revascularisation of necrotic, infected pulps in immature teeth (Iwaya et al., 2001, Banchs and Trope, 2004).

In the first of these case reports, Iwaya et al reported irrigation of an infected, immature root canal with 5% sodium hypochlorite, and 3% hydrogen peroxide, followed by root canal dressing with ciprofloxacin and metronidazole. A thin layer of non-setting calcium hydroxide paste was placed at the open apex, and the access cavity was restored without dressing or obturation of the root canal space. Three years later, Banchs and Trope reported disinfection of an infected root canal with 5.25% sodium hypochlorite, followed by root canal dressing with a triple antibiotic paste, containing ciprofloxacin, metronidazole, and minocycline. The antibacterial effectiveness of the triple antibiotic paste, had been previously demonstrated *in-vitro* and *in-vivo* (Hoshino et al., 1996, Sato et al., 1996), and has since been confirmed in a multitude of studies (Windley et al., 2005). Banchs and Trope described a deliberate over instrumentation of the apical soft tissues of a sound, non-vital, immature premolar that exhibited signs of dens evaginatus. The subsequent introduction of a blood clot to a level 3mm below the cemento-enamel junction was described, followed by the placement of a mineral trioxide aggregate plug in the coronal third of the root canal, and a bonded resin restoration to close the endodontic access cavity.

The authors of both case reports described signs of periapical healing, apical closure, and apparent thickening of the dentinal root walls. Whilst the radiographic appearance of the postoperative root canal in the first case was debatably consistent with that of pulp canal sclerosis, tooth development was indisputably apparent in both case reports. The potential for an endodontic intervention that might improve tooth survival following traumatic dental injuries was realised. A protocol for regenerative endodontic procedures began to emerge.

Over the course of the past decade, the concept of regeneration, revascularisation, or revitalisation, of necrotic pulps has developed. Regenerative endodontics aims to promote continued root development, including thickening of dentinal root walls. Thus, the technique aims to deliver an improvement in the long-term prognosis and clinical outcomes of the tooth compared to that achieved with either calcium hydroxide or mineral trioxide aggregate apexification. There is substantial variation amongst protocols for the clinical application, delivery, and follow-up of regenerative endodontic procedures (Kontakiotis et al., 2015a).

In-vitro evidence and descriptive studies have begun to surface, as the profession grapples with the ability to translate an endodontic intervention that aims to harness the regenerative potential of pulp into a chairside intervention, suitable for delivery to child patients.

Thus, there has been a call for action to generate evidence from comparative randomised controlled trials (Murray et al., 2007), and to standardise clinical protocols and reported outcomes measures for the facilitation of guideline development (Hargreaves et al., 2014).

A number of observational studies (Bose et al., 2009, Jeeruphan et al., 2012, Nagy et al., 2014, Chan et al., 2017), and a multitude of case series and case reports, have been recently published that encourage clinicians to use the novel intervention (Kontakiotis et al., 2014). Survival rates are reportedly optimal thus far, and developmental changes appear to be clinically significant (Narang et al., 2015, Li et al., 2017).

Review papers have supported the biological rationale for regenerative endodontic procedures, and agree that the novel intervention may increase the prognosis of compromised immature teeth if functional vital tissue is re-established that encourages continued root development (Jeeruphan et al., 2012, Mao et al., 2012, Hargreaves et al., 2013, Law, 2013).

There have recently been two studies reported that compared outcomes of regenerative endodontic procedures with those of MTA apexification. The first of these studies was not randomised, yet sought to compare two protocols for regenerative endodontic procedures (with and without the use of an injectable hydrogel scaffold impregnated with basic fibroblast growth factor), whilst using MTA apexification as a control group (Nagy et al. 2014a). The aim of the study was to compare the REP protocols in respect of tooth development. Root canals were irrigated with 2.6% sodium hypochlorite and dressed with triple antibiotic paste (metronidazole, ciprofloxacin, doxycycline mixed with saline) for three weeks. Digital alignment of intraoral radiographs was carried out to aid standardisation of outcome assessment. The authors conveyed that radiographic measurements for the REP groups were blinded, but not for the control group. Results were reported for 29 participants, of which three cases within the REP groups failed, and were subsequently managed with MTA.

No description of the statistical analyses used to manage these participants was reported, thus it is not known whether data was managed with intention to treat or per protocol analyses, nor were the causes of failure reported.

No significant differences were reported in relation to root length or root thickness between the REP groups (the MTA group were not reported). A statistical difference between the groups was described in relation to a decrease in apical diameter at 18-month follow-up (0.8mm SD 0.3 REP without scaffold, 0.9mm SD 0.2 REP with scaffold, 0.0mm MTA), however this difference may not be clinically significant. Periapical bone density, a reflection of radiographic periapical healing, was estimated preoperatively and at 12-month follow-up, and no statistical difference was reported between the groups. The authors concluded that use of an injectable scaffold was not essential for repair.

The second study employed block randomisation to allocate 20 participants into four intervention groups (MTA apexification control group, REP without an injectable scaffold, REP with a platelet-rich plasma scaffold, REP with a platelet-rich fibrin scaffold) (Narang et al., 2015). The aim of the study was also to compare the REP protocols in respect of tooth development.

Root canals were irrigated with 2.5% sodium hypochlorite and dressed with triple antibiotic paste (the composition of which was not described) for a four-week period. Outcome assessment of radiographic healing, apical closure, and tooth development was carried out on non-standardised plain film radiographs, which were subjectively scored as fair, good or excellent. The authors stated that outcome assessment was blinded, presumably for the REP groups only due to the distinct radiographic appearance of the control group.

Excellent clinical healing was reported for all participants. Analysis of the results revealed no apical closure, or tooth development for the control group, and a statistically significant difference in 'excellent' scores for the REP with platelet-rich fibrin group. The authors concluded that platelet-rich fibrin has 'huge' potential to accelerate growth characteristics in necrotic immature teeth. There was no discussion in relation to power of the study, nor of descriptors used by investigators to subjectively judge the outcomes. Thus, it is unfortunately likely that both of these studies exhibit systematic errors, and lack internal and external validity (Higgins et al., 2011). The limitations of these studies will be further discussed in chapter 8.

In the absence of quality controlled, comparative randomised trials there is a lack of adequate evidence to support the current literature (Kontakiotis et al., 2014), however, the current best available evidence enables clinicians to offer regenerative endodontic procedures to young patients in need of opportunistic outcomes.

Tooth loss following REP has been reported in only one observational study thus far, at a rate of 11.7% over a 20 to 37 month period, in which every case of failure was attributed to either persistent infection, or reinfection (Silujjai and Linsuwanont, 2017). As is typical of the nature of case reports, few authors have reported cases in which there has been a failure of tooth development following regenerative endodontic procedures (Kontakiotis et al., 2014). Furthermore, few authors report methods of outcome assessment for the measurement of tooth development, thus many describe a non-quantified increase in root canal length and dentinal root wall thickening from direct visual assessment of plain film intraoral radiographs (Cehreli et al., 2011, Jeeruphan et al., 2012, El Ashiry et al., 2016).

Other investigators have utilised digital software that is designed to standardise plain film radiographs to quantitatively assess changes in root dimensions that occur following intervention with a validated protocol (Bose et al., 2009, Flake et al., 2014). Therefore, it is likely that authors reporting tooth development following measurement of plain film radiographs are underestimating dimensional root development that has occurred. A clinically significant threshold of 20% reduction in apical patency has been described in a recent cohort study that reported success in this respect for 82% of teeth managed with a regenerative endodontic procedure at 30-month follow-up (Chan et al., 2017).

It has been suggested that non-vital, immature teeth of an otherwise poor prognosis should be managed firstly with regenerative endodontic procedures, particularly if such teeth present with a poor crown: root ratio and increased risk of root fracture. The intervention does not preclude the possibility of apexification procedures at a later date, if attempts at regeneration are unsuccessful (Diogenes et al., 2016). Case selection may be important but little is known yet about the teeth that may be most likely to respond positively (Shabahang, 2013).

5.3.3.1 Development of REP Protocols to Date

Practical complexities for the delivery of regenerative endodontic procedures have been reported by previous investigators (Petrino et al., 2010, Dabbagh et al., 2012), as might be expected with a novel intervention.

Protocols for regenerative endodontic procedures have developed accordingly, and rapidly over the course of the past decade (Galler, 2016, Kontakiotis et al., 2015a), to include injectable scaffolds impregnated with growth factor, platelet-rich plasma, and platelet-rich fibrin (Nagy et al., 2014, Narang et al., 2015), in-lieu of a blood clot created via instrumentation of the apical tissues as previously described (Banchs and Trope, 2004).

As previously discussed, it has been reported that radiographic signs of tooth development, and periapical healing, may be superior for regenerative endodontic procedures that include platelet-rich fibrin (Narang et al., 2015), but that use of artificial hydrogel scaffolds does not improve outcomes (Nagy et al., 2014), in comparison to apical bleeding that is manually induced.

It is agreed that clinicians should aim to remove necrotic pulp tissue and disinfect the root canal system whilst maintaining an environment that might be compatible with regeneration of vital tissues (Galler et al., 2016).

Concern has arisen within the *in-vitro* literature that commonly used endodontic irritants, including sodium hypochlorite, chlorhexidine, and chelating agents such as ethylenediaminetetraacetic acid (EDTA) might induce cell death, and are therefore unsuitable for future development of regenerative endodontic procedures (Essner et al., 2011, Kontakiotis et al., 2015a, N. et al., 2016). When in contact with vital tissues, sodium hypochlorite has a recognised cytotoxic effect that may lead to haemolysis and destruction of endothelial cells and fibroblasts (Guivarc'h et al., 2017).

It is accepted that the combined use of sodium hypochlorite and chlorhexidine as endodontic irrigants may have a synergistic effect in terms of antimicrobial activity (Kuruville and Kamath, 1998). Sodium hypochlorite has optimal antimicrobial at concentrations greater than 3%, but is toxic to periapical tissues, and may be cytotoxic to viable stem cells of the apical papilla (Martin et al., 2014). Chlorhexidine has antimicrobial activity and substantivity as an endodontic irrigant, and commonly replaces sodium hypochlorite for irrigation of root canals with immature apices, however, concentrations greater than 2% may also be cytotoxic (Trevino et al., 2011).

It has been reported that endodontic irrigation with 1.5% sodium hypochlorite, followed by a final rinse with 17% EDTA, may evade damage to stem cells of the apical papilla, facilitating their differentiation and survival (Martin et al., 2014). It is likely that the ideal endodontic irrigant for regenerative endodontic procedures has yet to be identified (American Association of Endodontists, 2011).

Change in tooth colour following regenerative endodontic procedures has been attributed to both the presence of minocycline in triple antibiotic paste, and to mineral trioxide aggregate placed intracoronally, near the cemento-enamel junction, leading to the suggestion that calcium hydroxide is used as an alternative dressing material for regenerative endodontic procedures (American Association of Endodontists, 2016, Galler, 2016).

Tooth discolouration has largely led to the replacement of triple antibiotic paste, with a double antibiotic paste incorporating only metronidazole and ciprofloxacin, or a modified antibiotic paste in which minocycline is substituted with cefaclor (Thibodeau and Trope, 2007). Neither calcium hydroxide nor any of the currently recommended antibiotic pastes are capable of completely eliminating bacteria from necrotic immature teeth (Latham et al., 2016). Antibiotic pastes may be difficult to remove from root canals, and irrigant activation regimes may be beneficial in this respect, but remain untested in studies of regenerative endodontic procedures to date (Akman et al., 2015).

Notably, previous authors have described difficulty inducing apical bleeding to the level of the cemento-enamel junction, and collapse of the coronal plug of mineral trioxide aggregate into the root canal (Petrino et al., 2010). It has been recommended that local anaesthetic without vasoconstrictor is utilised to reduce difficulties obtaining apical haemorrhage, and that clinicians consider using a collagen sponge within the root canal against which mineral trioxide aggregate can be gently placed (Galler et al., 2016, American Association of Endodontists, 2016). Approximately 15% of clinical protocols for regenerative endodontic procedures incorporate a collagen sponge that is designed to prevent collapse of a coronal plug of mineral trioxide aggregate (Kontakiotis et al., 2015a) and to enhance the ingrowth of vital tissue into the root canal (Jung et al., 2008).

There is discussion in the literature about the nature of the new tissue which revascularises the pulp space. *In-vitro* studies have suggested that the tissues formed via current protocols for regenerative endodontic procedures do not completely recapitulate the former pulp-dentine complex (Diogenes and Ruparel, 2017). It is possible that the tissue is more similar to periodontal ligament than pulp tissue (Thibodeau et al., 2007). Osseous tissue may also invade the apical aspect of the root canal, preventing the ingrowth of soft tissue.

Hence, there is some debate, supported by evaluation of the histological characterisation of tissue present in the pulp space following a regenerative endodontic procedure, as to whether a treated tooth undergoes 'revitalisation' or 'revascularisation' (Wang et al., 2010). The suggestion that revitalisation is more appropriate is based on the finding that although pulp tissue may survive the infection and recover, the procedure of revascularisation allows in-growth of vital tissue consisting of tissues resembling cementum, periodontal ligament (PDL) and bone, but not pulp parenchymal tissue. These tissues do not function like a pulp tissue and therefore, the authors conclude that revitalisation is not tissue regeneration but wound repair. The term revascularisation, is usually reserved for the description of the processes that occur following replantation of an avulsed, immature tooth, prior to any loss of vitality. Thus, the term regeneration has been proposed to better describe the guided tissue regeneration of interventions that are designed to recommence apexogenesis following loss of vitality (Huang and Lin, 2008). Further research, and appropriate case selection, may allow clinicians to more accurately predict the likely success of stimulating regeneration of dental pulp from the pluripotent cells in the periapical region (Sonoyama et al., 2008).

It has been suggested that the presence of a blood clot within the disinfected canal is essential in acting as a scaffold for the ingrowth of new vital tissue (Trope, 2008b). It is not yet known whether the necessary factors present in the blood clot can be isolated and perhaps then incorporated into a synthetic scaffold for use in the future. As previously discussed, platelet-rich plasma and platelet-rich fibrin have been identified as injectable scaffolds that might aid the regenerative potential of the intervention, and negate the need to induce bleeding via sharp instrumentation of the immature apex in a child. It is possible that the translation of these scaffold materials into primary clinical care may be limited by their availability and cost, hence there is rationale in continuing to develop REP protocols as first described (Banchs and Trope, 2004).

Concerns have been raised in the scientific literature about how stem cell therapies might be translated for clinical use to accomplish endodontic regeneration, and these will be discussed in the next section of this thesis. Regenerative techniques have advantages and disadvantages, and some of the experimental techniques in use in laboratories are currently only hypothetically bearing any clinical promise, or are at the earliest stages of protocol development.

However, there has been a push for development of regenerative therapies in recent years, and it is hoped that their clinical use may become more widely accepted (Murray, Garcia-Godoy, and Hargreaves 2007a). Traditionally, the regenerative potential of a non-vital pulp was considered to be extremely limited. However, our improved understanding of pulpal inflammation and repair, coupled with the availability of dental materials with enhanced and advantageous properties that allow clinicians to achieve the requirements of stem cell therapy within infected root canals, have led to pulpal regeneration becoming a viable alternative to apexification procedures, rather than a hypothetical possibility (American Association of Endodontists, 2016, Galler et al., 2016).

If the presence of a vital non-infected pulp prevents apical periodontitis, the potential to regenerate an injured or necrotic pulp provides the opportunity for the best root filling possible. This novel direction in the management of non-vital immature teeth presents an opportunity for a paradigm shift in the clinical approach.

Regenerative endodontic procedures represent an endodontic intervention that is conservative, may lend itself to undergraduate curricula, may therefore be more accessible in primary care, and may be well received by an engaged profession and affected children.

5.3.3.2 *Regenerative Science and Dentistry*

There has been a significant advancement in stem cell-based pulp and dentine regeneration research in recent years. There are two approaches to the regeneration of pulpal tissues; cell-based therapies that aim to introduce exogenous cells into the host, and those that are cell-free, and use materials other than cells, in an attempt to achieve tissue regeneration (Huang et al., 2013).

Animal studies have demonstrated that pulp and dentine-like tissues can be regenerated in the root canal space by transplanting scaffolds of stem cells from the apical papilla (SCAP) and dental pulp stem cells (DPSCs) into immature, extirpated root canals (Huang et al., 2010, Iohara et al., 2011). The cell-free approach has not yet produced convincing evidence on pulp regeneration. Pulpal regeneration in a clinical environment aims to reactivate the pluripotent stem cells present in the periapical tissues of the immature tooth by reintroducing them to a clean and empty root canal via a blood clot, which also serves as a potential scaffold for the ingrowth of new vital tissues and revascularisation of the regenerated pulp.

Over the course of recent years there have been great advances in the collaboration of tissue engineers and dental researchers (Grumezescu, 2016). Proliferation of knowledge in the field of stem cell research, coupled with a heightened understanding of the role of dental tissues as a valuable donor and recipient of stem cells, has led to intensification of efforts to advance the science of regenerative medicine (Abou Neel et al., 2014).

Although our knowledge of the processes underlying pulp regeneration have considerably improved, many questions remain regarding signalling pathways, timing, and the influence of various stress conditions, in translating regenerative science into predictable chairside interventions for dentistry (Rombouts et al., 2016).

Ameloblasts undergo apoptosis during formation of the enamel matrix. Tissues derived from neural crest ectomesenchyme, including dentine, pulp, cementum, periodontal ligament and alveolar bone, continue to regenerate throughout life, albeit at different rates and in response to a variety of stimuli.

The regenerative characteristic of these ectomesenchymal tissues has been channelled previously, and a number of dental interventions that feature tissue engineering have established a role in routine dentistry. For example, the aim of vital pulp therapy is to engineer the proliferation, migration and differentiation of progenitor cells in order to generate reparative dentine bridge formation and prevent pulp death (Rodd et al., 2006, Seale and Glickman, 2008, American Academy of Pediatric Dentistry, 2014). Guided tissue regeneration is frequently employed by periodontists and endodontists to replace tissues lost as a result of disease and surgical intervention (Tsesis et al., 2011, Cochran et al., 2016).

Likewise, regenerative endodontic procedures appear to propose a mechanism by which the dentine-pulp complex might be regenerated following traumatic or infective loss of vital tissue. Whole tooth replacement in lieu of provision of a prosthesis is unlikely in the near future, yet it has been demonstrated that it is possible to engineer developing dental tissues on biodegradable scaffolds in an appropriate culture (Young et al., 2002, Young et al., 2004).

5.3.3.3 *The Requirements of Tissue Regeneration*

Tissue engineering requires several key elements in order to be successful (Meyer, 2009). These keys elements include an autologous, allogenic or xenogeneic source of stem cells, an acceptable scaffold for stem cells to populate, morphogens to signal the subsequent pattern of tissue development and a conducive environment in which these processes can take place (Warburton, 2015). There are a number of important obstacles for tissue engineers and clinicians to consider before enabling the translation of expensive and complex laboratory science to safe, predictable and effective chairside tissue regeneration (Malhotra and Mala, 2012, Mao et al., 2012, Theodorou et al., 2016).

Stem cells have the ability to proliferate in an undifferentiated and pluripotent state. The plasticity of stem cells allows them to be pluripotent or multipotent. Embryonic stem cells have greater plasticity than post-natal stem cells which are more readily sourced (Brivanlou et al., 2003). Stem cells of dental origin include those sourced from dental pulp (DPSCs), stem cells of the apical papilla (SCAP), stem cells from human exfoliated deciduous teeth (SHED) mesenchymal stem cells (MSCs) (Rosa et al., 2016).

There is a concentrated effort underway to advance science in relation to regenerative medicine for the purposes of organ transplantation and tissue development (Vemuri and Chase, 2013).

Autografts, allografts, xenografts, and alloplast transplants composed of synthetic materials, are being gradually replaced with biodegradable scaffolds, supported by advanced molecular techniques, harnessed to direct stem cell proliferation and function to regenerate traumatised or missing tissues with those of an appropriate the function, size, shape and composition.

Stem cells may be delivered to damaged tissue directly via injection therapy, or following cell induction therapy, a process in which individual's own circulating cells are recruited. Indications include cartilage repair, craniofacial osteogenesis and for the treatment of ischaemic heart disease and spinal cord injury. However, the success of these processes is limited by suboptimal localisation of stem cells, by the immune response, and by the prerequisite for development of exogenous factors necessary to bring about cell differentiation and growth (Trindade et al., 2017). Tissue engineering has hence developed to isolate cells from an autologous or donor biopsy to seed within cell scaffolds *in-vitro*. 3D tissues are constructed prior to transplantation to a patient. The majority of studies investigating cell based approaches to pulp regeneration utilise DPSCs due to their availability and replicative potential. Alternatively, acellular scaffolds, such as scaffolds embedded with growth factors, can be transplanted and seed *in-vivo*, or enable construction of scaffolds for whole tooth regeneration (Sharma et al., 2014).

It is thought that of the known morphogens, bone morphogenic protein (BMP) and transforming growth factors (TGF- β) have a foremost role in dental tissue regeneration (Nakashima and Reddi, 2003).

Mesenchymal stem cells of the oral mucosa are often considered for the treatment of inflammatory diseases and for wound repair (Vemuri and Chase, 2013). DPSCs are considered by some investigators to be a particularly promising and easily accessible resource of stem cells for applications in tissue repair and regenerative medicine (Nakashima et al., 2013). It is agreed that hypoxia, resulting from injury to an otherwise healthy pulp, drives angiogenesis, and that vascularisation is key for dental pulp regeneration and healing (Rombouts et al., 2016).

It can therefore be assumed that revascularisation of vacant root canals is a necessary feature of successful pulp regeneration procedures. This theory supports the employment of the term pulp revascularisation, which preceded the current designation of regenerative endodontic procedures. DPSCs, SCAP and SHED have successfully demonstrated endothelial differentiation in animal and *in-vitro* studies (Rombouts et al., 2016). DPSCs in particular, may contribute to angiogenesis by guiding endothelial cells, and may enhance this process by differentiating into endodermal-like cells themselves. Hence, it can be assumed that DPSCs may have a role in regenerative endodontics, although much remains unclear about the extent and reliability of this role, and the importance of the origin of signaling pathways.

Perhaps the simplest of applications for tissue engineering might be discovered in the capacity of clinicians to harness the therapeutic potential of native stem cells of the apical papilla. In doing so, they might reliably induce apexogenesis for a previously non-vital tooth by replacing the lost tissue of the dental pulp. It has been recently suggested that establishment of regulatory guidelines for stem cell therapy in clinical endodontics is a realistic prospect in the near future (Nakashima and Iohara, 2014).

Much debate remains with regards the ability of clinicians to predictably regenerate functional dental tissues, and to successfully translate *in-vitro* studies to chairside applications that might be suitable for use in children, and primary care. Doubt prevails that a simple chairside procedure could renew the complex process of root development using little more than a non-infected, extirpated root canal, filled with blood sourced from the open apex that may, or may not, act as a suitable scaffold for the ingrowth of vital tissue enabling revascularisation of a previously avascular micro-environment. Little is known about how such an intervention may generate the signals required by stem cells to initiate and direct their division and maturation.

Whilst these techniques hold promise for regenerative dentistry, much remains uncertain in relation to the future of cell-based therapies for dentistry, and little is understood about how clinicians might be able to deliver signalling molecules to a transplanted scaffold that itself is suitable for placement within a root canal (Gupte and Ma, 2012, Kuang et al., 2015).

Complications have arisen in light of unrealistic expectations and the rapid advancement of science, and caution in the application of these techniques is advised until the limitations are better understood (Brooks, 2017).

5.4 Appraisal of the Literature

In 1972, Archie Cochrane proposed that healthcare interventions used within the NHS should be properly evaluated in terms of data arising from randomised controlled trials, to ensure effective use and maximum value of resources (Cochrane, 1972). Systematic reviews are considered the gold standard approach to developing evidence-based guidelines, and is a process by which the best available evidence relating to a research question is located, appraised and synthesised. The term meta-analysis developed later to describe statistical methods for combining the results of independent studies, and to distinguish the two different methodologies (Glass, 1976).

The Oxford Centre for Evidence-Based Medicine has defined levels of evidence (OCEBM Levels of Evidence Working Group 2011). Randomised controlled trials provide the highest levels of evidence that arise from comparative, experimental studies of healthcare interventions to determine treatment benefits and harms, as well as for diagnostic, prognostic and screening studies. The customary intention of systematic reviewers is to analyse data extracted from randomised controlled trials, describe the collective results, and to combine that data, if appropriate, with meta-analysis (Gosall and Gosall 2015).

Systematic reviews have the power to inform clinical decision-making in health care, thus it is imperative that a robust methodological approach is designed, conducted, and reported to minimise the risk of bias and error. Systematic reviews require investigators to assimilate critical appraisal skills and combine them with a transparent, explicit, predefined, reproducible and systematic protocol for appraising the literature. Systematic reviews may provide descriptive analysis of variations in study and intervention protocols, an estimate of the effects of an intervention, and may also describe areas where knowledge is lacking (Boland, Cherry, and Dickson 2014).

Four systematic reviews have previously addressed the efficacy, or effectiveness, of the individual interventions (Chala et al., 2011, Kontakiotis et al., 2014, Antunes et al., 2016, Lin et al., 2016b). No existing systematic reviews have sought to compare all the interventions, nor have they reviewed the literature for alternative approaches to the management of immature apices, despite the prevalent, and challenging, problem of non-vital, immature teeth, and the complexities of decision-making faced by clinicians.

It has been suggested that if existing reviews are identified that address the research question of interest, assessment of the review should take place to determine whether it is of sufficient quality to guide clinical practice (Centre for Reviews and Dissemination, 2009). Checklists are available for quality assessment of systematic reviews to aid critical appraisal (Table 2), (Centre for Reviews and Dissemination, 2009). There is great disparity in the methodological approaches of the existing systematic reviews, and in the subsequent equivocal conclusions that they have drawn, as presented in Table 3 Overview of previously published systematic reviews (continued overleaf) and discussed below. An optimal systematic review should use appropriate methods to carry out a comprehensive search, with clearly defined, criteria for study selection, quality assessment, and the extraction of data whilst remaining unbiased, reproducible and transparent (Gosall and Gosall, 2015). If these methodological and reporting processes are not well-documented, confidence in results and conclusions might be reduced.

Table 2 Checklist for quality assessment of systematic reviews

| | |
|----|---|
| 1. | Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs (PICOS)? |
| 2. | Was the search strategy adequate and appropriate? |
| 3. | Were preventative steps taken to minimise bias and errors in the study selection process? |
| 4. | Were appropriate criteria used to assess the quality of the primary studies, and were preventative steps taken to minimise bias and errors in the quality assessment process? |
| 5. | Were preventative steps taken to minimise bias and errors in the data extraction process? |
| 6. | Were adequate details presented for each of the primary studies? |
| 7. | Were appropriate methods used for data synthesis? Were differences between studies assessed? Were the studies pooled, and if so was it appropriate and meaningful to do so? |
| 8. | Do the conclusions accurately reflect the evidence that was reviewed? |

Table 3 Overview of previously published systematic reviews (continued overleaf)

| | Chala et al 2011 | Kontakiotis et al 2014 | Antunes et al, 2016 | Lin et al 2016 |
|--------------------|---|---|--|---|
| Journal | Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology | Journal of Endodontics | Acta Odontologica Scandinavica | Journal of the Formosan Medical Association |
| Aim | Compare the efficacy of CaOH and MTA for root end induction in immature roots and relative effectiveness regarding clinical success (systematic review and meta-analysis) | Assign levels of evidence to existing articles related to the outcome of REP and evaluate the clinical and radiographic outcomes of this treatment modality (systematic review) | Analyse the effectiveness of REP in the root formation of necrotic immature permanent teeth (systematic review) | Compare the efficacy of CaOH and MTA for apexification of immature permanent teeth (systematic review and meta-analysis) |
| Language | English and French | English | No language restriction | Not stated |
| Search date | 1966-November 2009 | January 1993-second week of December 2013 | Unclear - July 2014 | Inception-November 2015 |
| Databases | Medline, Scopus, hand searching | PubMed, Scopus, Cochrane, hand searching specific journals | Medline, Cochrane, Scopus, Web of Science, BVS, hand searching | Medline, Cochrane, Embase, Google Scholar, hand searching |
| MESH terms | Apexification, dental pulp necroses, root canal therapy, MTA cement, MTA, calcium hydroxide | Dental pulp, revascularization, revitalization, regenerative endodontic therapy | Pulp revascularization, endodontics | Apexification, permanent teeth, MTA, calcium hydroxide |
| Inclusion criteria | CaOH vs MTA Controlled trials Immature permanent teeth with unformed apices Irreversible pulp disease or chronic periapical periodontitis | Clinical study related to REP outcome Size of sample given Outcome based on clinical examination and radiographic interpretation Adequate clinical and radiographic follow-up of at least 6 months | Clinical studies evaluating pulp revascularization for incomplete root formation with pulp necrosis NaOCl for disinfection Antibiotic medication dressing Apical bleeding initiated | CaOH vs MTA Randomised controlled trials, prospective studies, retrospective studies, case series Immature permanent teeth requiring apexification Quantitative primary outcome data |
| Exclusion criteria | In-vitro Non-randomised studies Non-comparative studies | Not REP Animal studies, in vitro or ex vivo studies, review articles, letters, and opinion articles | Reviews, dissertations, theses, qualitative studies, case reports, textbooks, conference proceedings | <i>In-vitro</i> Letters, comments, editorials, case reports, personal communications |

| | Chala et al 2011 | Kontakiotis et al 2014 | Antunes et al, 2016 | Lin et al 2016 |
|--------------------------|--|---|--|---|
| Primary outcome | 'Success': Clinical (pain, TTP, root fracture, sinus) & radiographic (normal PDL, completion of lamina dura, absence of root resorption) | Not defined Assign levels of evidence to existing publications related to the outcome of REP | Not defined | Clinical success rate (not defined) |
| Secondary outcome/s | Apical barrier formation | Not defined Clinical and radiographic outcomes of regenerative endodontic therapy | Not defined | Radiographic success rate Apical barrier formation rate Time required for apical barrier formation |
| Assessed for eligibility | 24 (22 excluded as non-comparative studies) | 53 (2 excluded as inadequate clinical and radiographic findings, follow-up less than 6 months) | 17 (6 excluded as case report, irrelevant, no antibiotics used) | 15 or 16 (unclear) (10 or 12 excluded as qualitative outcomes, non-comparative studies or pulpotomy) |
| Conclusion | No statistically significant differences in success or apical barrier formation. Use CaOH or MTA Risk of bias (Jadad) | No RCTs included. No statistical analyses. 2 retrospective cohort studies likely biased (Newcastle-Ottawa Scale), low study quality. Regenerative endodontic therapy safe and effective. RCTs and/or more high-quality cohort studies would strengthen evidence | Heterogeneity and high risk of bias (interpret with caution). Pulp revascularization has capacity to stimulate apical closure and thickening of radicular dentine but much remains unknown. | No statistically significant differences in clinical or radiographic success or apical barrier formation rate. Time required for apical barrier formation significantly less in MTA group. MTA may be more successful if shorter treatment time equals improved patient compliance High risk of performance bias (Cochrane) |
| Studies included | El-Meligy et al 2006 Pradhan et al 2006 | 2 high-level cohort studies: Bose et al 2009 Jeeruphan et al 2012 8 case series 41 case reports | Jung et al 2008 Ding et al 2009 Petrino et al 2010 Nosrat et al 2011 Kim et al 2012 Jeeruphan et al 2012 Sonmez et al 2013 Jadhav et al 2013 Nagy et al 2014 Kahler et al 2014 Nagata et al 2014 | El-Meligy et al 2006 Pradhan et al 2006 Damle et al 2012 Bonte et al 2015 |

5.4.1 Review of the Existing Systematic Review Literature

Existing systematic reviews serve as a reference tool, and help to establish the justification for a novel review. Additionally, they are suitable sources for handsearching for studies that meet the inclusion criteria of a novel review. Study of existing systematic reviews, and of the guidance available for assessing the quality of systematic reviews as described, helps to inform future study design. Thus, a brief review of the systematic reviews introduced in Table 3 follows.

Chala et al, 2011

Chala, of Morocco, published a systematic review and meta-analysis that sought to compare the efficacy and effectiveness of calcium hydroxide apexification (control group) and mineral trioxide aggregate apexification (experimental group) for the endodontic management of immature teeth. Clinical and radiographic outcomes were combined to a single primary outcome of success which was assessed on binary data (e.g. success or failure). No description was provided of whether the included studies provided this data in binary format or whether the authors of the review modified and combined the results into a binary format.

No clarification of the reported outcomes of the included studies was provided. The radiographic arm of the primary outcome was met if a normal periapical area was present, there was completion of the lamina dura and the absence of root resorption. Clinical success was defined as the absence of pain, tenderness to percussion, root fracture and sinus tract. A secondary outcome was defined in relation to the osteoinductive properties of CaOH and MTA.

Screening for study design included only experimental, comparative studies and identified 300 records, of which 24 full texts were assessed for eligibility by two investigators. Two studies, reporting intervention for 50 teeth, were eligible for data extraction (El-Meligy and Avery, 2006, Pradhan et al., 2006).

Risk difference was calculated for the experimental and control groups with 95% confidence intervals. Reported similarities between the included studies were the use of dental dam, protocol for root canal dressing prior to mineral trioxide aggregate apexification, method of detection of apical barrier formation and final obturation material. Quality assessment of the included studies was completed using the Jadad scale (Jadad et al., 1996).

Quality scores were determined of 3 for the El-Meligy study and 1 for the Pradhan study. The included studies were reported to have homogeneity and no statistically significant differences between the interventions in relation to the primary outcome (risk difference $p=0.29$) or apical barrier formation ($p=0.76$). The authors concluded that either calcium hydroxide or mineral trioxide aggregate could be recommended for the apexification of immature teeth, as no discrepancy was apparent in terms of intervention outcome.

Kontakiotis et al, 2014

Kontakiotis, of Greece, published a systematic review that sought to assign levels of evidence, as defined by The Oxford Centre for Evidence-Based Medicine, to existing clinical articles related to the outcome of regenerative endodontic therapy. The study also aimed to evaluate the clinical and radiographic outcomes of REP and to evaluate them according to PICO format. Inclusion criteria were applied to 329 records, of which 53 full texts were assessed for eligibility. Some 41 case reports, 8 case series and 2 retrospective cohort studies (Bose et al., 2009, Jeeruphan et al., 2012) were eligible for data extraction.

No definition of the reported outcomes of the included studies was provided. No description was provided of how the authors extracted outcome data, or how the included studies described it, however resolution of periapical radiolucency and continued root development were the outcomes reported. The authors concluded that the majority of teeth exhibited a resolution of radiolucency, further increase in root length and root wall thickness, and apical closure at the follow-up period, and that there was not enough high quality evidence to answer the review question. Quality assessment of the included studies was completed using the Newcastle-Ottawa scale (NOS) for cohort studies. The authors awarded 6 stars for Bose study, and 7 stars for Jeeruphan study. No statistical tests were computed.

Antunes, of Brazil, published a systematic review that sought to complete a qualitative analysis of the effectiveness of regenerative endodontic procedures, referred to by the authors as pulp revascularization, for the endodontic management of immature teeth. The authors describe the conducting of an undefined sample search for studies using a combination of keywords, defined as pulp revascularization and endodontics, and chosen from Descriptors of Health Science (DeCS). Clinical research studies and case series published up to 2014 were included with the prerequisite that they met strict criteria in relation to the authors' chosen protocol for regenerative endodontic procedures (Banchs and Trope, 2004) as follows:

- Sodium hypochlorite had been used as a root canal disinfectant
- Triantibiotic medication had been used as a dressing material
- Apical bleeding had been induced and a blood clot produced

Primary or secondary outcomes were not defined. Data were extracted that related to the REP protocol, such as the method of root canal disinfection, the antibiotics employed, and the period of root canal dressing observed.

Screening identified 277 records of which 17 full texts were assessed for eligibility by two investigators. Eleven studies were eligible for data extraction. The number of participants reported in the included studies varied from 2 to 61. An account of the study design of those studies included in the final analysis was not provided. No assessment of risk of bias was carried out. Of interest, eight of the eleven included studies were published in the *Journal of Endodontics*. This contrasts with the previously discussed systematic reviews that compared CaOH and MTA. All studies included in those reviews were published in journals relating directly to the field of Paediatric Dentistry.

Diverse clinical protocols emerged from the included studies, despite the authors strict inclusion criteria. Examples include use of irregular concentrations of sodium hypochlorite (2.5-6%), the omission of minocycline from the antibiotic dressing material in three studies (each of which replaced minocycline with a unique antibiotic), and a variable root canal dressing period of between 1-4 weeks.

Sizable disparity was noted in relation to sealing of the coronal access, and in supplementation of the blood clot induced by manipulating the scaffold within the root canal with autologous platelet rich plasma or impregnating it with basic fibroblast growth factor. Participant withdrawal due to drop out, failure of compliance and failure to recall was a common finding. No quantitative data was extracted; hence no statistical analysis was carried out.

It was conveyed that there is a lack of standardisation in protocols and reported outcomes for REP and that modification of the previously described protocol used to define the inclusion criteria may have limited the usefulness of the review, and that caution is required in interpretation of the available evidence. Sufficient qualitative analysis took place to enable the conclusion that REP has the capacity to stimulate apexogenesis, albeit with reservations in relation to the means by which this process is resurrected, and the subsequent prognosis in later life.

Lin et al, 2016

Lin, of China, also published a systematic review and meta-analysis that sought to compare the efficacy and effectiveness of calcium hydroxide apexification (control group) and mineral trioxide aggregate apexification (experimental group) for the endodontic management of immature teeth. The primary outcome was clinical success rate. The authors did not further define this outcome or describe the data extracted from the studies in order to assimilate their results or carry out meta-analysis. Secondary outcomes were radiographic success rate, apical barrier formation rate and the time required for apical barrier formation. No descriptions were reported of how the authors determined whether the included studies met the review outcomes.

Screening identified either 216 or 217 records, of which either 15 or 16 full texts were assessed for eligibility by two investigators, and either 10 or 12 of those studies were excluded; unfortunately, data published in the text and in the flow diagram of study selection is contradictory. Four studies, reporting intervention for 80 teeth, were identified for data extraction in the published results tables (El-Meligy and Avery, 2006, Pradhan et al., 2006, Damle et al., 2012, Bonte et al., 2015).

Pooled odds ratios were calculated for the clinical, radiographic and apical barrier formation outcomes with 95% confidence intervals. Differences in means for the time taken to achieve apical barrier formation were calculated for the interventions. The authors reported that there was no significant heterogeneity between the studies. Similarities between the included studies were not described. An account of the study design of those studies included in the final analysis was not provided. Quality assessment of the included studies was completed using the Cochrane Collaboration's tool for assessing risk of bias (Higgins and Green, 2011).

The included studies were reported to have no statistically significant differences between the interventions in relation to clinical success rate (OR = 3.03, CI 0.42-21.72, $p=0.27$), radiographic success rate (OR = 4.30, CI 0.45-41.36, $p=0.20$) or apical barrier formation rate (OR=1.71, CI 0.59-4.96, $p=0.32$). There was a statistically significant difference in the time required for apical barrier formation between the interventions, with a pooled difference in means of -3.58 months, (CI -4.91 to -2.25, $p<0.001$). The authors concluded that CaOH and MTA have similar success rates, and that MTA may be more successful if it is assumed that a number of patients are expected to fail to complete treatment due to the increased intervention times necessitated by the CaOH technique in order to achieve an apical barrier.

The Lin review reported a low risk of bias for each of the four included studies in relation to incomplete outcome data and selective reporting. There was a high or unclear risk of bias present in the assessment of all studies in at least one other domain. The Pradhan study was reported to have the highest risk of bias, and the Bonte study the lowest risk of bias.

5.4.2 Methodological Quality and Internal Validity

In order to assess the quality of published studies that might be included in a systematic review, appraisal of the literature for reporting methodological qualities of comparative studies will be briefly described.

The methodological quality of studies included in a systematic review can have a substantial impact on the estimates of the treatment effect, yet there is no agreed single tool available for measurement of the methodological quality of randomised control trials (Verhagen et al., 2001). Study quality has been defined many times in the literature. For example, the quality of randomised controlled trials has been defined as “*the likelihood of the trial design to generate unbiased results*” (Jadad et al., 1996) and more recently, as “*the likelihood of the trial design to generate unbiased results, that are sufficiently precise and allow application in clinical practice*” (Verhagen et al., 2001). For all study types, quality has been described as “*the degree to which a study employs measures to minimise bias and error in its design and analysis*” (Khan, 2011).

Quality assessment allows systematic reviewers to identify methodological quality, and hence the risk that bias may have been inadvertently introduced to the planning, conduct, analysis or reporting of a study (Gosall and Gosall, 2015). Quality assessment might also include consideration of errors such as whether those responsible for delivering the interventions had been appropriately trained and calibrated, and whether a valid, reliable and appropriate outcome measure had been used. Thereby, critical appraisal of study quality determines methodological rigor and internal validity, and in the case of randomised trials defines those studies that are, in fact, pseudo-randomised, enabling clinicians to make trustworthy, evidence-based choices about the healthcare that they provide.

Statistical analysis and reporting of randomised controlled trials in dentistry are suboptimal (Jokstad et al., 2002, Harrison, 2003, Tu et al., 2006, Dumbrigue et al., 2006, Al-Namankany et al., 2009, Marshman and Farid, 2010, Pandis et al., 2010, Cioffi and Farella, 2011, Bearn and Alharbi, 2015). A minority of authors adhere to revised CONSORT guidelines, designed to aid the transparent reporting of randomised controlled trials (Moher et al., 2001).

Many authors do not appropriately minimise selection, allocation detection, or attrition bias, compromising the validity of the results (Tu et al., 2006, Leow et al., 2016, Higgins et al., 2011). It is thought that quality of published studies and journal impact factor are not correlated (Barbui et al., 2006, Cioffi and Farella, 2011).

Registration of randomised controlled trials prior to study commencement at the ISRCTN registry (World Health Organisation and International Committee of Medical Journal Editors) and ClinicalTrials.gov (National Library of Medicine) is encouraged by many peer reviewed journals in an attempt to improve the methodological quality, statistical analysis, and reporting of studies. Likewise, the prospective registration of systematic reviews at PROSPERO (National Institute for Health Research) is encouraged in order to avoid duplication of effort, and reduce opportunity for reporting bias.

Systematic reviewers may pool homogeneous results from well-conducted randomised controlled trials for meta-analysis. Combining the results of individual studies in a meta-analysis increases power and precision in estimating intervention effects. Careful judgement is required when integrating different study types. If meta-analysis is not appropriate due to the nature or number of the studies, it is important that systematic reviews instead assess that adequate statistical design and analysis has been conducted (Centre for Reviews and Dissemination, 2009)

5.4.3 Quality Assessment Tools

Methodological quality measurement tools for randomised controlled trials have been designed to aid the critical analysis and quantification of a study's internal validity (Moher et al., 1995). In excess of 200 quality assessment tools have been previously identified, few of which are suitable for assessment of randomised studies in health care (Centre for Reviews and Dissemination, 2009). Assessment tools may be limited in relation to both reliability, and validity, hence even following methodological quality measurement, the results of randomised control trials should be interpreted with caution (Moher, Jadad, and Tugwell 2009). Tools are frequently constructed as checklists or scales. Whilst numerical scores obtained from the use of scale tools may appear to grade studies according to quality, a total quality score does not provide information about which components of a study did not minimise bias and error.

Frequently used tools in the methodological quality measurement of randomised control trials in dentistry include the Jadad scale (Jadad et al. 1996), the Cochrane Collaboration's tool for assessing risk of bias (Higgins and Green 2011), and the CRD's checklist (Centre for Reviews and Dissemination 2009).

The Newcastle-Ottawa scale (Wells et al. 2012) is commonly used for assessing non-randomised studies. Notably, the Cochrane Collaboration recently recognised the value of developing a tool for risk of bias assessment for non-randomised studies and are in the process of piloting a novel tool that will be discussed later in this thesis (Sterne et al. 2014).

There is currently no consensus on how investigators should incorporate quality assessment for a range of study designs within a systematic review (Centre for Reviews and Dissemination 2009). Additionally, it is noted that individual studies may have conflicting results as a result of variations in study methodology, delivery of the interventions, outcome measurement, bias, and chance.

5.4.3.1 *The Jadad Scale*

The Jadad scale is a tool used to determine the quality of randomised studies by assessing the description and extent of randomisation, blinding, and complete outcome data. The tool is composed of three questions, supported by additional instructions. The questions are as follows:

1. Was the study described as randomised?
2. Was the study described as double-blind?
3. Was there a description of withdrawals and dropouts?

A study may score up to five points from these three questions as per the tool's instructions to provide additional points to studies in which the authors describe an appropriate method of sequence generation for randomisation, and an appropriate method of double-blinding. Likewise, points may be deducted for studies that describe inappropriate methodology for sequence generation or blinding.

The inter-rater reliability of the Jadad scale is high (0.48-1.00 intraclass correlation coefficients, 0.37-0.89 Kappa values, test retest reliability 0.98). However, the scale is simple and does not take in to account additional criteria of methodological quality. The scale is strongly affected by blinding which may not be appropriate in all clinical comparator studies, such as those investigating endodontic interventions with differing radiographic appearances to one another, hence validity of this tool may be questionable.

5.4.3.2 *The Cochrane Collaboration's Tool for Assessing Risk of Bias*

The Cochrane Collaboration discourage the use of scoring systems, such as the Jadad scale, for assessment of the internal validity of a study (Higgins and Green 2011). Moreover, The Cochrane Collaboration prefer to omit the term 'quality' in describing the assessment of internal validity. Differences between research conduct and adequacy of the subsequent reporting of that research are cited as reasons for this preference. Use of the Jadad scale is explicitly discouraged due to the tool's emphasis on research reporting, and due to its omission of analysis of allocation concealment in randomised trials.

The Cochrane Collaboration's tool for assessing risk of bias for parallel group trials is constructed across the following six domains;

1. Sequence generation (selection bias)
2. Allocation sequence concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective outcome reporting (reporting bias)
7. Other potential sources of bias (such as systematic differences between the groups at baseline, at delivery of the interventions, or in how outcome assessments are determined and reported).

Investigators attempting to use this tool are perhaps more likely to encounter difficulties in completing risk of bias assessment if incomplete reporting prevents completion of the analysis for each domain. The tool requires investigators to make supported judgements based upon the information available to them in terms of risk of bias being high, low or unclear.

Furthermore, the use of both a content and a methodological expert in data extraction is encouraged, in order that bias is correctly assessed and weighted in terms of importance in formation of this judgement.

5.4.3.3 The Centre for Reviews and Dissemination Checklist

The CRD's checklist for quality assessment is accompanied by detailed guidance for its appropriate use (Centre for Reviews and Dissemination 2009). Subjective judgements are made of allocation, selection, detection, attrition and outcome reporting bias. The tool is adaptable to suit the needs of individual systematic reviewers (Boland, Cherry, and Dickson 2014).

5.4.3.4 Quality Assessment of Studies Using the Newcastle-Ottawa Scale

The content validity and inter-rater reliability of the Newcastle-Ottawa scale (Wells et al. 2012) for assessing non-randomised studies have been established. The tool is widely used and is frequently adapted by investigators in order that it meets the needs of their study (Boland, Cherry, and Dickson 2014). The 8-item checklist developed as a result of recognition of the biases that are inherent to non-randomised studies. Studies are scored with stars that are used to indicate quality elements in respect of cohort selection (e.g. representativeness of the target population), comparability of the cohorts (e.g. accounting for confounding factors), and assessment of outcome (e.g. follow-up). A maximum of 9 stars can be awarded to a study, and this score represents the highest quality.

5.4.3.5 The MINCIR Scale

The MINCIR scale may be a valid and reliable tool for assessment of study quality in dental research (Cartes-Velasquez et al. 2014), however its use is not widely reported in English speaking journals.

5.4.3.6 *The Delphi List*

The Delphi list is a 9-item criteria checklist devised following Delphi consensus by methodological experts, with a trichotomous (yes/no/don't know) scoring system (Verhagen et al. 1998). Inter-rater reliability is reported to range from 0.54 to 0.85 intraclass correlation coefficient. The questions are as follows:

1. Was a method of randomisation performed?
2. Was the treatment allocation concealed?
3. Were the groups similar at baseline regarding the most important prognostic indicators?
4. Were the eligibility criteria specified?
5. Was the outcome assessor blinded?
6. Was the care provider blinded?
7. Was the patient blinded?
8. Were point estimates and measures of variability presented?
9. Did the analysis include an intention-to treat analysis?

5.4.3.7 *Further Considerations*

Quality criteria, specifically designed for evaluation of randomised controlled trials in which an active-control group is used, have been described in periodontal research (Tu et al. 2006):

1. Did the research aim describe test of equivalence or superiority?
2. Was the superiority/equivalence margin specified before study commencement?
3. Was the appropriate null hypothesis tested?
4. Was the required sample size calculated?
5. Was the active control used shown to be effective?
6. Were both treatment regimens applied in an optimal fashion?
7. Was the appropriate statistical analysis chosen, and was its interpretation correct?

Tu et al. reported that there was a lack of compliance with the quality criteria described that might undermine the validity of the included studies. The authors stated that by publishing the findings of their review there might be a subsequent improvement in the quality of periodontal research.

It has been suggested that a number of factors may be correlated with research quality that are not routinely assessed using established quality measurement tools, for example, collaboration between a large group of authors on one paper (Cartes-Velásquez and Manterola 2017). Incorporation of additional criteria in the assessment of methodological quality of comparator studies with an active control group may be judicious, to distinguish between studies that have been appropriately designed to test superiority and equivalence, and those which have not. Finally, it has been proposed that the external validity of a study should also be considered when determining the overall quality of research, in order to consider the likely impact of the results in a real-world setting (Khan 2011).

In summary, a great many tools are available for quality assessment and critical appraisal of published research, and in particular, for randomised controlled trials. Systematic reviewers have a wealth of choice for the tool that they employ to report study quality, and thus, risk of bias, in order that the trustworthiness of the evidence-base can be established and guidance for clinical practice disseminated.

5.5 Securing the Opinion of Clinicians through Surveys

The optimal intervention for non-vital, immature permanent teeth requiring root end closure is a matter of debate amongst specialists in paediatric dentistry, endodontics and across the wider arena of dentists who provide treatment to children. Survey of clinicians who provide endodontic treatment for children may provide insight into treatment planning and intervention practices.

5.5.1 Designing a Survey of Multidisciplinary Specialists

Surveys may be classified as a type of descriptive, or exploratory, or explanatory, observational study that use correlational techniques to enable investigation of whether experience, opinions, behaviours and knowledge are related to, and can predict, one another (Burns et al., 2008). The dental literature contains a multitude of surveys, many of which target specialists and consultants for their perceptions and management approaches to a variety of clinical situations. These studies demonstrate a varied approach towards data collection, as will be illustrated in chapters 6 and 7.

A small number of surveys have been published that relate, in part, to the management of non-vital, immature teeth. The first of these surveys was designed to determine the level of agreement between a total of 354 paediatric dentists and endodontists, attending a symposium of the American Association of Endodontists and the American Academy of Pediatric Dentistry, in relation to vital pulp therapy (Seale and Glickman, 2008). Of the participants, 71% were paediatric dentists. An electronic audience response system with a 5-point Likert scale was used to survey agreement from participants about whether, from a public health perspective, regenerative endodontic procedures might become an acceptable intervention.

Sufficient agreement was found to support the collaborative production of pulp therapy guidelines, the latest revision of which endorse the use of MTA apexification procedures (American Academy of Pediatric Dentistry, 2014). Most participants agreed that regenerative endodontic procedures would become a viable treatment modality for immature, permanent teeth with apical periodontitis prior to 2018. Concerns raised by both specialities in relation to regenerative endodontic procedures included a lack of evidence, unpredictability, complex case selection criteria and the use of an antibiotic intracanal medicament.

A postal survey of 56 UK consultants in paediatric dentistry, with a specialist society cohort and a response rate of 78.6%, found that at least half of responders agreed that material and equipment costs, coupled with a lack of available evidence were disadvantages to the use of MTA for apical barrier formation of non-vital immature permanent incisors (Mooney and North, 2008). Some 54.5% of responders used MTA as an alternative to calcium hydroxide apexification and 36.4% used MTA when calcium hydroxide apexification had failed. Regenerative endodontic procedures were not investigated.

An online survey, with an Australian endodontic specialist society cohort of 499 members and a response rate of 41.7%, investigated the use of MTA for endodontic procedures with the primary purpose of assessing the perceived need for receiving further training (Ha et al., 2016). The authors reported that 77.2% of responders had carried out a regenerative endodontic procedure, and that 96.3% would choose MTA apexification where an apical barrier is required. This study did not compare use of the two interventions but did conclude that the greatest barrier to use of MTA for Australasian general dental practitioners is lack of experience.

This contrasts with an earlier survey of 29 European postgraduate paediatric dentists in which the authors concluded that although MTA is in regular endodontic use in postgraduate training across Europe, material cost and the appropriateness of alternative materials are recognised barriers to its increased use (Foley, 2013). There are no previously reported surveys of specialists in paediatric dentistry, or endodontics, to determine their experiences, opinions, and decision-making practices, in relation to the common and complex clinical problem of non-vital, immature incisors.

5.5.2 Survey Design Features That Encourage Participation

A cover letter that is designed to appeal to those with positive attitudes toward surveys may produce behavioural intentions that encourage a response, as per the reasoned action theory (Ajzen and Fishbein, 1980). Questionnaires with cover letters from universities may have a greater response rate than those which originate from commercial organisations (Edwards et al., 2002). An unpredictable percentage of the study cohort are likely to have a tendency to be consistent in responding to received surveys in order to help others, as per the cognitive dissonance theory (Festinger, 1957).

Responders may enjoy completing surveys and contributing to research (Dillman et al., 2014). The concept of social exchange in relation to survey design determines that people are more likely to comply with a request to respond if the survey incorporates elements that appeal to such behaviours, such as personalisation of the cover letter and repeated follow-up (Dillman, 1978, Dillman et al., 2014). Non-response postcards may capture non-responders' reasons for opting out of participation and encourage those who had little time to respond to take part (Locker, 2000).

5.5.3 Development of a Novel Survey Tool

Development of a survey tool is facilitated by item generation, the purpose of which is to address themes on which to construct a questionnaire in order to answer the research question (Saris and Gallhofer, 2014). Item generation might consider the evidence-base and include discussion of the research question with potential responders and clinical content experts. Item reduction serves to balance the researcher's requirements for information with the length of a questionnaire and responder burden (Abbott and McKinney, 2013). Iterative pre-testing and piloting of a novel survey tool, such as a newly designed questionnaire, enhances item reduction.

Most research questions are addressed with fewer than 25 items (Passmore et al., 2002). However, reducing the length of a questionnaire does not necessarily improve the response rate unless it is considerably shortened (Bolt et al., 2014). Question stems should contain fewer than 20 words and should be non-judgemental (Stone, 1993, Burns et al., 2008).

It is generally accepted that question stems should adopt a neutral tone if responders are required to express their opinion (Creswell, 2009). Response formats may be designed to include open-ended or closed-ended questions. Closed-ended questions may include binary, nominal (unordered, mutually exclusive options) or ordinal (such as Likert-type scales) responses. Likert-type scales can be incorporated to determine participant agreement with a statement according to predetermined categories ranging from "strongly agree" to "strongly disagree". Providing an "other" response option is appropriate in enabling participants to provide unanticipated answers and is thought to alter the balance of power between the participant and the investigator, and may improve response rates (O'Cathain and Thomas, 2004).

5.5.4 Survey Administration

Self-administered postal questionnaires enable contact with large study cohorts quickly and efficiently, in a standardised and prespecified approach, particularly where contact address information is readily available. Electronic prompts may increase response rates for postal questionnaires and reduce the overall time taken to receive responses (Clark et al., 2015). Web-based surveys may be 2.68 times more cost-effective than postal surveys, and allow for pre-programmed data extraction, reducing the possibility of human error (Hardigan et al., 2012).

Interestingly, although email is a common method of invitation for completion of Web-based questionnaires, there is some debate as to whether it is the most effective approach, and it has been suggested that text message invitations to complete smartphone surveys result in a greater and faster response (De Bruijne and Wijnant, 2014).

Email addresses may be recorded incorrectly, or infrequently accessed. It has been suggested that younger dentists, and those who routinely handle electronic dental records, may be more likely to complete a web-based rather than a postal survey (Funkhouser et al., 2014). It is noted that responders may be less likely to misplace an email than a postal survey, received to a busy workplace or to a personal residence. The possibility of untrustworthy electronic contact and fraudulent links, or the mishandling of personal data, may discourage participation in web-based surveys. There is a lack of agreement about whether offering a choice of response modes increases (Scott et al., 2011), or decreases survey participation (Smyth et al., 2010, Millar and Dillman, 2011, Medway and Fulton, 2012).

5.5.5 Reminders and Repeat Contact

There is a lack of agreement regarding the benefit of reminders to participate in survey research. A response rate of 40% to the first mailing of a postal survey is expected to have a response rate of between 12 and 50% following distribution of a follow-up reminder to non-responders (Dillman, 1978, Sierles, 2003, Glidewell et al., 2012). The employment of multiple strategically timed mixed-mode reminders may be useful in increasing participation (Dillman et al., 2014).

A randomised controlled trial concluded that there was no difference in response rate for those who receive an e-mail reminder compared with those who receive a postal reminder, and that pre-notification of questionnaire delivery and email delivery of questionnaire reminders do not improve response rates (Starr et al., 2015). It is noted that actions that are taken to encourage return of a completed postal survey, may not aid those who intend to participate, but simply forget to respond, return or misplace, their replies.

5.5.6 Confidentiality Without Anonymity

Self-administered postal questionnaires that incorporate identifier codes allow for tracking and targeted engagement of the study population, and enable repeat contact of non-responders. The external validity of a survey may be improved if a greater response rate can be achieved by tracking non-responders. Identifier codes can be used with confidentiality to protect anonymity once response data has been collated and the codes have been destroyed.

Confidentiality without anonymity surveys may reduce the financial burden of survey administration as they allow direct contact of non-responders, and avoid additional response burden from those who have already responded (Sierles, 2003).

5.5.7 Dillman's Total and Tailored Survey Design Methods

Dillman's principles for survey design and administration provide the basis of a classic, and updated, total and tailored design method for survey research that claims to guarantee a response rate of 75-80% (Dillman, 1978, Dillman et al., 2014). This claim has been tested with success (Hoddinott and Bass, 1986).

The principles of the total design method stipulate design features for a questionnaire, and the inclusion of a personalised cover letter which clearly describes the purpose of a study, with an explanation of why the invited participant's opinion is important. Investigators are advised to sign by hand each individual cover letter in blue ink. A return postcard and stamped, preaddressed envelope is suggested for inclusion.

Dillman advises that responses may be either anonymous or trackable. It is suggested that a reminder is sent one week following mailing, and that repeat contact with new copies of the questionnaire, and a precisely formatted cover letter, is made at three and seven weeks following the first mailing.

It is recommended that the third mailing of the questionnaire is via recorded delivery. Drawbacks of the total design method include the financial costs associated with repeated contact and utilisation of recorded delivery of questionnaires.

The tailored design method considers the potential of technology, such as email and web-based applications, to decrease the financial costs associated with the total design method, and the time required to collect and enter data in to databases for analysis. The limitations of these approaches in relation to the quality of responses returned, and the reduced ability to track responders is acknowledged.

5.5.8 Bias in Surveys

Intentional and unintentional bias may be introduced by the researchers in relation to their questions if question stems are directive and introduce the preconceptions of the researcher (Dillman et al., 2014).

It is often impracticable for researchers to administer a survey to an entire study population; hence, a sample is often selected following identification of an appropriate sampling frame. Sample selection can be random (via probability design) or deliberate (via non-probability design). If the sampling frame does not reflect the population of interest, selection bias will be introduced, limiting the generalisability of the results (Burns et al., 2008).

The return of incomplete responses may introduce incomplete response bias if partially completed questionnaires are excluded from analysis, and therefore if the actual response rate differs from the analysable response rate. If incomplete questionnaires account for less than 5% of responses, complete case analysis is considered to be an acceptable method of addressing missing data (Graham and Schafer, 2009). If complete case analysis is conducted when a large number of incomplete responses are received there is a risk of making incorrect assumptions about the missing data which may result in biased estimates and a reduction of power (Schafer, 1999). If incomplete responses account for greater than 5% of responses, missing data can be managed with multivariate imputation by chained equations (MICE) (Raghunathan et al., 2001, Azur et al., 2011). Alternatively, item non-response may be managed with imputation. It is suggested that imputation is carried out if item non-response is greater than 10% (Aday, 1996).

Social desirability and recall bias may obstruct survey research. Social desirability bias tends to be of greatest concern when researchers are in direct contact with participants, for example in structured interviews and telephone surveys, and lowest for surveys completed in the absence of the researcher (Kreuter et al., 2008). However, it is noted that even in the case of pertinent, anonymous online surveys, such as that to determine the management of wrong site surgery by oral surgeons, social desirability bias, and perhaps an aversion towards admitting human error, may obstruct participation (McKernon et al., 2017).

The validity, reliability and generalisability of survey research might be undermined by poor participation rates, and a failure of the researchers to consider the impact of non-response bias. Recommendations for minimum response rates to ensure the validity of the results is not affected by non-response bias varies between 60 and 70% (Sierles, 2003, Burns et al., 2008).

A response rate of 80% is deemed to be high (Evans, 1991). It has been suggested that results of greater validity will be achieved if random sampling of the target population is carried out to reduce the size of study cohort, and subsequent efforts are focused on achieving as high a response rate as possible (Parashos et al., 2005).

A review of 77 self-administered postal surveys of dentists, published in 4 dental journals (British Dental Journal, Journal of Prosthetic Dentistry, Journal of the American Dental Association and Dental Update) carried out in 1997, reported a mean response rate of 64% (range 17-100%) (Tan and Burke, 1997). The authors concluded that the subject of interest, questionnaire length and inclusion of an incentive might influence response rate. They found that specialists tended to provide a better response rate than general dentists, and that paediatric dentists had a mean response rate of 85%, however, only one survey of paediatric dentists was included. Nevertheless, the response rate for paediatric dentists was higher than for all other dental specialties, such as oral surgery (73%), orthodontics (73%), conservative dentistry (69%) and periodontology (42%). No surveys of endodontists included.

Mean response rates of 54% to 61% for postal surveys of medical clinicians have been reported in systematic reviews (Asch et al., 1997, Cummings et al., 2001). It has been reported that survey response rates of medical physicians in the USA were fairly static between 1985 and 1995, at an average of 61% (Cummings et al., 2001). The same authors reported that response rate decreased to an average of 52% for studies with a cohort larger than 1000 participants, and that only 44% of survey researchers discussed non-response bias.

More recently, it has been reported that survey response rates of healthcare professionals are frequently low and may be declining (Cook et al., 2009). Response rates of Canadian medical clinicians are reportedly declining as a result of office policy and agreement (Wiebe et al., 2012). Thus, the reasons for clinician response and non-response may be complex and may include such a predetermined decision not to voluntarily participate in surveys.

Factors influencing response rates of clinicians in survey research will be investigated further in the next chapter of this thesis.

5.5.9 Reporting

Complete and transparent reporting of research is imperative in order that the relevance of the results can be fully understood. It is recognised that recommendations for the reporting of research may improve study quality (Plint et al., 2006). Unfortunately, dental journals may not endorse the use of reporting guidelines or provide instructions for authors (Hua et al., 2016).

The *strengthening the reporting of observational studies in epidemiology* (STROBE) statement has been developed as a reporting guideline by a network researchers and methodologists to provide guidance on how to report observational studies (von Elm et al., 2014). There is limited consensus and guidance regarding the optimal reporting of survey research in medical journals, and it has been suggested that an extension of the STROBE guidelines to incorporate surveys may enhance the quality of published survey research (Bennett et al., 2011). Without such guidance, quality criteria are predictably variable, resulting in inconsistency that may affect the validity and reliability of the results.

Authors frequently do not transparently report survey methodology (Cummings et al., 2001). An analysis of the reporting practices of survey researchers published in renowned medical specialty journals revealed that only 25-50% published response rates (Bennett et al., 2011). Likewise, when perusing the literature, it appears that an overwhelming majority of authors do not report sampling frame, eligibility criteria, mode of administration, handling of missing item data, or methods of data analysis. As a result of this lack of guidance for survey researchers, it was proposed that a study of the recent survey literature of UK dentists be carried out, in order to analyse the factors that influence clinician response rates, and to aid design of a valid survey of clinicians who provide endodontic treatment for children.

5.6 Outcomes of Endodontic Intervention

Endodontic success encompasses outcomes that are primarily patient-based, such as tooth survival, resolution of infection, and acceptable dental aesthetics, combined with outcomes that are primarily clinician-based, such as radiographic healing, apical closure, and in the case of regenerative endodontic procedures, continued root development and response to vitality testing. It is noted that clinician-based outcomes, such as radiographic healing and the absence of root resorption, are associated with patient-based outcomes, such as tooth survival and the resolution of inflammation.

The importance of clinician vs patient-based outcomes is of interest and is investigated later in this thesis (chapter 7: Investigating the Decision-Making Practices of Specialists in Paediatric Dentistry and Endodontics: A Self-Administered Postal Survey). Evidence from *in-vitro* and *in-vivo* studies supports the importance of coronal seal and root canal obturation in combination for successful, predictable endodontics (Williams and Williams, 2010). Regenerative endodontic procedures challenge this evidence and perhaps indicate the imperative role of coronal seal.

There is little consistency in the reporting of outcome measures in studies of traumatic dental injuries. A systematic review of the outcomes reported in clinical trials of traumatic dental injuries reported that apical closure was the only outcome reported consistently in five included studies that compared interventions for non-vital immature teeth (Sharif et al., 2015). Few studies reported clinical outcomes. Outcomes assessed radiographically were restricted to the absence of root resorption, and the time taken for apical closure. Studies of clinical and radiographic outcomes of interest in the endodontic intervention of non-vital, immature teeth are discussed as follows, and a newly defined primary outcome measure is proposed.

5.6.1 Clinical Assessment of Periapical Health and Disease

Patient-based outcomes, including resolution of the clinical signs and symptoms of periapical disease and functional tooth retention, are arguably of greater importance for patients and the carers of children than clinician-based, notably radiographic, outcomes.

Clinical assessment of periapical health and disease is frequently defined as the absence of signs and symptoms of periapical inflammation. The characteristics of periapical disease include the presence of pain, soft tissue pathology or swelling, tooth mobility, and tenderness to percussion. The clinical outcomes of endodontic intervention are similarly defined, and also include tooth survival, clinical success, avoidance of the need for a repeat endodontic procedure, avoidance of adverse events, and retention of an aesthetically acceptable tooth (de Chevigny et al., 2008, Kontakiotis et al., 2014, Alobaid et al., 2014, Diogenes et al., 2016).

Clinical outcomes that may predict a successful regenerative endodontic procedure have been widely discussed in the literature. It has been suggested that magnetic resonance imaging, or laser Doppler blood flowmetry, that provide objective measurement of clinical outcome are necessary to detect true endodontic regeneration and vitality assessment (Murray et al., 2007). However, due to the expense and impracticalities of introducing such assessments into routine practice, the literature supports clinical outcomes that encompass asymptomatic teeth that do not require further endodontic intervention.

To date, the following guidance suggests that clinical outcomes recorded for regenerative endodontic procedures include:

5.6.1.1 *Clinical procedures for revitalization: current knowledge and considerations (Galler, 2016)*

- Absence of signs and symptoms of inflammation
- Positive response to sensibility testing

5.6.1.2 *European Society of Endodontology position statement: Revitalization Procedures (Galler et al., 2016)*

- Absence of pain
- Absence of signs and symptoms of inflammation
- Positive response to sensibility testing
- Patient acceptance
- No unacceptable colour changes

5.6.1.3 *American Dental Association Specialty Update (Diogenes et al., 2016)*

- Resolution of disease (absence of swelling, drainage, and pain)
- Tooth survival and function
- Tooth aesthetics
- Positive vitality response

5.6.1.4 *The American Association of Endodontists Clinical Considerations for a Regenerative Procedure Revised 6-8-16 (American Association of Endodontists, 2016)*

- Absence of pain, soft tissue swelling or sinus tract
- Positive pulp vitality test response

5.6.2 Radiographic Assessment of Periapical Health and Disease

Periapical health, or post-endodontic healing, is anticipated in the absence of clinical indicators of periapical disease, coupled with radiographic assessment of the root, apex and the surrounding tissues to confirm the absence, or healing, of periapical infection and bone destruction. Clinical indicators may be absent despite existing, or escalating, periapical infection. Histological review of the periapical tissues is impracticable. Clinicians are, therefore, compelled to perform visual evaluation of intraoral, bidimensional, conventional periapical radiographs as a fundamental component of routine examination when diagnosing periapical disease to evaluate the success of endodontic intervention.

5.6.3 Imaging and Image Analysis

Non-standardised intraoral, bidimensional, conventional radiographs may produce inconsistent images at different angulations as a result of craniofacial growth and tooth development. Such images should be interpreted with caution when monitoring changes in root canal length and thickness, and likely lack construct validity. Furthermore, it is accepted that definitions and interpretation of radiographic success varies amongst clinicians (Bender et al., 1966b). Hence, the interpretation of conventional radiographs is subject to intra and inter-rater variation in perception that may reduce the reliability of outcome assessments (Bender et al., 1966a, Brynolf, 1970, Goldman et al., 1972, Reit and Hollender, 1983, Zakariassen et al., 1984).

Tridimensional cone beam computerised tomography (CBCT) has recently established a recognised role in evaluation of endodontic lesions (Lofthag-Hansen et al., 2007, Durack et al., 2011, Patel et al., 2012, Tyndall and Kohltfarber, 2012). The prevalence of periapical periodontitis is reported to be significantly higher with CBCT than with conventional radiography (Estrela et al., 2008, de Paula-Silva et al., 2009, Tsai et al., 2012). CBCT is considered to have a useful role in endodontics where conventional radiography fails to provide adequate diagnostic information and is justified only at limited-volume, high-resolution exposure for selected cases, such as resorption lesions, atypical root canal anatomy and surgical endodontic procedures (Horner and Eaton, 2013, Patel et al., 2014).

The effective dose of ionising radiation for a CBCT with a small field of view is estimated to range from 11-214 μ Sv, compared to 0.3-21.6 μ Sv for a single intraoral plain film radiograph (Horner and Eaton, 2013). In keeping with the ALARA principle for minimising the effective dose of ionising radiation, the benefits of transformation of plain film intraoral radiographs outweigh the risks of CBCT, particularly in radiosensitive children (ICRP, 2007, Patel et al., 2014).

ImageJ software, (ImageJ v 1.48, US National Institutes of Health, Bethesda, MD), with TurboReg plug-in, (Lausanne, VD, Switzerland), is an open source processing software designed for use with multidimensional scientific images. The programme, and various others available on the market, allows mathematical transformation of JPEG format images following their morphological standardisation, in order to achieve digital alignment (Pérez and Pascau, 2013) .

The digital alignment of non-standardised radiographs with the use of ImageJ software permits unbiased assessment of radiographic dimensional changes over time and retrospectively in a growing patient with developing teeth (Bose et al., 2009).

It has been reported that not all teeth may undergo digital standardisation successfully, and that whilst quantitative analysis may control for changes in radiograph angulation it may conversely introduce errors as a result of tooth positioning and dental development (Kahler et al., 2014). For example, multirooted teeth may be difficult to analyse with ImageJ software if there is overlap of the roots. The ImageJ technique for the digital alignment of non-standardised radiographs has been refined to develop and validate a reliable method of reporting radiographic outcomes following endodontic intervention for immature teeth by defining radiographic root area (RRA), which is useful for studies of regenerative endodontic procedures of single rooted teeth (Flake et al., 2014). The purpose of measuring RRA is to account for dimensional changes that may occur in a developing root, if the location of those changes is unknown.

No significant differences were reported between conventional radiographic images analysed following standardisation with ImageJ software and CBCT images for measurements of root length, root thickness and apical diameter taken *in-vitro* in a sheep model (Altaii et al., 2016a).

However, the same authors also reported that *in-vivo* conventional radiographs reliably reveal significant increases in root length, root wall thickness and narrowing of the apical diameter of the canals following regenerative endodontic procedures in the mandibular incisors of sheep (Altafi et al., 2016b).

Prior to Flake et al.'s validation of this method of measuring RRA, investigators typically measured dimensional changes in root width over time by choosing a single point for measurement on the dentinal root wall, usually, at the commencement of the apical third (Cehreli et al., 2011, Jeeruphan et al., 2012). This point may not have been reproducible in a growing child, and it is not known whether root development occurs at a consistently progressive rate over the entire root surface area. Hence, measurement of RRA may be more reliable. RRA accounts for the entire planar surface area of the immature root, providing a more comprehensive assessment than a single linear measurement.

Teeth treated with regenerative endodontic procedures have been reported to exhibit a significant increase in root length and width in comparison to control teeth treated with MTA apexification, or calcium hydroxide apexification, following digital standardisation of radiographs, which may validate the biological changes of maturogenesis that occur following regenerative endodontic procedures (Jeeruphan et al., 2012, Nagy et al., 2014). However, other similar, retrospective studies that employed digital standardisation, ImageJ software and RRA reported radiographic changes following regenerative endodontic procedures but did not detect statistically significant differences between regenerative endodontic procedures and mineral trioxide aggregate apexification (Alobaid et al., 2014).

5.6.4 Outcome Reporting of Radiographic Assessment of Periapical Health and Disease

In routine practice, resolution of periapical infection is assessed both clinically and radiographically, with clinical judgement applied to determine the outcome. Clinicians may conclude that the radiographic predictors of periapical health are present or absent, or that they are favourable, uncertain, or unfavourable.

Radiographic outcomes recorded for the purposes of research can be measured on intraoral, bidimensional, conventional, plain film radiographs, consistent with routine clinical practice, or with the aid of image processing software programmes as discussed. Reporting of dichotomous measurements, supported by qualitative descriptions of root development, is typical of case reports and retrospective studies of regenerative endodontic procedures (Chueh et al., 2009, Chen et al., 2012b). Quality guidelines for endodontic treatment indicate that the radiographic outcomes of root canal treatment may alternatively be categorised as favourable, uncertain or unfavourable, when considered in the absence or presence of clinical signs or symptoms of periapical infection (Claus, 2006, Sarris et al., 2008).

Three indices, the Strindberg index, (Strindberg, 1956) probability index, (Reit and Gröndahl, 1983) and periapical index, (Orstavik et al., 1986) have been widely used for evaluation of periapical radiographs.

The Strindberg index utilises a trichotomous outcome for success (healthy) and failure (diseased), plus a third category for uncertain outcomes, provided that the preoperative periapical condition and the treatment completion time are known. The index is used to determine health if there is radiological evidence of a normal periodontal ligament space, a decrease in the size of the periapical lesion compared with preoperative radiographs, and the absence of root resorption

The probability index was later proposed as an application of statistical decision theory to the diagnosis of periapical radiographs in response to the impact of different observers applying different diagnostic criteria for periapical disease. This index requires assessment of the presence of periapical destruction of bone according to five defined categories.

The periapical index (PAI) was presented latterly as a valid and reasonably accurate scoring system for registration of apical periodontitis in radiographs. The PAI presents an ordinal five score scale ranging from healthy to severe periapical periodontitis with exacerbating features. Scoring is determined by visual and descriptive comparison of the radiograph in question with a PAI reference radiograph, of which five are available. These reference radiographs and corresponding line drawings were chosen as characteristic of the five steps of periapical inflammation from a study that correlated the radiographic appearance of periapical lesions with histological examination (Brynolf, 1967). The system was designed for use in epidemiological studies, clinical trials and retrospective analyses of treatment outcomes and has similar accuracy and reproducibility to the periodontal index (Shaw and Murray, 1977). The PAI scores appear to have prognostic value for the course of periapical disease over a period of five years for root filled and non-root filled teeth (Kirkevang et al., 2015).

The Strindberg system has been reported to have a lower intra-rater variation compared with the PAI and the probability index, whilst the PAI has a lower inter-rater variation compared with the Strindberg system and the probability index (Tarcin et al., 2015). The PAI and the probability index may both be considered to have cut off points for success (health in which periapical structures are normal or small) and failure (disease associated with changes in bone structure or destruction) to provide dichotomous outcomes which may enhance intra and inter-rater agreement.

Radiographic outcomes that may predict a successful regenerative endodontic procedure have been widely discussed in the literature. To date, the following guidance suggests that radiographic outcomes recorded for regenerative endodontic procedures include:

5.6.4.1 Clinical procedures for revitalization: current knowledge and considerations (Galler, 2016)

- Evidence of resolution of periapical lesions
- Continued root development, visualised as an increase in root length and root width
- Completion of root formation

5.6.4.2 *European Society of Endodontology position statement: Revitalization Procedures (Galler et al., 2016)*

- Healing of pre-existing bony periapical lesion
- Increase of root thickness and length
- Absence of (continued) external root resorption
- Radiographic detection of a new PDL along the inner wall of the root canal

5.6.4.3 *American Dental Association Specialty Update (Diogenes et al., 2016)*

- Radiographic signs of healing
- Radiographic signs of root development (recorded either with non-quantitative dichotomous (yes/no) outcomes supported by qualitative descriptors of the radiographic findings, or with radiographic software that enables digital alignment of non-standardised plain film radiographs for unbiased measurement of dimensional changes).

5.6.4.4 *The American Association of Endodontists Clinical Considerations for a Regenerative Procedure Revised 6-8-16 (American Association of Endodontists, 2016)*

- Resolution of apical radiolucency (often observed 6-12-months after treatment)
- Increased width of root walls (this is generally observed before apparent increase in root length and often occurs 12-24 months after treatment)
- Increased root length

The American Association of Endodontists further advise that radiographic outcomes that suggest maturogenesis are desirable but not essential, for the success of regenerative endodontic procedures, and secondary to elimination of symptoms and evidence of bone healing, albeit of greater importance than positive response to vitality testing.

In addition to outcomes of endodontic success, preoperative root dimensions may also be assessed radiographically and may influence treatment planning of non-vital, immature teeth. For example, radiographic assessment that reveals the presence of a particularly immature tooth, with divergent apical morphology, an unfavourable crown root ratio, and thin dentinal walls that are liable to fracture during instrumentation or under masticatory forces, may lead a clinician to decide that attempting a regenerative endodontic procedure might be beneficial, rather than resign the tooth to predetermined fate if it is managed with an apexification procedure that affords no scope for further development. It is expected that not all clinicians planning the endodontic management of immature teeth will have the knowledge, skill, experience or materials required to offer a range of endodontic interventions for the purposes of root end closure, hence, root dimensions may play a lesser role in the treatment planning of these clinicians.

Formation of an apical barrier, against which gutta percha can be condensed, can be assessed at the time of placement of an apical plug of mineral trioxide aggregate with conventional radiography. Apical closure with calcium hydroxide is expected to progress more slowly, and may be assessed both clinically, via tactile instrumentation, and via repeat radiographic assessment at each occasion of root canal dressing. Apical closure with regenerative endodontic procedures might also be expected to take place over a period of time which has yet to be narrowly defined, but which might be similar to 'natural' apexogenesis, and which may be monitored radiographically. Apical closure is notably absent in most of the guidance for radiographic outcomes for regenerative endodontic procedures presented above.

Periapical bone healing is an intended outcome of both regenerative endodontic procedures and mineral trioxide aggregate apexification, as a consequence of resolution of periapical infection. However, root development is not expected following mineral trioxide aggregate apexification. Radiographic evidence of continued root development following regenerative endodontic procedures provides clinicians with dependent measurements that inform decision-making and substantiate clinician-based outcomes. Various degrees of root development have been reported; as a lack of subgroup analysis within those studies, the factors that contribute to predictable root development and maturogenesis following regenerative endodontic procedures remain largely unknown (Diogenes et al. 2016).

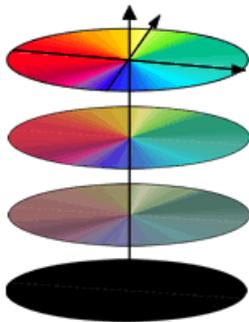
5.6.5 Outcome Assessment Observation Period

Post-endodontic follow-up typically takes place up to 12-months following obturation of the root canal in order that clinical and radiographic assessment of periapical healing can occur (Ross et al., 2009). Standardised protocols do not yet exist for follow-up of regenerative endodontic procedures, in which obturation does not occur, but in which the process of apexogenesis is anticipated. Final follow-up periods in the literature range from six months (Jeeruphan et al., 2012), 24 months (American Association of Endodontists, 2016) to five years (Galler et al., 2016). Three monthly follow-up for one year has been advocated (Wigler et al., 2013).

5.6.6 Tooth Colour

Spectrophotometry is the science of quantifying and describing human colour perception. Tristimulus is the amount of each of the primary light colours (red, green, blue) needed to create a given colour. A colour space describes a model for quantifying a colour, most frequently as tristimulus values, representing positions in a three-dimensional space of colour (Figure 1). Such descriptive mathematical models exist because humans perceive colours differently to one another, and scientists and artists alike strive to communicate colour precisely.

Figure 1 CIE L*a*b* colour space



The CIE colour space system is an internationally approved method of quantifying, reliable and specific descriptions of all possible colours that the human eye can detect (Commission Internationale de l'Eclairage, 1931, Choudhury, 2014). CIE colour spaces are device-independent, unlike for example, the RGB (red, green, blue) additive colour space, and the CMYK (cyan, magenta, yellow, key) subtractive colour space, both of which are device-dependent.

The CIE $L^*a^*b^*$ colour space model is a linear colour chart that uses lightness (L^*), red-greenness (a^*), and yellow-blueness (b^*) as its tristimulus values. The vertical axis represents lightness (L^*) and its value ranges from zero to 100 in which zero is absolute blackness and 100 is maximum lightness. Lightness is the degree to which colours appear to reflect light. Two horizontal axes, at right angles to each other, are represented by a^* and b^* . These axes cross in the neutral centre. The a^* axis is green at one extremity (represented by $-a$), and red at the other ($+a$). The b^* axis has blue at one end ($-b$), and yellow ($+b$) at the other. The value of the centre of each axis is zero.

A spectrophotometer is a device used to record, and match, colour. The device records 31 reference points along the visible colour spectrum and reduces these to tristimulus values in order to convert them to coordinates for a desired colour space.

VITA Easyshade® (Panadent) is a spectrophotometer with a measurement range of 400-700nm. The manufacturer's user guide indicates that this electronic shade matching system may be utilised to support tooth shade determination and communication when combined with clinical photography.

The digital device has been primarily designed for the assessment of tooth shade and shade matching in relation to porcelain or composite restoration or for placement of prosthetic teeth to aid patient satisfaction.

The device features a calibration feature to enhance accuracy of its measurements and its outputs have been designed to incorporate those of established standard shade matching systems, also produced by VITA.

The difference between two colours can be expressed as Delta E (ΔE). The difference between the L^* , a^* and b^* values of two measurements of tooth shade may be calculated as ΔE . The ΔE single value for colour and lightness shows how far apart in distance visually two measurements of tooth shade are in the colour space. ΔE is calculated as follows (CIE 1976):

$$\Delta E_{ab}^* = \sqrt{(L_2^* - L_1^*)^2 + (a_2^* - a_1^*)^2 + (b_2^* - b_1^*)^2}$$

The significance of colour difference, for example, between the pre- and postoperative clinical crown of an endodontically treated tooth, may be considered in terms of the colour difference that is detectable visually (perceptibility) and the colour difference that most individuals would consider unacceptable (acceptability) (Alghazali et al., 2012). The perceptibility and acceptability of colour difference varies between, and within individuals, over time. Perceptibility and acceptability of colour difference may be affected by viewing conditions, the position of the observer, and the object being viewed (Ragain Jr and Johnston, 2000).

The clinical significance of colour difference has been reported in the literature. In a study of dentists' tolerance of colour difference of prosthetic teeth, 50% of individuals perceived colour difference at 2.6 ΔE units, and 50% of individuals were reported to reject acceptability of colour difference at 5.5 ΔE units (Douglas et al., 2007). A further study of a larger group of individuals that included technicians, dentists, nurses and researchers' tolerance of colour difference of prosthetic teeth reported that 50% of all observers could detect a colour difference at 1.9 ΔE units and that 50% of all observers found colour difference to be unacceptable at 4.2 ΔE units (Alghazali et al., 2012). All observers could detect colour difference at 5 ΔE units and found colour difference to be unacceptable at 8.6 ΔE units. (95%CI). There were significant differences between the observer groups; there were however, no significant differences between the dentists and non-dental researchers who acted as lay people. The authors concluded that mean colour perceptibility thresholds were significantly lower than mean colour acceptability thresholds for all observer groups.

This conclusion supported earlier research that thresholds for colour difference perceptibility were significantly lower than thresholds for acceptability, and that mean acceptability thresholds for colour difference was 1.1 ΔE units for red-varying metal-ceramic crowns (CIEa) and 2.1 ΔE units for yellow-varying metal-ceramic crowns (CIEb) (Douglas and Brewer, 1998).

A study of 22 participants with tooth discolouration that occurred following root canal dressing of avulsed, replanted teeth with either Ledermix (Henry Schein UK [Holdings Limited]) or calcium hydroxide reported that both medicaments induced colour difference over a 12-month period (Day et al., 2011). ΔE was deduced following assessment of clinical photographs, rather than with a spectrophotometer; mean ΔE for the Ledermix group was 8.1 units (described as a grey-brown discolouration) and for calcium hydroxide was 5.4 units (described as a yellowing discolouration). It can therefore be deduced that for this group of participants who had suffered tooth avulsion, endodontic intervention resulted in both perceptible and unacceptable colour difference in tooth shade.

An *in-vitro* study of the tooth staining potential of endodontic materials has been reported that utilised a spectrophotometer to deduce ΔE following preparation of bovine teeth to receive prespecified endodontic cement, irrigants and dressing materials (Dettwiler et al., 2016). ΔE was deduced at specified intervals for a period of 12 months.

Calcium silicate cements containing additional bismuth oxide induced ΔE values of 22.2 units, whereas alternative, commercially available cements containing bismuth oxide, did not induce colour difference. Endodontic irrigants, including chlorhexidine 2% solution, did not induce colour difference. Triple and double antibiotic pastes that did not contain tetracycline derivatives, such as minocycline, induced ΔE values of 14.9 units, hence the authors concluded that omission of tetracycline derivatives may not guarantee colour stability following regenerative endodontic procedures.

An earlier study of colour difference induced by root canal dressing materials containing clindamycin, doxycycline or demeclocycline (Ledermix) in extracted human teeth with mature apices investigated the role of exposure to light on colour change (Chen et al., 2012a).

The authors reported that all tested dressing materials contributed to reduced tooth lightness values, with the greatest darkening of tooth roots induced by demeclocycline, a material with a yellow/green appearance.

The implications of altered dental appearance that arises as a result of incisal fractures is reported in the literature as follows, however, no studies of tooth colour difference as a result of regenerative endodontic procedures vs mineral trioxide aggregate apexification could be found.

Assessment of appearance is subjective, yet there is a recognised association between quality of life and dental appearance (Jokovic et al., 2002, Broder et al., 2007). If an iatrogenic change in tooth colour is induced following endodontic intervention for a traumatic dental injury, perceptible and unacceptable colour difference might impact on a young person's quality of life. Children may raise concerns in relation to tooth colour and their perception of the appearance of traumatic dental injuries may be unpredictable; young children may be more concerned about tooth discolouration and fractured incisors than young adults, perhaps due to an association of fractured teeth with dental pain, or perhaps as a result of impact on dental appearance (Vlok et al., 2011).

A validated tool is available for chairside assessment of whole mouth dental aesthetics that may aid communication between clinicians and young patients (Modi et al., 2010). No validated tools are available to support the assessment or communication of dental appearance following a traumatic dental injury or endodontic intervention. Such a tool would be beneficial for this population who often experience tooth colour change following a traumatic dental injury. Self-perception of smile attractiveness is reported to be critically affected by tooth colour (Van der Geld et al., 2007). A cross-sectional survey of adult female dental patients has revealed that tooth discolouration may negatively influence social perceptions; individuals with discoloured teeth were deemed to have poorer social competence, intellectual ability, psychological adjustment and relationship status than those with whiter teeth (Kershaw et al., 2008). A high proportion of the UK adult population report dissatisfaction with mild tooth discolouration (Alkhatib et al., 2004).

Dental appearance may also influence the self-esteem of children of primary school age. Children with a self-perception of attractive dental appearance are more likely to believe themselves to be better performers at school, be slimmer, have more friends, more money and better health than children with a self-perception of poor dental appearance (Bos et al., 2008). Children transitioning to secondary school who are satisfied with their physical appearance, and who do not have visible dental differences such as tooth discolouration, report fewer impacts on their oral health related quality of life than children with visible dental differences, suggesting that visible dental differences impact on self-perception (Rodd et al., 2012).

Psychosocial factors may influence a child's adaptation following a traumatic dental injury (Porritt et al., 2015). Whilst coping strategies may play an important role in how children adjust to visible dental differences, dental appearance was reported to be the fourth most common reason for bullying of school children almost 40 years ago (Shaw et al., 1980). Dental clinicians have an important role in recognising the importance of bullying, the role of dental aesthetics as a possible contributor, and the associated likely impact on self-esteem and oral health-related quality of life (Seehra et al., 2011).

Simple interventions aimed at addressing tooth discolouration resulting from enamel defects can achieve an improvement in self-perception of school children's confidence and happiness (Rodd et al., 2011). Restoration of incisal fractures following dental injury might have psychosocial benefits (Rodd et al., 2010a). Hence, it can be presumed that interventions aimed at addressing tooth discolouration following dental injury, such as appropriate access to tooth whitening procedures, are important to children and young people. Regrettably, a legal and ethical dilemma was imposed on dental clinicians wishing to manage tooth discolouration for children by the introduction of an amendment to the EU Directive concerning cosmetic products (Council Directive, 2011/84/EU).

As a consequence of the directive, an amendment to the law governing cosmetic products was made, and on 31 October 2012, tooth whitening products containing or releasing more than 0.1% hydrogen peroxide were prohibited for use on any person under 18 years of age (Asch et al., 1997). The legislation appropriately limited tooth whitening procedures to the practice of dentistry.

Unfortunately however, the regulations did not provide therapeutic exception for children with tooth discoloration, resulting following a traumatic dental injury, or as a consequence of endodontic intervention (Kelleher, 2014). The General Dental Council advised registrants that any dental professional in breach of the legislation would be subject to fitness to practise proceedings, despite producing standards that preclude dental professionals from discriminating in relation to age in their clinical practise, and requiring that they act in the best interests of their patients (General Dental Council, 2013).

On 29th May 2014, the General Dental Council updated their position statement in relation to tooth whitening, advising that “*products containing or releasing between 0.1% and 6% hydrogen peroxide cannot be used on any person under 18 years of age except where such use is intended wholly for the purpose of treating or preventing disease*”. Dental clinicians continue to face a legal and ethical dilemma, albeit without the likelihood of imposition of fitness to practise measures, in relation to addressing tooth discoloration for children who have suffered traumatic dental injuries. Hence, it is imperative that for children in the UK at present, endodontic interventions induce minimal iatrogenic change in tooth colour, and serve to correct tooth discoloration established as a result of injury and pulpal necrosis.

Review of the colour literature has drawn together subjective assessments of tooth colour difference that can be recorded chairside via clinical photography, with the objective spectrophotometry recordings of researchers measuring colour difference that might occur, for example, following the delivery of dental interventions for non-vital, immature teeth. It has been established that ΔE values of greater than 2 units may be perceptible to an observer, and that ΔE values of greater than 4 units may be unacceptable.

In summary, review of the literature has revealed disparity in the outcome measures that are used in diverse study types to define endodontic outcomes for non-vital, immature teeth. Endodontic outcomes may be of primary interest to patients, clinicians, or researchers. If an ideal outcome were to be defined, it might aim to incorporate the interests of these parties, whilst establishing a consistent measure for standardisation of outcome reporting for affected children.

6 How do UK Dentists, Paediatric Dentists and Endodontists Respond to Survey Research? A Study of Response Rate

6.1 Research Question

- 6.1.1 Do dentists and dental specialists participate favourably in survey research?
How do survey design and administration influence response rates?

6.2 Clarification of Research Question and Scope

6.2.1 Introduction

Surveys of dental professionals generate research questions, inform practice, and guide innovation. Well conducted surveys are valid and reliable research tools that report the experience, knowledge, opinion and practices of clinicians. Poor response rates may undermine external validity. Critical appraisal of the literature in relation to survey methodology has revealed a multitude of design and administration features that may influence response rate (chapter 5).

Despite the availability of opinion papers, published within the dental literature to aid survey researchers, little agreed guidance exists that might improve the quality of survey research. Those that seek to guide researchers in light of this sparsity of guidance have discussed that the design and method of questionnaire administration influence response rate and the quality of collected data (Williams, 2003), and highlighted the need for transparent reporting guidelines (Sierles, 2003, Bennett et al., 2011). A study of the recent survey literature of UK dentists and the factors that influence clinician response rates is described.

6.2.2 Response Rates for Surveys of Paediatric Dentists and Endodontists

A postal survey of 234 UK specialists in paediatric dentistry to determine knowledge of behavioural management techniques, was designed according to Dillman's and Edwards' recommendations and yielded a response rate of 45% (Coxon et al., 2017). Responders were tracked and non-responders received repeat contact on two occasions. There was no financial cost associated with participation. No incentive was offered. Questionnaire length was relatively short. The researchers discussed the implications of non-response and concluded that non-response may be associated with poor knowledge or experience in the subject matter.

An online survey, distributed via email to 52 members of a specialist society of UK paediatric dentistry trainees, to determine their experience of molar incisor hypomineralisation, yielded a response rate of 71% (Kalkani et al., 2016). Data collection was anonymous, no reminder or repeat contact was made and no incentive was offered. There was no financial cost associated with participation. Questionnaire length was relatively short. The researchers briefly discussed the effect of non-response bias on the validity of the survey's results.

A postal survey of 180 systematically selected UK endodontists yielded a higher response rate of 82.8% in relation to attitudes towards fractured endodontic instruments (Madarati et al., 2008). No information was available with regards to survey length or costs of participation, however, non-responders were tracked and contacted on a further occasion. A prize draw incentive was offered. The researchers discussed that 70-80% response rates are optimal to minimise the risk of bias, however, they also referenced literature that suggests that response rates of 50-70% should be expected in surveys of the dental profession, and that a response rate of 43% may have minimal response bias if interpreted appropriately.

A postal survey of 170 specialist UK endodontists yielded a response rate of 79% (Orafi and Rushton, 2013). The survey was designed to compare the practice of the endodontists with that of 857 general dental practitioners in relation to length determination in endodontics. No information was available with regards survey length. Non-responders were tracked and contacted on two further occasions. There was no financial cost associated with participation. No incentive was offered. The researchers concluded that their response rate was at the top end of the typical response rate for dental surveys.

Interestingly, survey research of dentists carried out in the USA reports far lower response rates than survey research of UK dentists. A 25-item online survey of members of the American Academy of Pediatric Dentistry aimed to determine the practice of responders in relation to the use of coolant in high speed handpieces (Kupietzky et al., 2013). The investigators concluded that the response rate of 43% was higher than expected and noted the inclusion of a large, but unspecified, number of incomplete responses.

A later, 55 item, online survey, disseminated to 6335 members of the American Academy of Pediatric Dentistry to investigate practice with nitrous oxide sedation, yielded a response rate of 26%, leading the investigators to conclude that the practice of non-responders may not be reflective of current standards of care (Wilson and Gosnell, 2016).

A similar 28 item online survey was disseminated to 1973 members of the International Association of Paediatric Dentistry (IAPD) and the European Academy of Paediatric Dentistry (EAPD) to establish the opinion of members in relation to sedation in paediatric dentistry. A response rate of 16% was reported, leading the investigators to conclude that the cohort may have little interest in the subject, and that reliable email contact may be limited by incorrect contact details and language barriers (Wilson and Alcaino, 2011).

An 8 item online survey of 3076 members of the American Association of Endodontists which aimed to determine practice in relation to cone-beam computed tomographic (CBCT) imaging in endodontics yielded a completed response rate of 35.2% despite the brevity of the questionnaire and the specialty's evolving interest in CBCT (Setzer et al., 2017).

A 40-item paper survey was distributed to a group of 32 specialty dental trainees attending a study day to determine their expectations for regenerative endodontic procedures. The response rate was 97% which might be predicted given the nature of the opportunistic environment and cohort available for data collection (Manguno et al., 2012).

A 24 item online survey of 3255 active members of the American Association of Endodontists in relation to the impact of the US economy on their practice yielded a response rate of 26.9% (Lin et al., 2015), which was similar to an online survey of the same cohort in relation to trends in endodontic irrigation materials which yielded a response of 28.5% (Dutner et al., 2012).

Survey Methodology and Response Rate

It is sensible to accept that survey design and administration are likely to influence response rate. A substantial portion of the survey methodology literature is focused on improving response rates by increasing the benefits of participation, reducing the costs of participation, and establishing the trust of the study cohort (Burkell, 2003, Parashos et al., 2005, Stephen et al., 2007, Wren and Showers, 2010, Scott et al., 2011, Glidewell et al., 2012, Sánchez-Fernández et al., 2012, Olsen et al., 2012).

It is suggested that there are many variables that may impact on an individual's decision to participate in a survey of clinicians. The style, appearance and layout of a self-administered survey may be as important as a topical and interesting research question in generating a response (Edwards, 2010). Commencing a survey with non-sensitive demographic questions may aid response rate, yet tracking of responders may reduce response rate (Burns et al., 2008). Response rates may also decrease if participants are offered the opportunity to opt out (Edwards et al., 2009).

The target population may be more likely to respond if the benefits of doing so outweigh the costs (Singer, 2011). Survey completion demands participant attention and time. Reducing the length of a survey, avoiding question repetition and negating the need for responders to answer every question in full might improve response rate (Brace, 2013, Dillman et al., 2014). It is noted that this approach may introduce item response bias.

The importance of the research question to the individual clinician, the inclusion of a cover letter that provides a good first impression, the attractiveness of the questionnaire, and the burden of time required to complete responses are considered to be important (McColl et al., 2002). The evidence in relation to the importance of questionnaire length and item number is inconclusive (Asch et al., 1997).

It has been suggested that monetary incentives (Singer, 2002, Singer and Ye, 2013), investigating interesting questionnaire topics and using recorded mail delivery may double the odds of receiving a response, whilst pre-notification, assurance of confidentiality, follow-up contact that provides a second copy of the questionnaire, shorter and personalised questionnaires, university sponsorship and the use of stamped rather than franked return envelopes may also substantially increase response rates (Edwards et al., 2009).

The literature supports the effective use of financial incentives, such as gift certificates or small gift items (Stephen et al., 2007, Wren and Showers, 2010, Olsen et al., 2012). Evidence for the effectiveness of an incentive is not always supportive (Glidewell et al., 2012), however, it indicates that fewer small prizes may be an effective means of improving response rate and that the incentive offered should appeal to the target population (Sánchez-Fernández et al., 2012, Buck et al., 2012).

6.2.3 The Significance of Response Rate

It has been suggested that a survey's response rate serves only as an indication of the extent of study non-response bias and that thresholds for response rate may be inappropriate (Asch et al., 1997). Despite this, it is noted that a high response rate produces more precise data for analysis, hence improving generalisability, thereby increasing the confidence in the results of a study (Burkell, 2003). It is suggested that response rate may be indicative of the quality of data collected in survey research (Williams, 2003).

It is recommended that response enhancement strategies and the handling of the direction and extent of non-response is taken in to account when determining the validity and generalisability of survey research (Locker, 2000). Race and ethnicity do not appear to be related to response rate (Sykes et al., 2010).

Hence, a study of the literature was proposed to determine whether UK dentists, paediatric dentists and endodontists, participate favourably in survey research, and to ascertain whether survey response rates had remained static in dentistry over the course of recent decades, following the advent of the online administration of surveys. Additionally, the literature was searched to summarise the factors of survey design and administration that might influence response rates in surveys of UK dentists.

6.2.4 Primary Objective

- Compare mean response rate for surveys of UK dentists, paediatric dentists and endodontists, and compare this data to that reported by previous authors.

6.2.5 Secondary Objectives

- Describe recent survey research to assess the experience, knowledge, opinion and practices of UK dentists.
- Describe methodological factors that may influence response rates.
- Determine whether survey researchers consider non-response bias in the external validity of their publications.
- Inform the design of a novel survey tool

6.3 Method

A literature search was conducted using the terms dent*, survey, questionnaire, experience/knowledge/opinion/practice. The results were limited to self-administered surveys of UK dentists. Duplicate results were removed. Surveys of undergraduates, non-dentists, and those with a sample size of less than 10 were excluded. The 100 most recently published surveys of UK dentists were identified.

6.4 Data Collection and Analysis

A standardised, pre-piloted data collection form was used to extract data from the included studies. Data extracted included:

- Name of first author
- Year of publication
- Journal
- Primary objective (experience/knowledge/opinion/practice)
- Field of dentistry
- Sample size (n)
- Method of administration (postal/online/mobile application/in person)
- Repeat contact (yes/no)
- True anonymity for participants without any reporting of tracking non-responders, including coded tracking (yes/no)
- Estimated time taken to complete survey (minimum <5minutes/moderate 5-10 minutes/complex >10 minutes/unclear)
- Copy of the survey questions provided (yes/no)
- Financial cost of participation (e.g. if postal, provision of a stamped return envelope yes/no)
- Incentive for participation (yes/no)
- Number of responders (n)
- Response rate reported (yes/no)
- Calculated response rate (n)
- Discussion of non-response bias/generalisability of response rate (yes/no)

If any of the above data were not described they were assumed to be absent from the methodology, hence, not included, with the exception of estimated time taken to complete the survey, in which an unclear option was reported. Response rate was calculated for all included studies (number of responders / sample size x 100) in order to standardise a true response rate, prior to the management of partially completed responses by the researchers. It was accepted in advance that researchers would likely manage missing response data and partially completed responses using a variety of techniques, hence this predetermined approach to the calculation of response rate for the purposes of this review.

Data was entered into SPSS software (Statistics 24, IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) for statistical analysis.

6.5 Results

Data from 100 surveys were available for data extraction and analysis.

6.5.1 Mean response rate for surveys of UK dentists, paediatric dentists and endodontists

Response rate was analysed for all included studies and described as mean response rate per specialty (Figure 2).

Surveys of dentist's career choices (n=1, 92% response rate), dental materials (n=2, 86% response rate), continuing professional education (n=5, 69% response rate), radiography (n=2, 68% response rate) and oral medicine (n=1, 67% response rate) achieved the highest response rates of all included studies. Surveys of paediatric dentistry (n=14), stress in dentists (n=2) and endodontics (n=4) each achieved a response rate of 66%. Surveys of general dental practice (n=17) which had a response rate of 56%.

Mean response rate for all included surveys was 59.6% (SD 18.1, range 16-100%).

Mean response rate for paediatric dentists was 66.1% (SD 15.8, range 24-87%).

Mean response rate for endodontists was 65.7% (SD 16.3, range 42-77%).

Response rate data were categorised as follows:

- <25%
- 25-50%
- 51-75%
- >75%

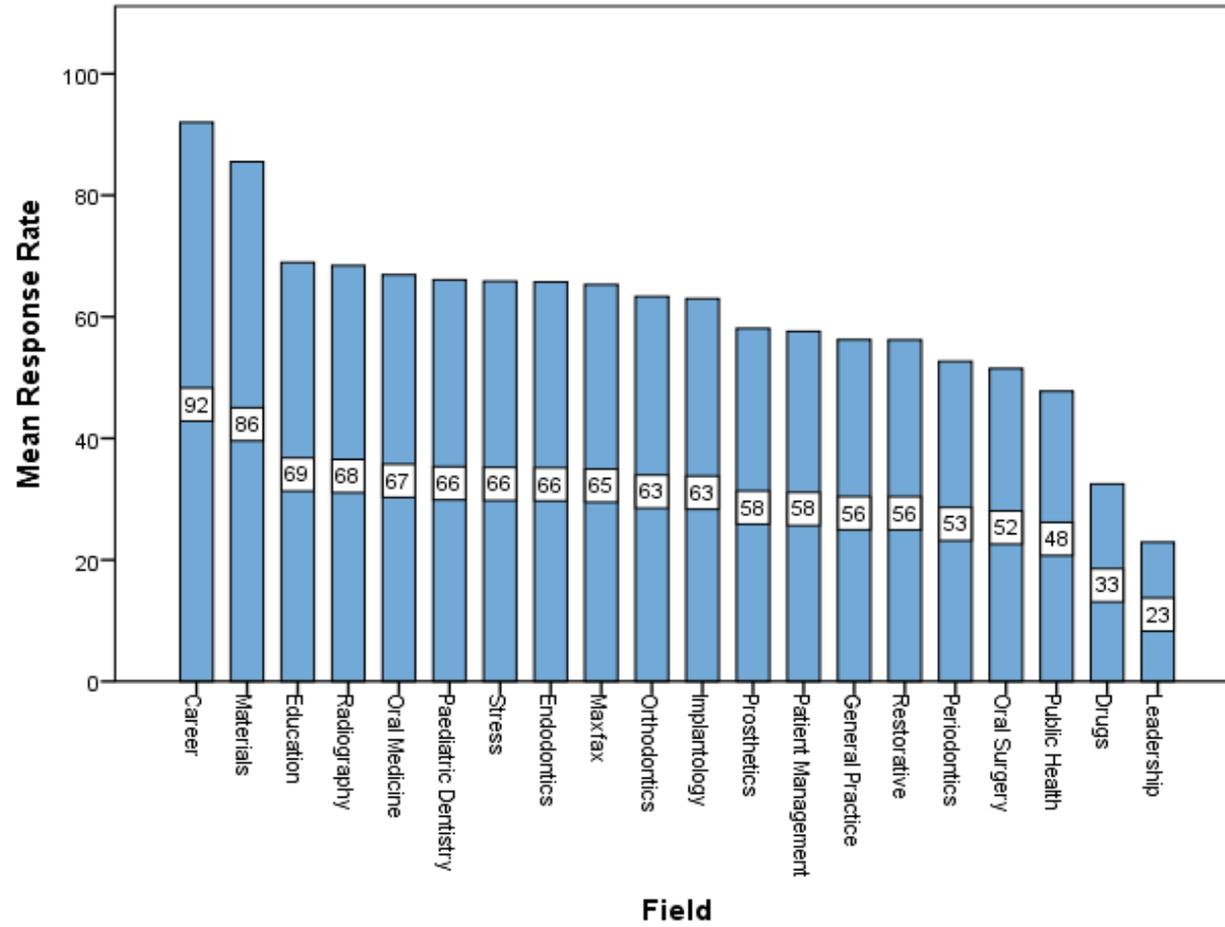
A majority of all included surveys (56%), surveys of paediatric dentists (64%, n=9) and of endodontists (50%, n=2) had a calculated response rate of 51-75% (Table 4).

Table 4 Response rate of 100 most recently published surveys of clinicians in dentistry

| | | Response Rate | | | | Total No. Surveys/Field |
|-------|-----------------------|---------------|--------|--------|------|----------------------------|
| | | <25% | 25-50% | 50-75% | >75% | |
| | Stress in Dentistry | 0 | 0 | 1 | 1 | 2 |
| | Restorative Dentistry | 1 | 2 | 7 | 0 | 10 |
| | Radiography | 0 | 0 | 2 | 0 | 2 |
| | Public Health | 1 | 0 | 3 | 0 | 4 |
| | Prosthetics | 0 | 2 | 3 | 0 | 5 |
| | Periodontics | 0 | 2 | 0 | 1 | 3 |
| | Patient Management | 0 | 3 | 5 | 1 | 9 |
| | Paediatric Dentistry | 1 | 0 | 9 | 4 | 14 |
| | Orthodontics | 1 | 1 | 3 | 3 | 8 |
| | Oral Surgery | 1 | 1 | 1 | 1 | 4 |
| | Oral Medicine | 0 | 0 | 1 | 0 | 1 |
| | Maxillofacial | 0 | 0 | 3 | 0 | 3 |
| | Dental Materials | 0 | 0 | 1 | 1 | 2 |
| | Leadership | 1 | 0 | 0 | 0 | 1 |
| | Implantology | 0 | 1 | 0 | 1 | 2 |
| | General Practice | 1 | 4 | 11 | 1 | 17 |
| | Endodontics | 0 | 1 | 2 | 1 | 4 |
| | Education/CPD | 0 | 0 | 4 | 1 | 5 |
| | Drugs | 0 | 3 | 0 | 0 | 3 |
| | Career Choices | 0 | 0 | 0 | 1 | 1 |
| Total | | 7 | 20 | 56 | 17 | 100 |

Some 92% (n=92) of researchers reported response rate. There was variation in the reporting practices of response rate. Researchers reported total response rate, response rate following inclusion or exclusion of incomplete responses, and in some cases, response rates which did not match the sample size and number of responders reported. The field of dentistry with the greatest percentage of published surveys that did not report a response rate was paediatric dentistry (14% of paediatric dentistry surveys, n=2).

Figure 2 Mean response rate per field of dentistry



6.5.2 Recent survey research in dentistry to assess the experience, knowledge, opinion and practices of UK dentists

The most recent 100 surveys of UK dentists that met the inclusion criteria were published 1990-2017. 40% (n=40) of all surveys were published in the British Dental Journal. Surveys in the field of paediatric dentistry were published in the International Journal of Paediatric Dentistry (7%, n=7), the European Journal of Paediatric Dentistry (2%, n=2), The British Dental Journal (2%, n=2), Community Dentistry and Oral Epidemiology (2%, n=2), and Dental Traumatology (1%, n=1). All surveys in the field of endodontics were published in the International Endodontic Journal (4%, n=4).

Surveys were designed to investigate experience (5%, n=5), knowledge (9%, n=9), opinions (40%, n=40), and practice (46%, n=46). 20 fields of dentistry were surveyed (Table 4). Some 14% (n=14) of surveys were of paediatric dentists, second only to that of surveys of those working in general dental practice (17%, n=17). Some 4% (n=4) of surveys were of endodontists.

Median sample size of all included surveys was 434 (SD 673, range 12-15836). Median sample size of surveys of paediatric dentists was 434 (SD 694, range 52-1290). Median sample size of surveys of endodontists median was 403 (SD 700, range 500-1027).

Due to the wide variation in sample size, data were categorised in to appropriate groups following analysis:

Table 5 Sample size of 100 most recently published surveys of clinicians in dentistry

| Sample size (up to): | Number of all included surveys | Number of surveys of paediatric dentistry | Number of surveys of endodontics |
|----------------------|--------------------------------|---|----------------------------------|
| 50 | 7 | 3 | 0 |
| 100 | 5 | 0 | 0 |
| 250 | 22 | 4 | 0 |
| 500 | 29 | 1 | 1 |
| 750 | 10 | 1 | 2 |
| 1000 | 19 | 2 | 1 |
| 1500 | 1 | 1 | 0 |
| 2500 | 3 | 1 | 0 |
| 5000 | 2 | 0 | 0 |
| 10000 | 1 | 1 | 0 |
| 15000 | 1 | 0 | 0 |

6.5.3 Methodological factors that may influence response rate

Some 75% (n=75) of surveys were via postal administration, 15% (n=15) were distributed online, 7% (n=7) were distributed in person, for example at study days, and 3% (n=3) offered mixed-mode postal and email contact. Some 100% (n=4) of surveys of endodontists, and 86% (n=12) of surveys of paediatric dentists, were administered via post.

The first included survey with online distribution was published in 2010 in the International Journal of Paediatric Dentistry (Foley, 2013). The sample size was 59, and the response rate 64%. The survey was truly anonymous, moderate in complexity, and involved repeat contact of specialists in paediatric dentistry.

Some 65% (n=65) of researchers described a method of tracking non-responders followed by repeat contact. Some 64% (n=9) of surveys in paediatric dentistry, and 75% (n=3) in endodontics, described repeat contact. Some 32% of researchers described true anonymity for participants. Some 29% (n=4) of surveys in paediatric dentistry, and 25% (n=1) in endodontics, described true anonymity.

Surveys varied in complexity (Table 6). Approximately 25% of surveys were either minimum, moderate, or complex in their demands on the time of participants. A further 25% of studies did not describe the survey format, items or length, hence, time taken for completion could not be estimated. Surveys of general practice (53%, n=9) and restorative dentistry (50%, n=5) were most likely to be complex.

Table 6 Estimated time taken (complexity) for survey completion

| | Minimum | Moderate | Complex | Unclear | Total |
|----------------------|---------|----------|---------|---------|-------|
| All surveys | 22 | 29 | 28 | 21 | 100 |
| Paediatric dentistry | 1 | 7 | 4 | 2 | 14 |
| Endodontics | 0 | 2 | 1 | 1 | 4 |

Survey design was variable (Table 7,

Table 8). Some 29% (n=29) of researchers published the survey questions or a copy of the questionnaire employed. 57% (n=8) of surveys in paediatric dentistry, and no surveys in endodontics, published any copy of the survey questions. Some 88% (n=88) of researchers negated costs of participation (e.g. by including a stamped return envelope for postal surveys). Some 93% (n=13) of surveys in paediatric dentistry, and 75% (n=3) in endodontics, described negating financial costs of participation.

Surveys that did not describe negating costs of participation were administered via post, hence it was assumed that no stamped return envelope was provided. Only 6% (n=6) of researchers offered incentives for completion. No surveys of paediatric dentistry, and 50% (n=2) of surveys of endodontics offered incentives for completion.

The incentives on offer in endodontics were entry in to prize draws (prizes not described). Chi-square test for independence in relation to the effect of factors of survey design revealed that sample size ($p < 0.006$) and repeat contact had a statistically significant effect on response rate ($p < 0.059$).

6.5.4 Discussion of non-response bias in the external validity of published survey research.

Some 45% of all researchers made some reference to non-response bias or generalisability of the achieved response rate. Only 50% of surveys of both paediatric dentistry (n=7) and endodontics (n=2) referenced bias in relation to response rate (Table 9, Table 10).

Reference to non-response bias was not associated with response rate; those surveys with the lowest response rates (e.g. paediatric dentistry 24%, endodontics 42%) did not make any reference to the impact of response rate on the analysis or generalisability of survey results or conclusions. Researchers with a response rate of 51-75% were most likely to reference non-response bias.

Table 7 Surveys in paediatric dentistry: methodological factors that may influence response

| Year | Journal | Sample Size | Administration | Objective | Repeat Contact | Anonymous | Time | Survey included | Cost | Incentive |
|------|---|-------------|----------------|------------|----------------|-----------|----------|-----------------|------|-----------|
| 2016 | Community Dentistry & Oral Epidemiology | 972 | Postal | Practice | No | Unclear | Complex | No | No | No |
| 2016 | European Journal of Paediatric Dentistry | 52 | Email | Practice | No | Yes | Moderate | Yes | No | No |
| 2015 | British Dental Journal | 1000 | Postal | Experience | Yes | No | Unclear | No | No | No |
| 2015 | Community Dentistry & Oral Epidemiology | 2035 | Postal | Opinion | Yes | No | Unclear | No | Yes | No |
| 2010 | International Journal of Paediatric Dentistry | 59 | Email | Opinion | Yes | Yes | Moderate | No | No | No |
| 2008 | Dental Traumatology | 56 | Postal | Opinion | No | No | Minimum | Yes | No | No |
| 2007 | British Dental Journal | 648 | Postal | Practice | Yes | No | Complex | Yes | No | No |
| 2007 | International Journal of Paediatric Dentistry | 215 | Postal | Practice | Yes | No | Moderate | No | No | No |
| 2005 | International Journal of Paediatric Dentistry | 1023 | Postal | Knowledge | No | Yes | Moderate | No | No | No |
| 2004 | International Journal of Paediatric Dentistry | 216 | Postal | Knowledge | Yes | No | Complex | No | No | No |
| 2004 | International Journal of Paediatric Dentistry | 222 | Postal | Practice | Yes | No | Moderate | No | No | No |
| 2003 | European Journal of Paediatric Dentistry | 1290 | Postal | Practice | No | Yes | Complex | Yes | No | No |
| 2003 | International Journal of Paediatric Dentistry | 212 | Postal | Practice | Yes | No | Moderate | Yes | No | No |
| 2000 | International Journal of Paediatric Dentistry | 437 | Postal | Practice | Yes | No | Moderate | Yes | No | No |

Table 8 Surveys in endodontics: methodological factors that may influence response

| Year | Journal | Sample Size | Administration | Objective | Repeat Contact | Anonymous | Time | Survey included | Cost | Incentive |
|------|----------------------------------|-------------|----------------|-----------|----------------|-----------|----------|-----------------|------|-----------|
| 2013 | International Endodontic Journal | 1027 | Postal | Practice | Yes | No | Moderate | No | No | No |
| 2008 | International Endodontic Journal | 500 | Postal | Practice | Yes | No | Complex | No | Yes | Yes |
| 2001 | International Endodontic Journal | 720 | Postal | Practice | No | Yes | Moderate | No | No | No |
| 2000 | International Endodontic Journal | 643 | Postal | Practice | Yes | No | Unclear | No | No | Yes |

Table 9 Surveys in paediatric dentistry: reporting of response rate and non-response bias

| Year | Journal | Responders | Response Rate Reported | Response Rate | Reference to Non-Response Bias |
|------|---|------------|------------------------|---------------|--------------------------------|
| 2016 | Community Dentistry & Oral Epidemiology | 229 | No | 24 | No |
| 2016 | European Journal of Paediatric Dentistry | 37 | Yes | 71 | Yes |
| 2015 | British Dental Journal | 613 | Yes | 61 | Yes |
| 2015 | Community Dentistry & Oral Epidemiology | 1090 | Yes | 54 | Yes |
| 2010 | International Journal of Paediatric Dentistry | 38 | No | 64 | Yes |
| 2008 | Dental Traumatology | 44 | Yes | 79 | Yes |
| 2007 | British Dental Journal | 437 | Yes | 67 | Yes |
| 2007 | International Journal of Paediatric Dentistry | 162 | Yes | 75 | No |
| 2005 | International Journal of Paediatric Dentistry | 693 | Yes | 68 | No |
| 2004 | International Journal of Paediatric Dentistry | 179 | Yes | 82 | No |
| 2004 | International Journal of Paediatric Dentistry | 167 | Yes | 79 | No |
| 2003 | European Journal of Paediatric Dentistry | 687 | Yes | 53 | No |
| 2003 | International Journal of Paediatric Dentistry | 184 | Yes | 87 | No |
| 2000 | International Journal of Paediatric Dentistry | 271 | Yes | 62 | Yes |

Table 10 Surveys in endodontics: reporting of response rate and non-response bias

| Year | Journal | Responders | Response Rate Reported | Response Rate | Reference to Non-Response Bias |
|------|----------------------------------|------------|------------------------|---------------|--------------------------------|
| 2013 | International Endodontic Journal | 735 | Yes | 73 | Yes |
| 2008 | International Endodontic Journal | 357 | Yes | 71 | Yes |
| 2001 | International Endodontic Journal | 299 | Yes | 42 | No |
| 2000 | International Endodontic Journal | 492 | Yes | 77 | No |

6.6 Discussion

The primary objective of this study was to compare the mean response rate for surveys of UK dentists, paediatric dentists and endodontists, and compare this data to that reported by previous authors. Mean response rate for all surveys was 60%, and for both paediatric dentists and endodontists was 66%.

Mean response rate following review of 77 surveys of dentists was similar at 64% (range 17 – 100%) (Tan and Burke, 1997). The authors concluded that the subject of interest, questionnaire length and inclusion of an incentive might influence response rate. Specialists tended to provide a better response rate than general dentists, and paediatric dentists had a mean response rate of 85%, although it should be noted that only one survey of paediatric dentists was included in the 77 publications. There were no surveys of endodontists included. The same authors reported that mean response rate decreased to 52% for studies with a cohort greater than 1000 participants.

In this review, 14 surveys of paediatric dentists were identified with a mean response rate 66% (SD 19, range 25-100), and a significant effect of sample size in relation to response rate has been revealed. The response rate reported in this review is also in agreement with response rates of 54% to 61% reported for postal surveys of medical clinicians (Asch et al., 1997, Cummings et al., 2001), indicating that response rates of UK dental clinicians are reflective of those achieved from medical colleagues around the world, and supporting that response rates appear to be static. Hence, this review has determined that the mean response rates of UK dentists is in agreement with that of the only published similar review, conducted 20 years previously, and that reported in the medical literature. A response rate of 60% appears to be acceptable, in line with methodological literature and recent published surveys of UK dentists. Response rates of 66% of paediatric dentists and endodontists may be achievable with robust survey methodology.

The methodology employed for this review has been appropriate to investigate whether UK dentists, paediatric dentists and endodontists, participate favourably in survey research, and to ascertain whether survey response rates had remained static in dentistry over the course of recent decades, following the advent of the online administration of surveys.

Optimal response rates might be achieved by applying evidence-based methods of survey design and administration, as recommended by Dillman. Reporting guidelines for survey research in dentistry would be beneficial, would reduce research waste, and may encourage and establish enhanced methodological and reporting practice, despite previous acknowledgement that journals may not endorse the use of reporting guidelines or provide instructions for authors (Hua et al., 2016).

It is apparent that survey researchers employ a range of survey designs and administrative approaches to enhance response rate, with varying degrees of success. Few researchers adhered in full to Dillman's design methods which guarantee a response rate of 75-80% (Dillman, 1978, Dillman et al., 2014). Those researchers who utilised repeat contact and who sampled a smaller population achieved greater response rates than those who did not.

The findings of this study support the findings of previous authors in relation to the reporting of key quality criteria in published surveys of medical specialities (Bennett et al., 2011). In that review, the authors carried out a review of reporting for surveys published in 15 journals, identified and ranked according to impact factor. They found that a copy of the survey was provided in 35% of questionnaires, compared to 29% in this review.

The same authors found that researchers defined the response rate in 25% of publications and that 11% discussed the implications of non-response bias. In this survey, survey researchers in dentistry fared better with 92% reporting response rate and 45% discussing non-response bias. This difference may occur as a result of the more optimal reporting and review practices of the dental journals concerned. However, in this review, any discussion of non-response bias, non-responders and representativeness of the responders to the population resulted in positive review of this quality criterion whereas for Bennett et al, authors had to meet specifically defined criteria.

The positive finding of discussion of non-response bias in this survey is in line with that reported by the authors of a previously discussed review of 44% (Cummings et al., 2001). Cummings reported that fewer than 7% of peer reviewed medical journals provided reporting guidance for survey researchers, despite their frequent publication of surveys of clinicians.

The methodology employed for this review, which did not identify studies according to the impact factor of the publishing journal, has been appropriate to summarise the factors of survey design and administration that might influence response rates in surveys of UK dentists. Identifying studies according to the date of publication has revealed an interesting perspective of the dental literature in terms of journals that appear to encourage the publication of survey research. Some 40% of included surveys were published in the British Dental Journal between 2001 and 2016. Of note, instructions for authors made available by the editors of British Dental Journal do not include reporting guidelines for survey researchers (British Dental Journal, 2017).

Clinical practice is demanding and labour intensive. 'Survey fatigue' may play a role in determining whether busy professionals are willing to commit their valuable time and effort towards survey completion for researchers, the priorities of whom may appear to be at odds with those of industrious clinical practitioners. Nevertheless, surveys of dental professionals generate research questions and inform practice. Well conducted surveys are valid, reliable research tools for scientific enquiry that may guide the development of care pathways and knowledge acquisition of emerging trends and attitudes in the dental workforce. Furthermore, appropriately designed questionnaires may detect the tentative steps of healthcare providers towards emerging trends and treatment modalities.

Perhaps the timely and transparent dissemination of the results of survey research, coupled with engagement of the workforce in discussion of the benefits of a symbiotic relationship between clinicians and researchers, may further aid survey response rate.

6.7 Future Work

Transparent reporting of research aids its interpretation and allows clinicians to critically appraise the strengths or weaknesses of a study's design. There is little guidance and agreement in relation to the approach to survey of clinicians in dentistry. It is suggested that, for the purposes of clarification and to enhance the validity of survey research in healthcare, self-administered surveys of dental professionals should be designed based on an evidence-based methodology for design, administration and reporting (Table 11). Standardisation of the reporting of survey research may be facilitated by the future dissemination of proposed reporting guidelines for surveys of dental professionals based on these recommendations.

Table 11 Recommendations for reporting guidelines of survey research for dental professionals

| |
|--|
| Field of interest |
| Sampling frame: population of interest, source and methodology |
| Primary and secondary objectives |
| Survey design: Item generation and reduction Design features e.g. colour, attractiveness Estimation of the time required for completion or a copy of the questionnaire included as appropriate Validity and reliability of established survey tool Pre-testing of novel survey tool |
| Administration: Method of distribution Clarification of whether repeat contact was made, coupled with details of the format and number of contacts made Description of anonymity e.g. confidentiality without anonymity to track non-responders / truly anonymous / responders identifiable Benefits vs costs of participation e.g. inclusion of a stamped, preaddressed return envelope, incentive for completion |
| Sample size for individual and combined groups as appropriate, as number and percentage |
| Actual and analysable response rate for individual and combined groups as appropriate, as number and percentage, per contact |
| Results data, supported by appropriate statistical analysis, for individual and combined groups as appropriate |
| Reporting of data management e.g. in relation to incomplete responses |
| Reporting of sampling bias |
| Reporting of non-response bias |

6.8 Conclusions

- Paediatric dentists and endodontists tend to participate favourably in survey research. Mean response rates for dental professionals of 60% appear to be consistent with those of medical professionals, and static despite a paradigm restructuring of healthcare practice from paper to web-based formatting.
- Surveys of dental professionals across a wide variety of disciplines are designed to investigate experience, knowledge, opinions, and practice. Several well-known, peer reviewed dental journals publish a high proportion of recent survey research of UK dental professionals. There is a lack of instructions available to authors seeking to publish survey research.
- There is great variance in survey methodology in relation to design and administration. Reporting standards of survey research are also variable. Researchers employ a non-standardised approach to enhance response rate. Interpretation of non-response bias is often not considered, and should be encouraged.
- Response rate may be influenced by factors unrelated to methodology. It is possible that specialists, and registrants of certain specialties, seek consistency in their response to survey research as per the cognitive dissonance theory, and a desire to support fellow researchers.

Following review of the literature, it was proposed that a self-administered, postal survey of paediatric dentists and endodontists, was a suitable tool for investigation of the decision-making practices of specialists in relation to the management of non-vital, immature permanent teeth (chapter 7: Investigating the Decision-Making Practices of Specialists in Paediatric Dentistry and Endodontics: A Self-Administered Postal Survey).

7 Investigating the Decision-Making Practices of Specialists in Paediatric Dentistry and Endodontics: A Self-Administered Postal Survey

7.1 Research Question

7.1.1 How do Specialists in Paediatric Dentistry and Endodontics Manage Necrotic, Permanent Immature Teeth?

7.2 Clarification of Research Question and Scope

7.2.1 Introduction

Specialists in paediatric dentistry, and endodontics, may be considered to lead the profession in relation to the management of non-vital, immature incisors. A research question arose in relation to the experiences, opinions, and decision-making practices of specialists whose clinical practice that might include endodontic intervention for teeth with open apices.

It was envisaged that the research question would be most appropriately addressed by survey of the target population. There are no previously reported surveys of specialists in paediatric dentistry and endodontics to determine their management of this clinical problem.

It is hoped that by establishing the current practice of the specialties, communication with health care providers may be enhanced. This might enable appropriate recognition of the scale of the clinical problem, and the skills and resources required for its management.

Securing the opinion of specialists with regards the availability of access to good quality management of non-vital immature apices in primary care is of merit in order that the population who suffer traumatic dental injuries and who fail to present for treatment, or who present but remain untreated, can perhaps be reduced if agreement is found and viable solutions proposed.

A survey of this nature might be expected to generate important information of relevance to patients, clinicians, and providers of health care. Determining the level of agreement, within and between specialists, in relation to pertinent issues central to management of the clinical problem of non-vital, immature teeth might facilitate the development of clinical guidelines and provide data for benchmarking the care provided by those with postgraduate training in relation to complex endodontic interventions. Analysis of the demographics of the responders who chose to refer rather than manage non-vital, immature teeth might enable discussion in relation to the specialist resources available to patients across the UK. Similarly, consideration of the factors that may influence non-responders, might provide insight to this subpopulation, on which a number of hypotheses might be considered.

In light of a lack of evidence to support clinical decision-making practice in relation to non-vital, immature teeth, a survey was thus designed to determine current specialist clinical practice, and to investigate the relationships between specialty, experience, role, geographical location and practice environment.

7.2.2 Primary Objective

- Determine how specialists, working in the remits of paediatric dentistry and endodontics within the United Kingdom, approach the clinical problem of non-vital, immature incisors.

7.2.3 Secondary Objectives

- Gather demographic data for specialists in paediatric dentistry and endodontists.
- Establish the level of agreement amongst specialists in relation to the availability of access to good quality management of non-vital, immature teeth within primary care.
- Establish the extent to which evidence-based, clinical and environmental factors influence clinical decision-making practices in the management of open apices.

7.3 Method

7.3.1 Ethical Approval

Ethical approval was granted by the University of Liverpool, ILT Ethics Review Group (Appendix 1).

7.3.2 Survey Design

A self-administered postal questionnaire was the most suitable method of communicating with the study population in order to address the objectives of the study. A cover letter, questionnaire, and a non-response postcard were designed.

7.3.3 Cover Letter

Participation was voluntary; hence it was important to engage the interest of recipients from the outset. A cover letter was designed to inform the invited study population of the purposes of the research. The cover letter was limited in length to a double-sided, single sheet of A4 sized (120gsm) paper. The primary purposes of the cover letter were to draw upon the respective interests of all recipients, and to provide assurance in relation to confidentiality and the University's role in supervision and ethical approval of the study.

Included were the names, roles and associated specialties of the researchers in anticipation of positive regard for the multidisciplinary team and previously established professional relationships. University of Liverpool headed paper, incorporating the institutional logo, was utilised. Multiple-mode contact details were provided (Appendix 2).

The cover letter introduced the survey as a component of PhD research, to engage those who might be more likely to respond if they had previously been involved in research or academia. Recipients were informed that all UK specialists in paediatric dentistry and endodontics were invited to participate. The aim of including this information was to draw interest from professionals of two distinct specialties with regards to how they relate to one another in terms of clinical decision-making and expertise, and to encourage contribution. An explanation of the importance of achieving a high response rate was provided. Reassurance was made that no judgements would be formed with regards to an individual's clinical practice, and that survey responses would be analysed anonymously.

The cover letter closed with a statement that the profession would be informed of the survey results, to reinforce the importance of the subject, and each individual's participation. A modified cover letter was designed for dissemination to non-responders to the first mailing. The modified cover letter was reduced in length to a single-sided sheet of A4 sized (120gsm) paper. Modifications made included reduction in length of the purpose of the study, reiteration of the importance of the contribution of all registered specialists and an acknowledgement that a previous invitation had been sent.

Efforts were made to ensure that the cover letters and survey were designed to encourage response from all specialists, whether or not their clinical practice involved the management of non-vital, immature teeth.

7.3.4 Self-Administered Postal Questionnaire

A survey questionnaire was designed for dissemination. Item generation was conducted following literature review and via two focus-group sessions, hosted by the principal investigator, with local clinicians with a special interest in paediatric dentistry and endodontics. Concepts for exploration of the research question were defined. These concepts were defined within the following domains or constructs:

- Demographics of participants (speciality, role, employment base, geographical region).
- Agreement in relation to accessibility of young people to good quality management of non-vital, immature teeth in primary care.
- Current practice (experience, opinion, and clinical decision-making practices; in relation to the number of cases managed, utilisation of a microscope, protocol for apexification and regenerative endodontic procedures).
- Factors influencing clinical decision-making practices.

Item reduction was completed to restrict the questionnaire length and to minimise responder burden. Clinical and methodological content experts pre-tested the questionnaire on three separate occasions to provide binary responses (include/exclude) for each item. Impromptu written and verbal feedback was encouraged.

The questionnaire was limited in length to a double-sided, single sheet of A4 sized (120gsm) paper containing 13 items in six sections (Appendix 3). Identical copies of the questionnaire were posted to all participants. Section divides were not made visibly apparent to participants, with the exception of demographic data and subject field. Demographic data was gathered in the first items, followed by responder agreement, experience, knowledge, opinion and practice data. Influences on the decision-making practices of responders were extracted in the final item.

Closed-ended questions were utilised with the exception of the final, open-ended question in order to gather both quantitative and qualitative data, and to facilitate coding and data interpretation. Closed-ended questions included binary dichotomous, ordinal-polytomous, and nominal-polytomous response formats, which were exhaustive and mutually exclusive, with the exception of a single “other” response for a question that determined to investigate clinical decision-making practice.

A 5 point Likert-type scale was incorporated to determine participant agreement in relation to accessibility of young people to good quality management of non-vital, immature teeth in primary care. The concluding section (1 item) was composed of a single open-ended question to capture insights into the unconstrained opinions of responders. No patient information was collected. A biostatistician was available throughout development of the questionnaire to provide advice in relation to data extraction.

Pre-specified coded identification numbers were allocated to each individual specialist in the target cohort. Identifier codes were listed on a secure database coupled with registrant information as provided by the General Dental Council. Identifier codes were hand written on to each survey at the time of dissemination to enable repeat contact of non-responders, and to avoid additional response burden for responders. An explanation of this process of administrative confidentiality without anonymity was provided in the cover letters.

7.3.5 Non-Response Postcard

A non-response postcard was designed for distribution to those who failed to reply to the first mailing. Proposed reasons for non-response included clinical practice that excluded the management of open apices, insufficient time to participate in the survey, and judging the research to be lack relevance. A fourth “other” option was provided with accompanying space for specifying further details if desired.

7.3.6 Incentives for Completion

The cover letters provided an opportunity for participants to enter a prize draw for reimbursement of the cost of subscription to either the British Society of Paediatric Dentistry, or the British Endodontic Society, for the subsequent membership year. Participants opted in to this incentive by providing their email address in an allocated space on the survey. The applicable subscription fees ranged from £55 to £90, dependent on the choice of society and whether the applicant was entitled to a reduced subscription rate as a result of their status as a registered postgraduate student. Positive uptake of the incentive to complete the questionnaire was coded for during data extraction to determine whether or not this incentive might be a contributor to response.

7.3.7 Pre-Testing and Piloting of the Survey Tool

Pre-testing incorporated a face-to-face feedback discussion between the principal investigator, local clinicians with a special interest in paediatric dentistry and endodontics, and methodological content experts. The process established that the closed-ended questions contained adequate scope of option to qualify the meaning of the given answers, and that the recipients’ comprehension of each was as the investigator intended.

A pilot study of the draft questionnaire was conducted in order to further ensure that the questions posed were easily understood, correctly interpreted, and addressed the research question. The pilot study also incorporated a face-to-face feedback discussion between the principal investigator and the pilot participants following their reading of the cover letter and completion of the questionnaire.

This process enabled the investigator to corroborate the participants' comprehension of the questions and to ensure the intent of the investigator to each question was matched. Time for survey completion at piloting was between 5 and 10 minutes.

Pilot participants were asked to provide binary responses in relation to whether each of the question items was clear or unclear. Impromptu written and verbal feedback was also encouraged in relation to concepts or items that were considered by participants to be missing, redundant, irrelevant or confusing. This process enabled understanding of participants' appreciation of the questionnaire design, question stem, and response formats. The cover letters and questionnaire were minimally revised as indicated following the pilot study. Following completion of the pilot study a database for data extraction and analysis was designed.

Final versions of cover letters, questionnaire, and non-response postcard were peer reviewed in the University of Liverpool, School of Dentistry by methodological content experts as part of the process for obtaining ethical approval for the study.

7.3.8 Sampling Frame

The aim of this study was to determine the clinical approach of specialists in managing non-vital, immature teeth, and in doing so, to analyse the experiences, opinions, and decision-making practices of specialists in relation to treatment planning of root end closure procedures. Variations in practice were sought with respect to specialty, experience, role, geographical location and practice environment.

7.3.9 Participants

Registration with the General Dental Council is mandatory for dentists who maintain active clinical practice in the United Kingdom. Those dentists who wish to be registered as specialists must meet certain conditions imposed by the General Dental Council and must apply to join the appropriate Specialist list. All dental registrants provide the General Dental Council with their contact address annually by 31st December.

At the time of conducting this study, all registrant address information was publicly available through the General Dental Council. On 1st January 2016, the contact addresses for all registrants on the paediatric dentistry and endodontics Specialist lists were requested. This method of identifying the study cohort enabled the entire target population to be invited to participate in the survey.

7.3.10 Mode of Contact

For this study, it was considered most appropriate that distribution of postal surveys was made via Royal Mail, utilising the contact information provided by registrants to the General Dental Council for public access at the time the research was conducted.

7.3.11 Sample size

The sample size for this survey was inclusive of every member of the target population, and was determined by the number of clinicians registered on the General Dental Council Specialist lists for paediatric dentistry and endodontics. There were 234 paediatric dentists and 271 endodontists registered on the Specialist lists on 1st January 2016. (General Dental Council, 2016) Specialists who did not provide the General Dental Council with a registered address within the United Kingdom were excluded. The remaining specialists were allocated unique identifier codes in order that non-responders could be followed up whilst maintaining source anonymity. This was a voluntary study and participants opted in, if they wished to, by completing the questionnaire.

7.3.12 Administration

Pre-notification of the request for specialists to participate in research was emailed to all members of the specialist societies one week prior to the first mailing. At the first mailing, on 1st February 2016, each specialist received an A4 sized business envelope containing a copy of the appropriate cover letter, a survey and a stamped, rather than franked, preaddressed return envelope. An email reminder was sent to members of the specialist societies one week following the first mailing.

Three weeks following the first mailing, repeat contact was made with an identical copy of the questionnaire, a modified cover letter, a stamped, preaddressed return envelope, and a non-response postcard were mailed to all non-responders.

A reminder of the request for specialists to participate was emailed to all members of the specialist societies at this time. Mailing of the questionnaire on a third occasion was planned if a situation arose in which the response rate was less than 60% seven weeks following the first mailing. Twelve weeks following the first mailing, the survey period closed. Identifier codes and registrant address data were destroyed.

7.4 Data Collection & Analysis

7.4.1 Data Collection

Returned questionnaires were assessed for completeness. It was planned that if less than 5% of responses received were incomplete those questionnaires would be discarded. If greater than 5% of responses received were incomplete multivariate imputation by chained equations (MICE) was planned. Anonymised source data were numerically coded and entered in to SPSS software (Statistics 24, IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) for statistical analysis. The response rate of each specialty was compared, as this information was readily available from analysis of anonymised source data.

7.4.2 Analyses

Descriptive frequency tables were generated to examine quantitative data. Distributions were compared using chi-square or Fisher's exact tests (for data frequencies <5 observations per cell). Source data was imported in to NVivo software for qualitative data analysis. Data was coded into nodes and classified according to specialty. A word frequency query and a project map were outlined to explore connections.

Subgroup Analyses

Subgroup analyses were performed for:

1. Specialty
2. Role
3. Practice environment
4. Geographical location
5. Practitioner experience

7.5 Results

7.5.1 Response Rate

The total population of registered paediatric dentists was 234, and of endodontists was 271. Six paediatric dentists and seventeen endodontists did not provide a registered address within the United Kingdom, and were therefore excluded. A population of 482 specialists registered within the United Kingdom were mailed (228 Paediatric Dentists and 254 endodontists).

Three questionnaires were returned undelivered by Royal Mail with a note that the intended addressee was not registered at the given address. These specialists were excluded (n=1 paediatric dentist, n=2 endodontists). The subsequent eligible population was 479 specialists (227 paediatric dentists and 252 endodontists). Some 49.8% of paediatric dentists (n=113) and 47.6% of endodontists (n=120) responded to the first mailing. Some 17.2% of paediatric dentists (n=39) and 9.5% of endodontists (n=24) responded to the second mailing.

Excluding returned non-response cards, at completion of data collection, the actual response rate was 61.8% (n=296), with 67.0% of paediatric dentists (n=152) and 57.1% of endodontists (n=144) responding. Six surveys (representing 2.03% of responders) were incomplete and were discarded (n=3 paediatric dentists, n=3 endodontists). The analysable response rate was 60.5% (

Figure 3).

7.5.2 Non-Response

2.7% (n=13) of the eligible population returned non-response cards citing their reasons for declining to participate in the survey. Three paediatric dentists and three endodontists choose to identify themselves on their non-response cards (Table 12). The remaining seven specialists choose to return their non-response cards anonymously (Table 13). The geographic location of most non-responders was the South of England.

7.5.3 Effect of Incentive for Participation

30.0% of responders (n=87) opted into the incentive for participation of the questionnaire by providing their email address. The successful participant was identified via a computerised, random number generator and notified directly.

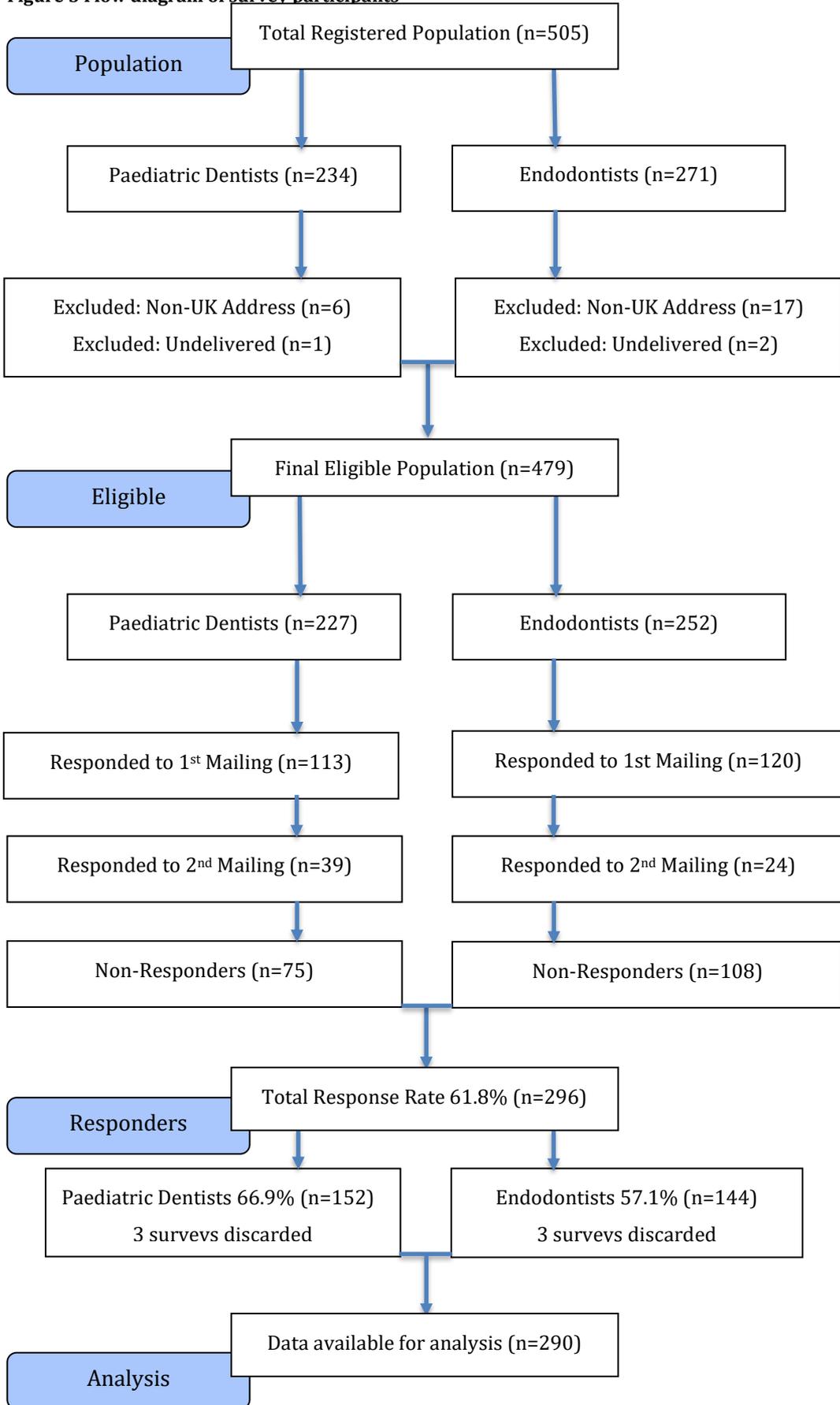
Table 12 Reasons for use of non-response card per specialty

| Reason for non-response | Endodontics | Paediatric Dentistry |
|--|-------------|----------------------|
| I do not manage open apices | 1 | 1 |
| This research is not relevant to me | 1 | 1 |
| Other: retirement / not currently practising | 1 | 1 |

Table 13 Anonymous reasons for use of non-response card

| Reason for non-response | Number |
|--|--------|
| I do not manage open apices | 5 |
| Other: retirement / not currently practising | 2 |

Figure 3 Flow diagram of survey participants



7.5.4 Demographics

7.5.4.1 Specialty

Data from 290 specialists (n=149 paediatric dentists, n=141 endodontists) were available for analysis. There was no significant difference between the groups in relation to number of responders per specialty ($p < 0.472$). The following results data is presented for responders and is not assumed to represent all specialist registrants as will be further discussed.

7.5.4.2 Role

The largest group of responders identified their primary role as specialist (54.8%, n=159), followed by consultant (31.4%, n=91) (Table 14). The smallest group of responders identified their primary role as academic (13.8%, n=40). Some 49.7% (n=74) of paediatric dentists, and 60.3% (n=85) of endodontists identified their primary role as specialist. There was no significant effect of specialty on primary role ($p < 0.192$).

Table 14 Primary role of responders per specialty and role

| | | | Specialty | | Total |
|-------|-------|--------|-------------|----------------------|-------|
| | | | Endodontics | Paediatric Dentistry | |
| | Count | | 17 | 23 | 40 |
| | | % | 12.1% | 15.4% | 13.8% |
| | Count | | 39 | 52 | 91 |
| | | % | 27.7% | 34.9% | 31.4% |
| | Count | | 85 | 74 | 159 |
| | | % | 60.3% | 49.7% | 54.8% |
| Count | | 141 | 149 | 290 | |
| | % | 100.0% | 100.0% | 100.0% | |

7.5.5 Practice environment

Most responding paediatric dentists (62.4%, n=93) identified the hospital dental services (HDS) as their primary place of work (Table 15). Less than 5% of paediatric dentists were based in dental practice. Most responding endodontists (57.4%, n=81) identified private dental practice as their primary place of work.

No responding endodontists were based in National Health Service (NHS) practice. Some 28.2% (n=42) of responding paediatric dentists were based in community dental services (CDS) compared to 2.1% of endodontists (n=3). There was a significant effect of speciality in relation to practice environment ($p < 0.001$), (Table 16).

Table 15 Practice environment per speciality

| | | | Specialty | | Total |
|--|-------|---|-------------|----------------------|--------|
| | | | Endodontics | Paediatric Dentistry | |
| | Count | | 3 | 42 | 45 |
| | | % | 2.1% | 28.2% | 15.5% |
| | Count | | 51 | 93 | 144 |
| | | % | 36.2% | 62.4% | 49.7% |
| | Count | | 6 | 5 | 11 |
| | | % | 4.3% | 3.4% | 3.8% |
| | Count | | 0 | 3 | 3 |
| | | % | 0.0% | 2.0% | 1.0% |
| | Count | | 81 | 6 | 87 |
| | | % | 57.4% | 4.0% | 30.0% |
| | Count | | 141 | 149 | 290 |
| | % | | 100.0% | 100.0% | 100.0% |

Table 16 Chi-square test for independence in relation to the effect of speciality on practice environment

| | Value | df | p-value | Exact Sig. (2-sided) |
|---------------------|----------------------|----|---------|----------------------|
| Pearson Chi-Square | 113.662 ^a | 4 | <.001 | <.001 |
| Fisher's Exact Test | 129.478 | | | <.001 |

7.5.6 Geographical location

There were fewer responding specialists in the Midlands, Northern Ireland, Wales, and Jersey combined (n=40) than in the North of England (n=84), (Table 17). There were almost twice as many responding specialists in the South of England (48.6%, n=141) than the North (29.0%, n=84). There were, however, similar numbers of paediatric dentists working in the North (35.6%, n=53) and South of England (38.3%, n=57).

Conversely, there were almost three times as many endodontists working in the South (59.6%, n=84) compared to the North of England (22%, n=31). Only 7.1% of endodontists (n=10) and 10.1% (n=15) of paediatric dentists were working primarily in Scotland. Some 3.4% (n=10) of all responding specialists were working in Wales, and in Northern Ireland. More paediatric dentists than endodontists were working in Wales and Northern Ireland. No response was received from paediatric dentists working in Jersey.

The majority of responding endodontists were working in private (76.5%, n=62), or mixed (83.3%, n=5), practice in the South of England. Responding endodontists based within the community dental services were working only in Scotland and the South of England.

Three responding paediatric dentists based in NHS practice were working in the North of England, the South of England, and Wales. There were fewer but similar percentages of paediatric dentists working in private (83.3%, n=5), or mixed (80.0%, n=4), practice in the South of England. There were equal numbers of paediatric dentists working in the hospital dental services in the North and South of England (36.6%, n=34).

The majority of endodontists based in the hospital dental services were working in the North of England (43.1%, n=22). The majority of paediatric dentists based within the community dental services were working in the North of England (42.9%, n=18). There was a significant effect of speciality in relation to geographical location ($p < 0.001$), (

Table 18).

Table 17 Geographical location and practice environment per specialty

| Specialty | | | | Majority of work base | | | | | Total |
|-----------|--|---------------|-------|-----------------------|-----|-------|-----|---------|-------|
| | | | | CDS | HDS | Mixed | NHS | Private | |
| | | Jersey | Count | 0 | 0 | 0 | 0 | 2 | 2 |
| | | Midlands | Count | 0 | 4 | 0 | 0 | 7 | 11 |
| | | North England | Count | 0 | 22 | 1 | 0 | 8 | 31 |
| | | N. Ireland | Count | 0 | 0 | 0 | 0 | 1 | 1 |
| | | Scotland | Count | 1 | 8 | 0 | 0 | 1 | 10 |
| | | South England | Count | 2 | 15 | 5 | 0 | 62 | 84 |
| | | Wales | Count | 0 | 2 | 0 | 0 | 0 | 2 |
| | | Midlands | Count | 2 | 5 | 0 | 0 | 0 | 7 |
| | | North England | Count | 18 | 34 | 0 | 1 | 0 | 53 |
| | | N. Ireland | Count | 2 | 6 | 0 | 0 | 1 | 9 |
| | | Scotland | Count | 4 | 11 | 0 | 0 | 0 | 15 |
| | | South England | Count | 13 | 34 | 4 | 1 | 5 | 57 |
| | | Wales | Count | 3 | 3 | 1 | 1 | 0 | 8 |

Table 18 Chi-square test for independence in relation to the effect of specialty on geographical location

| | Value | df | p-value | Exact Sig. (2-sided) |
|---------------------|---------------------|----|---------|----------------------|
| Pearson Chi-Square | 24.619 ^a | 6 | <.001 | <.001 |
| Fisher's Exact Test | 24.206 | | | <.001 |

There were similar numbers of responding academics in the North of England (6.2%, n=18) and the rest of the UK combined (7.6%, n=22), (Table 19). Of responding endodontists, there were similar numbers of consultants working in the North (9.9%, n=14) and South of England (12%, n=17). Of responding endodontists working as specialists, 75.3% (n=64) were working in the South, and 9.4% (n=8) were working in the North of England. Just 3.5% (n=3) and 1.2% (n=1) of responding endodontists were working as specialists in Scotland and Northern Ireland respectively.

Of responding paediatric dentists, there were equal numbers of consultants and specialists working in the North of England (14.7%, n=22 per region), and South of England (12.1%, n=18 and 21.5%, n=32 respectively).

Table 19 Geographical location and primary role per speciality

| Specialty | | | Primary role | | | Total |
|-----------|--|---------------|--------------|------------|------------|-------|
| | | | Academic | Consultant | Specialist | |
| | | Jersey | 0 | 0 | 2 | 2 |
| | | Midlands | 1 | 3 | 7 | 11 |
| | | North England | 9 | 14 | 8 | 31 |
| | | N. Ireland | 0 | 0 | 1 | 1 |
| | | Scotland | 3 | 4 | 3 | 10 |
| | | South England | 3 | 17 | 64 | 84 |
| | | Wales | 1 | 1 | 0 | 2 |
| Total | | | 17 | 39 | 85 | 141 |
| | | Midlands | 2 | 3 | 2 | 7 |
| | | North England | 9 | 22 | 22 | 53 |
| | | N. Ireland | 0 | 2 | 7 | 9 |
| | | Scotland | 4 | 5 | 6 | 15 |
| | | South England | 7 | 18 | 32 | 57 |
| | | Wales | 1 | 2 | 5 | 8 |
| Total | | | 23 | 52 | 74 | 149 |
| | | Jersey | 0 | 0 | 2 | 2 |
| | | Midlands | 3 | 6 | 9 | 18 |
| | | North England | 18 | 36 | 30 | 84 |
| | | N. Ireland | 0 | 2 | 8 | 10 |
| | | Scotland | 7 | 9 | 9 | 25 |
| | | South England | 10 | 35 | 96 | 141 |
| | | Wales | 2 | 3 | 5 | 10 |
| Total | | | 40 | 91 | 159 | 290 |

7.5.7 Responder Agreement

Some 88.9% of all responders (n=258) either strongly agreed (61.0%, n=177) or agreed (27.9%, n=81) that young people have difficulty accessing good quality management of non-vital, immature apices in general dental practice (Table 20).

Some 91.9% (n=137) of paediatric dentists strongly agreed (65.8%, n=98) or agreed (26.2%, n=39). Some 85.8% (n=121) of endodontists strongly agreed (56.0%, n=79) or agreed 29.7% (n=42). Only one responder (0.3%), an endodontist, strongly disagreed with this statement. There was no significant effect of speciality on agreement ($p < 0.235$).

Table 20 Agreement that young people have difficulty accessing good quality management

| | | | Level of Agreement | | | | | Total |
|--|--|-------|--------------------|-------|---------|----------|-------------------|--------|
| | | | Strongly agree | Agree | Neutral | Disagree | Strongly disagree | |
| | | Count | 79 | 42 | 15 | 4 | 1 | 141 |
| | | % | 56.0% | 29.8% | 10.6% | 2.8% | 0.7% | 100.0% |
| | | Count | 98 | 39 | 11 | 1 | 0 | 149 |
| | | % | 65.8% | 26.2% | 7.4% | 0.7% | 0.0% | 100.0% |
| | | Count | 177 | 81 | 26 | 5 | 1 | 290 |
| | | % | 61.0% | 27.9% | 9.0% | 1.7% | 0.3% | 100.0% |

The majority of responders who did not agree that young people have difficulty accessing good quality management of non-vital, immature apices in general dental practice were based in the South of England (Table 21). Only 8.9% of responders were neutral (6% in the South of England, 1.3% in the North of England, 1% in Scotland, 0.3% in Northern Ireland, 0.3% in the Midlands).

Table 21 Cross tabulation of agreement and geographical location

| | | Level of Agreement | | | | | Total |
|-------|---------------|--------------------|-------|---------|----------|-------------------|-------|
| | | Strongly agree | Agree | Neutral | Disagree | Strongly disagree | |
| | Jersey | 2 | 0 | 0 | 0 | 0 | 2 |
| | Midlands | 11 | 6 | 1 | 0 | 0 | 18 |
| | North England | 56 | 24 | 4 | 0 | 0 | 84 |
| | N. Ireland | 5 | 4 | 1 | 0 | 0 | 10 |
| | Scotland | 13 | 7 | 3 | 2 | 0 | 25 |
| | South England | 84 | 36 | 17 | 3 | 1 | 141 |
| | Wales | 6 | 4 | 0 | 0 | 0 | 10 |
| Total | | 177 | 81 | 26 | 5 | 1 | 290 |

7.5.8 Responder Experience

Paediatric dentists were significantly more likely than endodontists to manage non-vital immature teeth. A majority, 67.4% (n=95) of responding endodontists and 82.6% (n=123) of paediatric dentists, personally manage at least one case per month (Table 22). No endodontists were managing more than five non-vital, immature teeth per month. The majority of responders were managing between one to five cases per month. There was a significant effect of speciality in relation to the number of non-vital, immature teeth managed per month ($p < 0.001$), (Table 23).

Table 22 Number of non-vital immature teeth managed per month, per specialty

| | | | How many NVIA do you personally manage in an average month | | | | Total |
|-------|-------|-------|--|--------|-------------|-------|-------|
| | | | >5 | 1 to 5 | Less than 1 | None | |
| | Count | 0 | 95 | 2 | 44 | 141 | |
| | | % | 0.0% | 67.4% | 1.4% | 31.2% | 100% |
| | Count | 36 | 87 | 4 | 22 | 149 | |
| | | % | 24.1% | 58.4% | 2.7% | 14.8% | 100% |
| Total | | Count | 36 | 182 | 6 | 66 | 290 |

Table 23 Chi-square test for independence in relation to the effect of specialty number on non-vital immature teeth managed per month

| | Value | df | p-value | Exact Sig. (2-sided) |
|---------------------|---------------------|----|---------|----------------------|
| Pearson Chi-Square | 44.165 ^a | 3 | <.001 | <.001 |
| Fisher's Exact Test | 54.030 | | | <.001 |

The majority of endodontists who manage at least one non-vital, immature incisor per month were based in the hospital dental services (22.7%, n=32) or private practice (40.4%, n=57), (Table 24). The majority of endodontists who do not manage any immature teeth were also based in the hospital dental services (12.8%, n=18), or private practice (16.3%, n=23).

The majority of paediatric dentists who manage at least one non-vital, immature incisor per month were based in the hospital dental services (54.4%, n=81) or community dental services (21.5%, n=32). The majority of paediatric dentists who do not manage any immature teeth were also based in the hospital dental service (8.1%, n=12) or community dental services (4.0%, n=6).

Table 24 Cross tabulation of number of non-vital immature teeth managed per month, per specialty with practice environment

| Specialty | | | NVIA managed in an average month | | | | Total |
|-----------|-------|---------|----------------------------------|--------|-------------|------|-------|
| | | | >5 | 1 to 5 | Less than 1 | None | |
| | | CDS | 0 | 2 | 0 | 1 | 3 |
| | | HDS | 0 | 32 | 1 | 18 | 51 |
| | | Mixed | 0 | 4 | 0 | 2 | 6 |
| | | Private | 0 | 57 | 1 | 23 | 81 |
| | Total | | 0 | 95 | 2 | 44 | 141 |
| | | CDS | 2 | 30 | 4 | 6 | 42 |
| | | HDS | 33 | 48 | 0 | 12 | 93 |
| | | Mixed | 1 | 3 | 0 | 1 | 5 |
| | | NHS | 0 | 2 | 0 | 1 | 3 |
| | | Private | 0 | 4 | 0 | 2 | 6 |
| | Total | | 36 | 87 | 4 | 22 | 149 |

Some 73.0% (n=103) of responding endodontists would routinely use an endodontic operating microscope when carrying out root end closure procedures, compared to only 10.7% (n=16) of responding paediatric dentists (Table 25).

The majority of endodontists who manage at least one non-vital, immature incisor per month routinely use an endodontic operating microscope when carrying out root end closure procedures. The converse is true for paediatric dentists.

There was a significant effect of speciality on the routine use of an endodontic operating microscope ($p < 0.001$), (Table 26).

Table 25 Routine use of an endodontic operating microscope

| Routine use of a microscope for root end closure procedures | | | NVIA managed in an average month | | | | Total |
|---|----------------------|--|----------------------------------|--------|----|------|-------|
| | | | >5 | 1 to 5 | <1 | None | |
| | Endodontics | | 0 | 85 | 2 | 16 | 103 |
| | Paediatric Dentistry | | 8 | 8 | 0 | 0 | 16 |
| | Total | | 8 | 93 | 2 | 16 | 119 |
| | Endodontics | | 0 | 9 | 0 | 18 | 27 |
| | Paediatric Dentistry | | 17 | 13 | 0 | 1 | 31 |
| | Total | | 17 | 22 | 0 | 19 | 58 |
| | Endodontics | | 0 | 1 | 0 | 10 | 11 |
| | Paediatric Dentistry | | 11 | 66 | 4 | 21 | 102 |
| | Total | | 11 | 67 | 4 | 31 | 113 |

Table 26 Chi-square test for independence in relation to the effect of specialty on routine use of an endodontic operating microscope for root end closure procedures

| | Value | df | p-value |
|--------------------|----------------------|----|---------|
| Pearson Chi-Square | 137.048 ^a | 2 | <.001 |

Most specialists employing an endodontic operating microscope for root end closure procedures were based within the hospital dental services or private endodontic practice (Table 27). 57.0% (n=53) of responding paediatric dentists working in the hospital dental services do not routinely use a microscope. One paediatric dentist (2.38%) based in the community dental services routinely employed a microscope.

Table 27 Routine use of an endodontic operating microscope per specialty, per practice environment

| Practice Environment | | | Routine use of a microscope for root end closure procedures | | | Total |
|----------------------|-----------|----------------------|---|--------------|-----|-------|
| | | | Yes | Occasionally | No | |
| | | Endodontics | 2 | 1 | 0 | 3 |
| | | Paediatric Dentistry | 1 | 3 | 38 | 42 |
| | | Endodontics | 36 | 10 | 5 | 51 |
| | | Paediatric Dentistry | 14 | 26 | 53 | 93 |
| NHS | Specialty | Paediatric Dentistry | 0 | 0 | 3 | 3 |
| | | Endodontics | 3 | 2 | 1 | 6 |
| | | Paediatric Dentistry | 1 | 2 | 2 | 5 |
| | | Endodontics | 62 | 14 | 5 | 81 |
| | | Paediatric Dentistry | 0 | 0 | 6 | 6 |
| | | Endodontics | 103 | 27 | 11 | 141 |
| | | Paediatric Dentistry | 16 | 31 | 102 | 149 |
| Total | | | 119 | 58 | 113 | 290 |

Most responders had previous personal experience of managing non-vital immature teeth with apical plugs (Table 28). Some 19.5% (n=29) of paediatric dentists and 2.8% (n=4) of endodontists had not previously placed apical plugs in immature teeth. The most commonly used materials for apical closure were mineral trioxide aggregate and Biodentine (85.2% of all responders, n=247).

Table 28 Experience of root end closure with an apical plug per specialty

| | | Experience of carrying out root end closure with an apical plug | | | | | | | | Total |
|-------|----------------------|---|------------------|-----|-----|-------------|------------|--------------|----|-------|
| | | Amalgam or ZOE | Biodentine (Bio) | GIC | MTA | MTA and Bio | MTA and GP | MTA, Bio, GP | No | |
| | Endodontics | 1 | 0 | 2 | 98 | 31 | 3 | 2 | 4 | 141 |
| | Paediatric Dentistry | 0 | 3 | 1 | 98 | 17 | 1 | 0 | 29 | 149 |
| Total | | 1 | 3 | 3 | 196 | 48 | 4 | 2 | 33 | 290 |

Paediatric dentists were significantly less likely to have experience of carrying out root end closure with an apical plug ($p < 0.001$), (Table 29).

Table 29 Chi-square test for independence in relation to the effect of specialty on experience of root end closure with an apical plug

| | Value | df | p-value | Exact Sig. (2-sided) |
|---------------------|---------------------|----|---------|----------------------|
| Pearson Chi-Square | 30.158 ^a | 7 | <.001 | <.001 |
| Fisher's Exact Test | 30.931 | | | <.001 |

There was a lack of experience in managing non-vital immature teeth with regenerative endodontic procedures that was similar between the specialities (Table 30). A majority, 64.4% (n=96) of paediatric dentists and 66.6% (n=94) of endodontists, did not have personal experience of regenerative endodontic intervention. There was no significant effect of specialty on experience of carrying out root end closure with a regenerative endodontic procedure ($p < 0.391$).

Table 30 Experience of root end closure with a regenerative endodontic procedure

| | | | Experience of carrying out root end closure with a regenerative endodontic procedure | | Total |
|-------|--|-------|--|-------|-------|
| | | | Yes | No | |
| | | Count | 47 | 94 | 141 |
| | | % | 33.3% | 66.6% | 100% |
| | | Count | 53 | 96 | 149 |
| | | % | 37.5% | 64.4% | 100% |
| Total | | Count | 100 | 190 | 290 |

7.5.9 Responder Choice

Responders identified a variety of methods for disinfection and dressing of the root canal system that they would employ if carrying out a regenerative endodontic procedure over multiple intervention visits (Table 31). Double and triple antibiotic pastes were popular choices with responders, and particularly with paediatric dentists. The material of choice for endodontists was calcium hydroxide. A third of responders in both groups did not indicate a chosen material. There was a significant effect of speciality on the material chosen for disinfection and dressing employed ($p < 0.001$), (Table 32).

Table 31 Disinfection and root canal dressing methods per speciality

| | | | Disinfection and dressing methods for REP | | | | | Total | |
|-------|--|-------|---|-------|-------|------------|----------|-------|-------|
| | | | DAP | TAP | CaOH | Irrigation | Not sure | | Other |
| | | Count | 14 | 24 | 57 | 5 | 41 | 0 | 141 |
| | | % | 9.9% | 17.1% | 40.4% | 3.5% | 29.1% | 0.0% | 100% |
| | | Count | 34 | 31 | 34 | 0 | 49 | 1 | 149 |
| | | % | 22.8% | 20.8% | 22.8% | 0.0% | 32.9% | 0.7% | 100% |
| Total | | Count | 48 | 55 | 91 | 5 | 90 | 1 | 290 |

Table 32 Chi-square test for independence in relation to the effect of speciality on disinfection and root canal dressing methods

| Chi-Square Tests | | | | |
|---------------------|---------------------|----|---------|----------------------|
| | Value | df | p-value | Exact Sig. (2-sided) |
| Pearson Chi-Square | 21.544 ^a | 5 | <.001 | <.001 |
| Fisher's Exact Test | 21.416 | | | <.001 |

If a young patient presented with a non-vital, immature incisor, 16.3% (n=23) of responding endodontists would choose to refer the patient for management by a paediatric dentist (Table 33). Only 1.3% (n=2) paediatric dentists would refer the patient to an endodontist. Some 1.4% (n=2) endodontists and 2.0% (n=3) paediatric dentists would refer the patient to another member of their own speciality.

Approximately half of all responders, 57.2% (n=166), would plan mineral trioxide aggregate apexification as first line management of a non-vital, immature tooth (54.6% (n=77) of endodontists and 59.7% (n=89) of paediatric dentists). Endodontists were more likely to plan a regenerative endodontic procedure, 15.6% (n=22), than calcium hydroxide apexification, 12.1% (n=17).

Endodontists were more likely than paediatric dentists to plan a regenerative endodontic procedure (15.6% (n=22) endodontists and 1.34% (n=2) paediatric dentists). Approximately a third of paediatric dentists would plan calcium hydroxide apexification, 35.6% (n=53). Only 1.34% (n=2) paediatric dentists would plan a regenerative endodontic procedure as first line management of a non-vital, immature tooth. There was a significant effect of specialty on treatment planning ($p < 0.001$), (Table 34).

Table 33 Technique of choice for root end closure per specialty

| | | Technique of Choice | | | | | Total |
|-------|----------------------|---------------------|-----|-----|----------------------|----------------------|-------|
| | | CaOH | MTA | REP | Refer to Endodontics | Refer to Paediatrics | |
| | Endodontics | 17 | 77 | 22 | 2 | 23 | 141 |
| | Paediatric Dentistry | 53 | 89 | 2 | 2 | 3 | 149 |
| Total | | 70 | 166 | 24 | 4 | 26 | 290 |

Table 34 Chi-square test for independence in relation to technique of choice for root end closure

| | Value | df | p-value | Exact Sig. (2-sided) |
|---------------------|---------------------|----|---------|----------------------|
| Pearson Chi-Square | 54.128 ^a | 7 | <.001 | <.001 |
| Fisher's Exact Test | 57.596 | | | <.001 |

7.5.10 Influences on the Decision-Making Practices of Responders

Responders were asked to decide whether a variety of pre-specified factors had significant, some or no influence on their management of non-vital, immature teeth.

7.5.11 Material Cost

The majority (75.9%, n=220) of responders in both specialties reported that material cost had no influence on their management of non-vital, immature teeth (Figure 4). Some 4.1% (n=12) specialists reported that material cost had significant influence on their practice.

Paediatric dentists were more likely to experience significant, or some, influence (35.6%, n=53) than endodontists (12.1%, n=17). There was a significant effect of specialty on decision-making practice ($p < 0.001$), (Table 35).

Figure 4 Influence of material cost on management

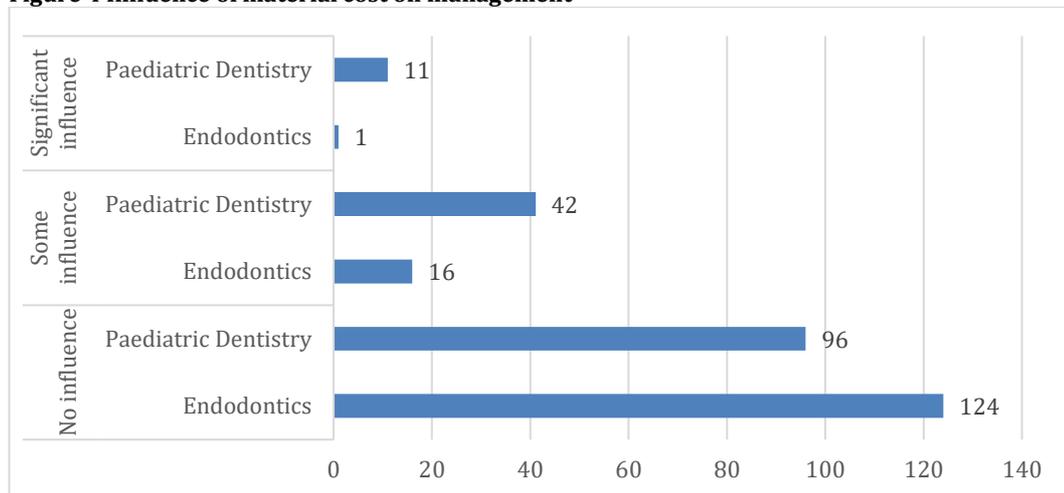


Table 35 Chi-square test for independence in relation to decision-making practice and material cost

| | Value | df | p-value | Exact Sig. (2-sided) |
|---------------------|---------------------|----|---------|----------------------|
| Pearson Chi-Square | 23.349 ^a | 2 | <.001 | <.001 |
| Fisher's Exact Test | 23.936 | | | <.001 |

7.5.12 Local Department / Practice Choice

The majority of endodontists, 65.2% (n=92), reported that local protocol had no influence on their management of non-vital, immature teeth (Figure 5). A similar number of paediatric dentists, 73.2% (n=109), reported that local protocol had significant, or some, influence on their practice.

Local protocol had no influence on management for 65.2% (n=92) of endodontists, and 26.8% (n=40) of paediatric dentists. There was a significant effect of specialty on decision-making practice ($p < 0.001$), (Table 36).

Figure 5 Influence of local protocol on management

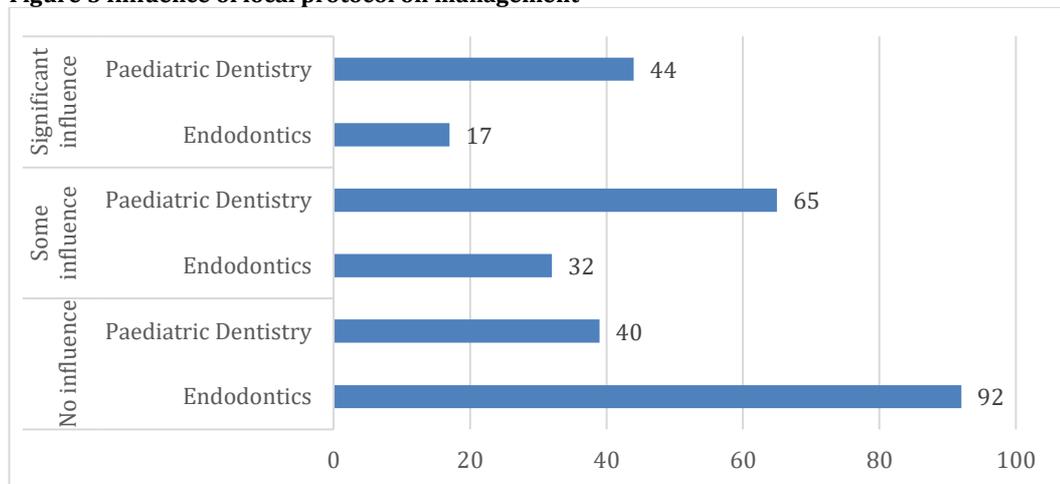


Table 36 Chi-square test for independence in relation to decision-making practice and local protocol

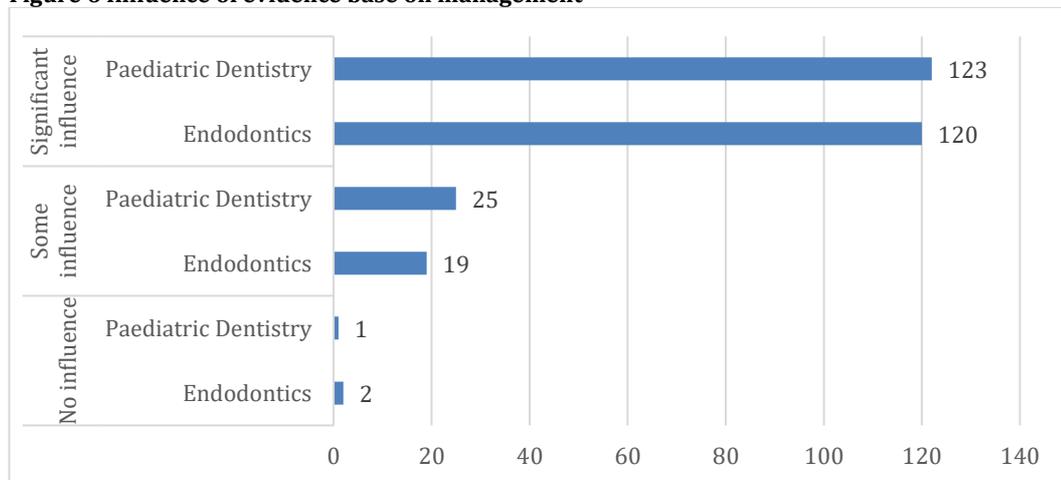
| | Value | df | p-value |
|--------------------|---------------------|----|---------|
| Pearson Chi-Square | 43.475 ^a | 2 | <.001 |

7.5.13 Evidence Based Literature

The majority (83.8%, n=243) of responders in both specialties (85.1%, n=120 endodontists, and 82.6%, n=123 paediatric dentists) reported that evidence based literature had significant influence on their management of non-vital, immature teeth (Figure 6).

Only 1.0% (n=3) specialists (1.4%, n=2 endodontists, and 0.7%, n=1 paediatric dentist) reported that evidence based literature had no influence on their practice. There was no significant effect of specialty on decision-making practice ($p < 0.597$).

Figure 6 Influence of evidence base on management

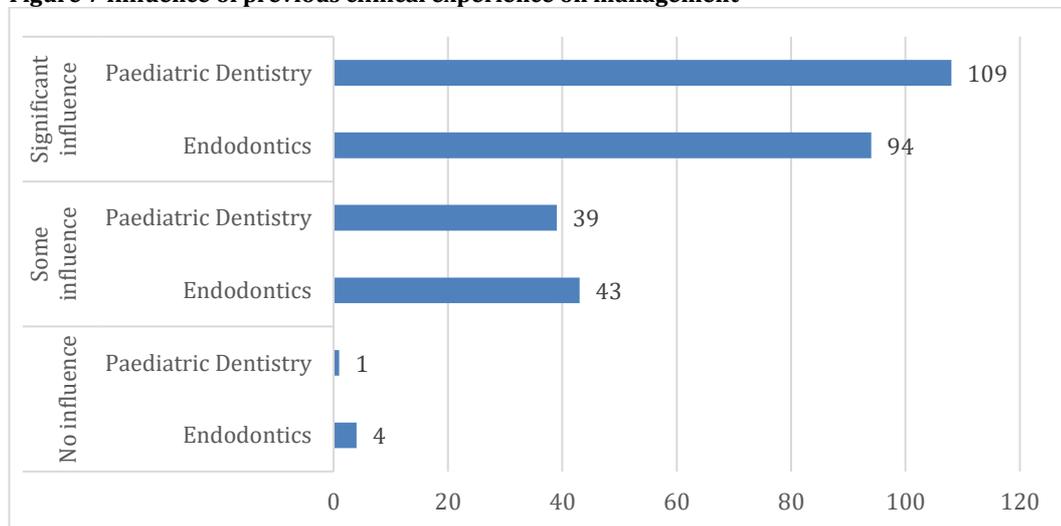


7.5.14 Previous Clinical Experience

The majority (70.0%, n=203) of responders in both specialties (66.7%, n=94 endodontists, and 73.2%, n=109 paediatric dentists) reported that their previous clinical experience had significant influence on their management of non-vital, immature teeth (Figure 7).

Only 1.7% (n=5) specialists (2.8%, n=4 endodontists, and 0.7%, n=1 paediatric dentist) reported that previous clinical experience had no influence on their practice. There was no significant effect of specialty on decision-making practice ($p < 0.226$).

Figure 7 Influence of previous clinical experience on management

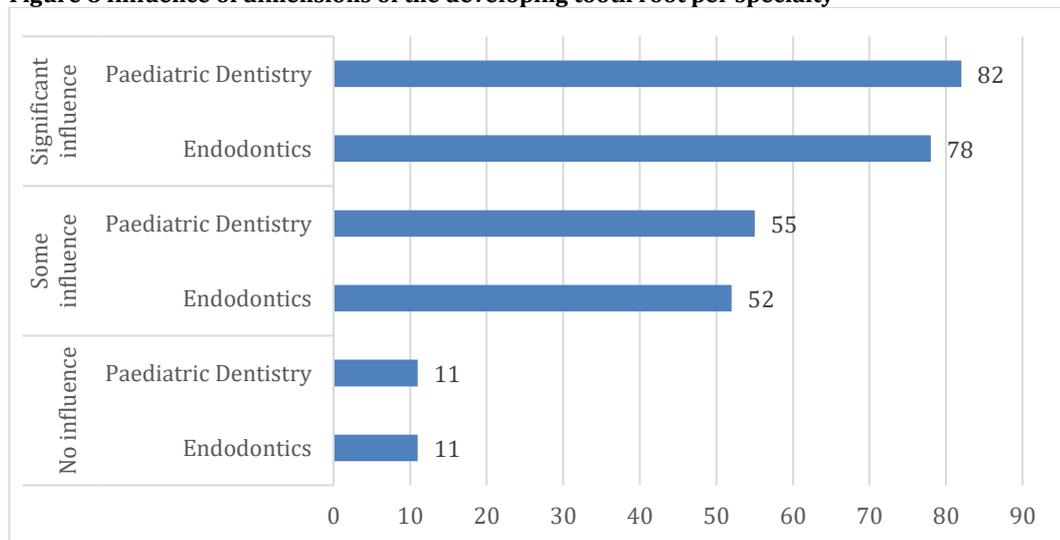


7.5.15 Dimensions of the Tooth Root

Approximately half (55.2%, n=160) of responders in both specialties (55.3%, n=78 endodontists, and 55.0%, n=82 paediatric dentists) reported that dimensions of the developing tooth root had significant influence on their management of non-vital, immature teeth (Figure 8).

7.8% (n=11) of endodontists and 7.4% (n=11) of paediatric dentists reported that dimensions of the tooth root had no influence on their management. There was no significant effect of specialty root on decision-making practice ($p < 0.086$).

Figure 8 Influence of dimensions of the developing tooth root per specialty



7.5.16 Likelihood of Resolution of Infection

The majority (65.9%, n=191) of responders in both specialties (58.9%, n=83 endodontists, and 72.5%, n=108 paediatric dentists) reported that the likelihood of resolution of infection following endodontic intervention had a significant influence on their management of non-vital, immature teeth (

Figure 9).

Paediatric dentists were more likely to be influenced. There was a significant effect of specialty on decision-making practice ($p < 0.003$), (Table 37).

Figure 9 Influence of likelihood of resolution of infection per specialty

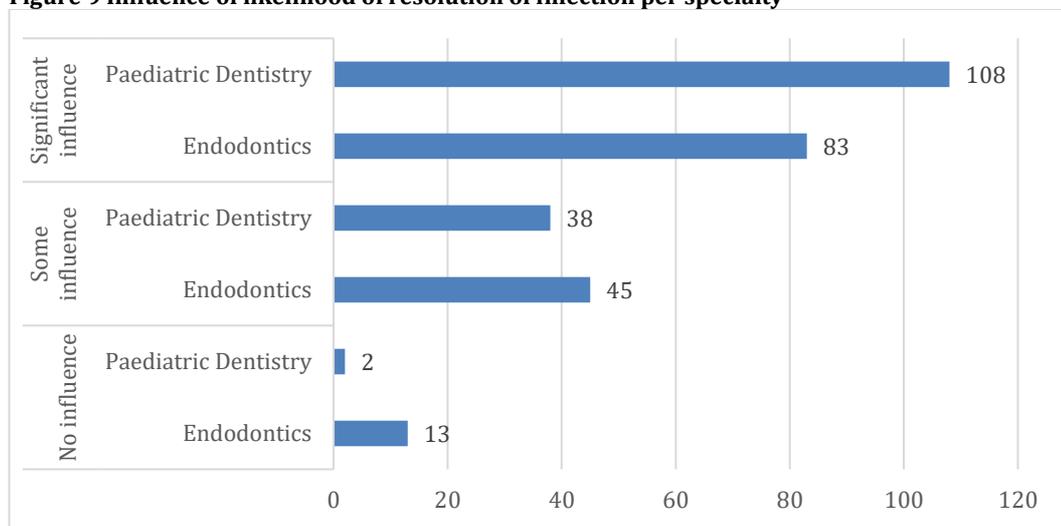


Table 37 Chi-square test for independence in relation to decision-making practice and likelihood of resolution of infection

| | Value | df | p-value | Exact Sig. (2-sided) |
|---------------------|---------------------|----|---------|----------------------|
| Pearson Chi-Square | 11.556 ^a | 2 | <.003 | <.003 |
| Fisher's Exact Test | 11.804 | | | <.003 |

7.5.17 Likelihood of Root End Closure

The majority (55.5%, n=161) of responders in both specialties (48.9%, n=69 endodontists, and 61.7%, n=92 paediatric dentists) reported that the likelihood of successful root end closure following endodontic intervention had a significant influence on their management of non-vital, immature teeth (Figure 10).

Paediatric dentists were more likely to be influenced. There was a significant effect of specialty on decision-making practice ($p < 0.050$), (Table 38).

Figure 10 Influence of likelihood of root end closure per specialty

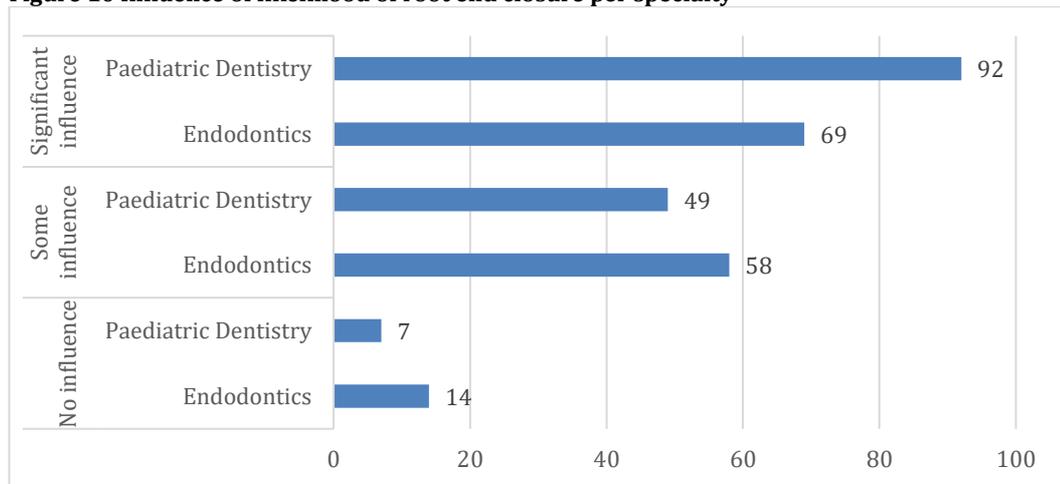


Table 38 Chi-square test for independence in relation to decision-making practice and likelihood of root end closure

| | Value | df | p-value |
|--------------------|--------------------|----|---------|
| Pearson Chi-Square | 5.996 ^a | 2 | <.050 |

7.5.18 Likelihood of Complications

47.9% (n=139) of responders (46.8%, n=66 endodontists, and 49.0%, n=73 paediatric dentists) reported that the likelihood of complications that arose as a result of endodontic intervention had some influence on their management of non-vital, immature teeth (Figure 11).

Paediatric dentists were more likely to be influenced. There was a significant effect of specialty on decision-making practice ($p < 0.018$), (Table 39).

Figure 11 Influence of likelihood of complications per specialty

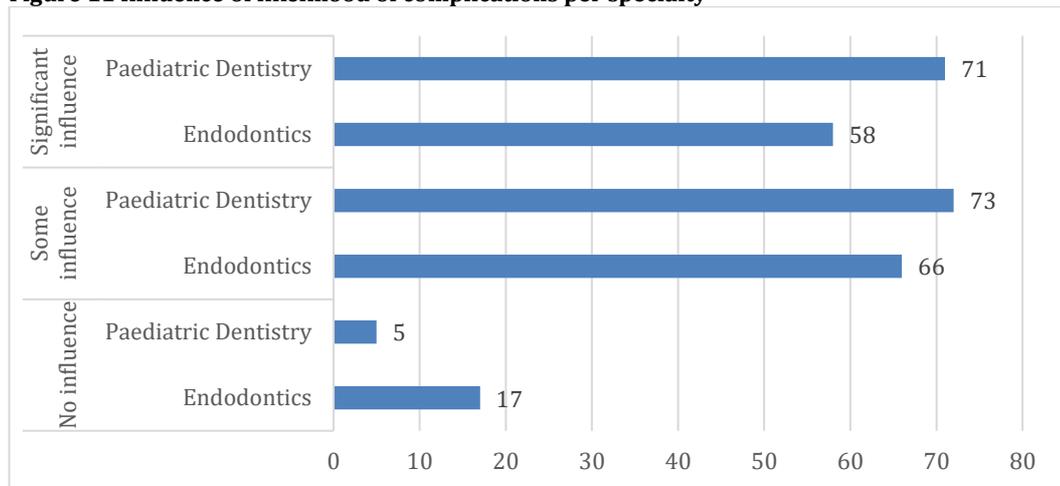


Table 39 Chi-square test for independence in relation to decision-making practice and likelihood of complications

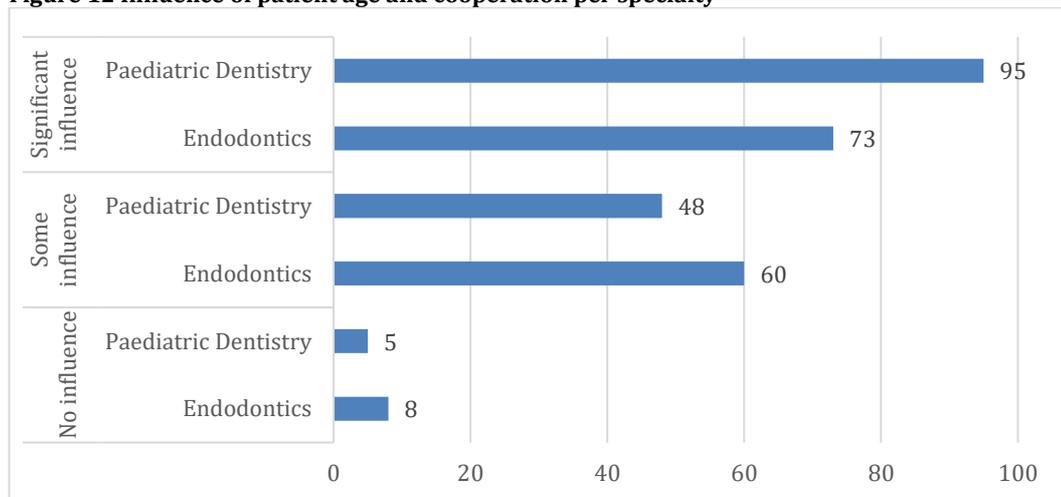
| | Value | df | p-value |
|--------------------|--------------------|----|---------|
| Pearson Chi-Square | 7.993 ^a | 2 | <.018 |

7.5.19 Patient Age and Cooperation

The majority (57.9%, n=168) of responders in both specialties (51.8%, n=73 endodontists, and 63.8%, n=95 paediatric dentists) reported that patient age and cooperation had significant influence on their management of non-vital, immature teeth (Figure 12).

Paediatric dentists were more likely to be influenced. There was no significant effect of specialty on decision-making practice ($p < 0.107$).

Figure 12 Influence of patient age and cooperation per specialty



7.5.20 Summary of Influences on the Decision-Making Practices of Responders

Availability of evidence based literature exhibited the greatest influence on the decision-making practices of all responders (Table 40).

Paediatric dentists were significantly more likely than endodontists to have their decision-making practices influenced by material cost, local protocol and the likelihood of resolution of infection.

Table 40 Summary of the factors influencing responders

| Factor of Influence | Specialists self-reporting significant influence of factor on their decision-making practice | Statistical effect of specialty | Group more likely to be influenced |
|---------------------------------------|--|---------------------------------|------------------------------------|
| Evidence Based Literature | 83.8% | <0.616 | None |
| Previous Clinical Experience | 70.0% | <0.236 | None |
| Likelihood of Resolution of Infection | 65.9% | <0.003 | Paediatric dentists |
| Patient Age and/or Cooperation | 57.9% | <0.107 | None |
| Likelihood of Root End Closure | 55.5% | <0.050 | Paediatric dentists |
| Dimensions of the Tooth Root | 55.2% | <0.986 | None |
| Likelihood of Complications | 44.5% | <0.018 | Paediatric dentists |
| Local Protocol | 21.0% | <0.001 | Paediatric dentists |
| Material Cost | 4.1% | <0.001 | Paediatric dentists |

Word frequency queries limited to 10 words are summarised below (Figure 16, Figure 17, Figure 18).

Figure 16 Word frequency query: all responders combined limited to 10 words

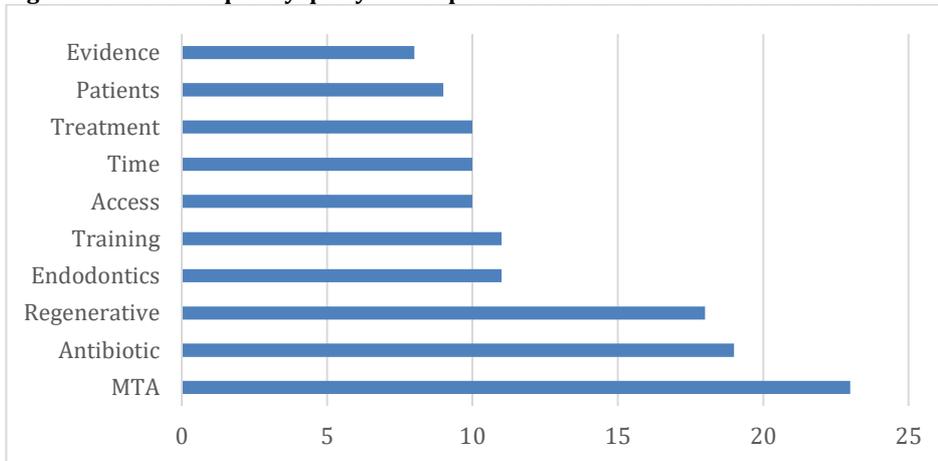


Figure 17 Word frequency query: endodontists limited to 10 words

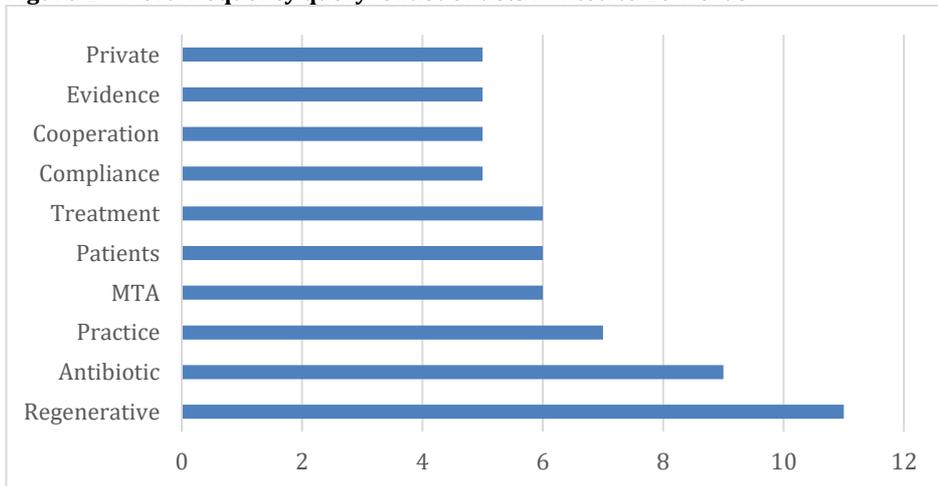
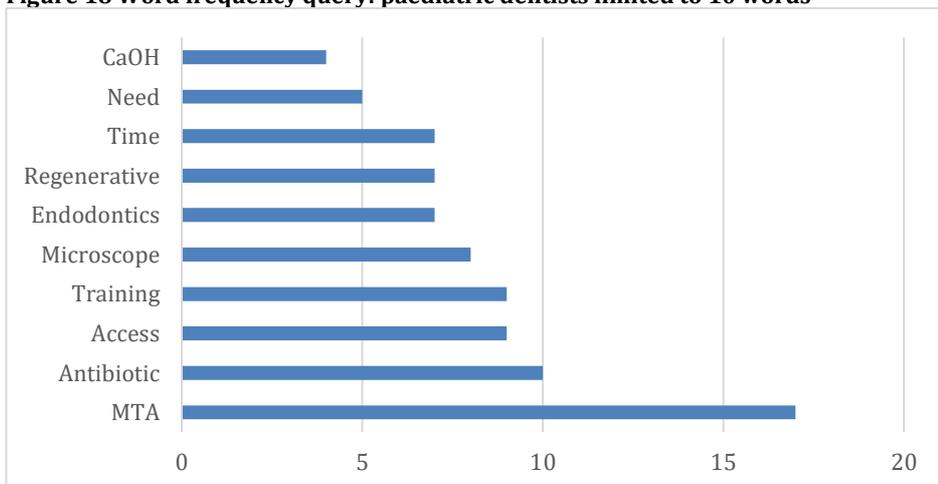


Figure 18 Word frequency query: paediatric dentists limited to 10 words



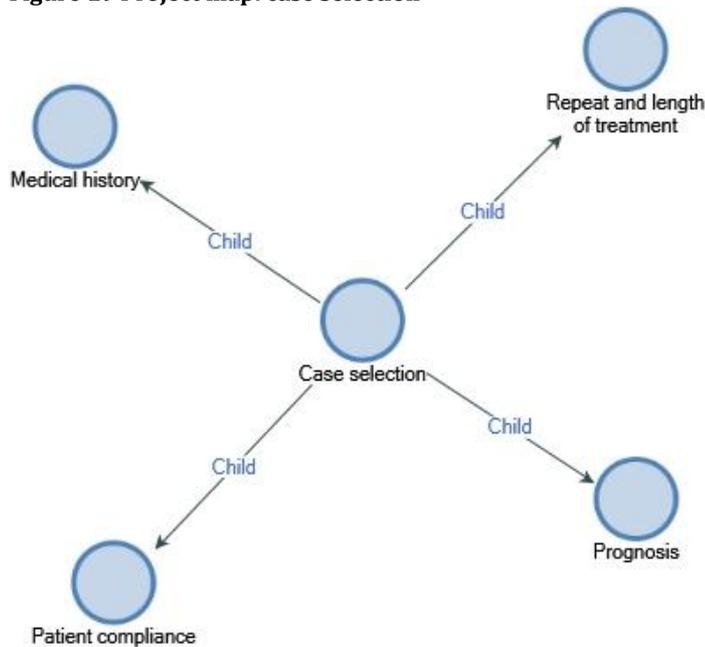
A number of comments have been extracted as examples of the free text comments provided by responders (Table 41).

Table 41 Selection of free text comments provided by responders

| Theme | Endodontists | Paediatric Dentists |
|-----------------------------|--|---|
| Clinician Experience | <p><i>My training and experience is the main limitation for not using regenerative procedures</i></p> <p><i>I would like to read more on regenerative endodontics</i></p> <p><i>As there are no definitive answers yet - I normally root fill as soon as possible</i></p> | <p><i>I need training in MTA</i></p> <p><i>There is the challenge of finding sufficient time within the trained workforce to carry out regenerative endodontics</i></p> <p><i>My department is negative about MTA – but I have arranged training</i></p> |
| Knowledge | <p><i>Regenerative endodontic procedures are definitely the way in which this clinical challenge will be managed in the near future. Within 5 years these techniques will be practiced regularly by endodontic specialists and will be taught on post-grad programmes</i></p> <p><i>Managing immature teeth is, in essence, pre-implant therapy</i></p> | <p><i>New guidelines are needed!</i></p> <p><i>I don't think enough is known about regenerative endodontics for me to start planning it for my patients</i></p> <p><i>I wouldn't know where to start with regenerative endodontics!</i></p> <p><i>I think the regenerative procedure shows promise – but it needs evidence behind it</i></p> |
| Patient Selection | <p><i>Restrictions are to be case specific with regards the limitations of restoration of the tooth</i></p> <p><i>Most patients I see with immature apices have had previous attempts at treatment carried out by other clinicians</i></p> <p><i>I don't treat open apices often due to limited compliance of the children</i></p> <p><i>Long term retention of these teeth is the aim</i></p> | <p><i>Few patients referred to community have compliance for endodontics</i></p> <p><i>To me the most important thing is how the patient feels about things</i></p> <p><i>I'm a little confused about how is most likely to benefit from regenerative endodontics</i></p> <p><i>Calcium hydroxide works for me!</i></p> |
| Local Factors | <p><i>Getting antibiotic paste is difficult. Pharmacists have laughed me out of the shop and no one supplies it commercially</i></p> <p><i>I can choose to work as I wish – but I can only do so when the materials I need are available to me – I have had no luck getting hold of antibiotic paste so far</i></p> | <p><i>I have no access to a microscope</i></p> <p><i>These procedures are not done by consultants in my unit</i></p> <p><i>It is difficult getting antibiotic paste</i></p> <p><i>No microscope or MTA carrier in my department</i></p> <p><i>By time the patient has waited for an appointment CaOH has worked!</i></p> <p><i>I am the only person in my unit treating open apices</i></p> |

Thirty two responders provided opinion in relation to careful case selection of patients (Figure 19). Additional themes identified were medical history, compliance for the proposed procedure, the length of treatment visits and the necessity for repeat treatment in the case of calcium hydroxide apexification, or the case of failure of regenerative endodontic procedures. Prognosis, and the ability of the responder to predict prognosis, were sometimes discussed with treatment outcomes.

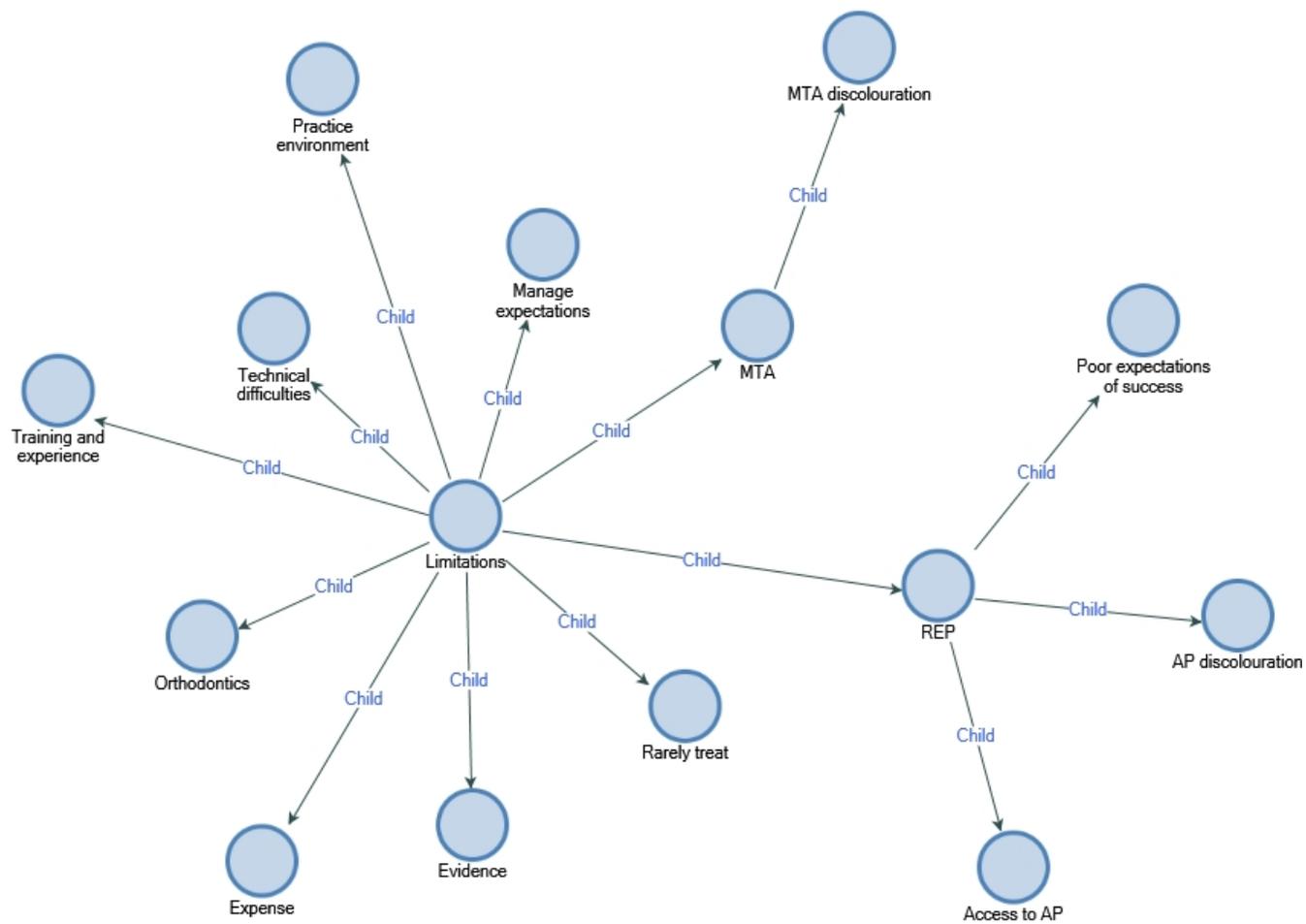
Figure 19 Project map: case selection



The remaining responders focused their opinion in relation to the limitations of delivering endodontic interventions for immature teeth (Figure 20). Distinct themes emerged in relation to practice environment, managing the expectations of the patient and parent, technical difficulties in ensuring optimal clinical outcomes for both MTA and REP, and the cost of providing treatment.

A number of endodontists described their hesitation to charge young patients for the time required to complete treatment. Poor expectations of success were associated with REP. Postoperative tooth discolouration was associated with both MTA and REP.

Figure 20 Project map: limitations of the interventions



7.6 Discussion

7.6.1 Study Population

This survey was appropriately designed to target specialists working in both paediatric dentistry and endodontics, to analyse, and compare, their clinical practice in relation to non-vital, immature teeth. Responses from specialists in both fields indicate an appropriate shared interest in this clinical problem (as discussed in chapter 5: Training the Workforce to Deliver Appropriate Care).

7.6.2 Sampling Frame

Paediatric dentists and endodontists lead the profession in relation to the development of interventions for immature teeth, and are probably best placed to manage this clinical problem. The population of interest for survey was thus identified. Inviting the entire eligible cohort to participate negated the need to account for selection bias as a result of sampling the population, however, it is noted that non-responders may have introduced self-selection bias. Population source was the General Dental Council's Specialist lists.

7.6.3 Primary and Secondary Objectives

This survey was designed to address the research question: *how do specialists in paediatric dentistry and endodontics manage non-vital, immature teeth?* Survey of specialists has been an appropriate research tool to investigate this research question successfully. It has emerged that 83.8% of all responding specialists are most significantly influenced by the available evidence base, and 70.0% by their previous clinical experience when planning the management of children who require endodontic intervention for immature apices.

These data support the case for a systematic review of the available literature to date, echo the call for a randomised controlled trial to compare the interventions, and highlight the demand of the profession for transparent clinical care pathways and evidence based guidelines for reference and conviction in an agreed management protocol for non-vital, immature incisors. The predefined secondary objectives have also been met and this novel survey tool has been successful in this respect.

Data analysis has revealed interesting information that may be of interest health care providers. Demographic data for responding specialists in paediatric dentistry and endodontists has been presented and the groups have been compared. Comparison of this data has revealed differences between the specialties in relation to geographic location and practice environment.

Specialist paediatric dentists tended to be found in the Hospital Dental Services of England providing treatment to young patients within the confines of NHS teaching hospitals. Conversely, specialist endodontists tended to be found in private practice in the South of England. It is possible that private practice may facilitate the access of young patients for dentistry if appointment visits can be offered out of school, and parental working, hours. No data was collected in relation to the financial costs associated with treatment for either the providers or the consumers of the endodontic interventions investigated. Academic specialists are under-represented.

A perhaps surprising, and informative, level of agreement has been established amongst specialists in both groups in relation to the availability of access to good quality management of non-vital, immature teeth within primary care. This information too is likely to be of interest to providers of health care, and supports a need for the facilitation of continuing professional education in this subject field.

The extent to which evidence-based, clinical and environmental factors influence clinical decision-making practice in the management of open apices has been established. The decision-making practices of paediatric dentists were more likely to be influenced by patient factors, including likelihood of resolution of infection, of root end closure and of complications, than endodontists. Paediatric dentists were also more likely to be influenced by local factors, including departmental or practice protocol and material cost. Both groups were most influenced by clinician factors, including the available evidence-based literature and their personal clinical experience. This could be reflective of the nature of specialists who have completed extensive training programmes.

Analysis of qualitative data provided by responders supports the need for facilitation of continued professional development for specialists who do not routinely manage this clinical problem. It is unfortunate that the practice of paediatric dentists is limited by material costs, and reflective of the nature of the health service in which the majority of care is provided (123 paediatric dentist and 95 endodontists completed between 1-5 or more than 5 non-vital, immature teeth per month). There is a stark difference in the practice of registrants of the different specialities in relation to the use of an endodontic operating microscope for root end closure procedures and this is perhaps reflected in the concerns of paediatric dentists' in relation to material costs.

Investigation of the clinical and radiographic outcomes of apexification and regenerative endodontic techniques may empower specialists to contest obstructive local protocols with a supportive evidence-base. It is reassuring that there was a lesser effect than might be expected of patient age or cooperation on the decision-making practices of endodontists. Strengthening of the curricula of endodontic training programmes may enable some responders to deliver care to more children with greater confidence.

Dimensions of the tooth root had lesser effect on decision-making practices of specialists in both groups than might be expected (significant influence for 55.3% of endodontists and 55.0% of paediatric dentists, no influence for 7.8% of endodontists and 7.4% of paediatric dentists). It is possible that many specialists have low expectations of endodontic interventions in relation to their ability to impact on root dimensions, hence ultimately, tooth survival. It is however, remarkable that there was almost identical agreement between the specialties in the influence of dimensions of the tooth root on management.

Likelihood of complications had a significant, or some, influence on the treatment planning of 93% of specialists. Complications were not prespecified which might have aided participant understanding of the investigator's intentions, yet they might be expected to include tooth discolouration, root fracture, and tooth loss. If evidence to support regenerative endodontic procedures is lacking credibility, and there is a known association between triple antibiotic paste and tooth discolouration, clinicians may opt to manage immature teeth with an apexification procedure.

Two thirds of responders in both groups (64.4% paediatric dentists and 66.6% endodontists) do not yet have personal experience of carrying out a regenerative endodontic technique, for which a variety of root canal disinfection and dressing materials are employed. Interestingly, only one third of responders (32.9% paediatric dentists and 29.1% endodontists) were not sure what dressing material might be suitable for a regenerative endodontic procedure. This might be expected in light of rapid development of protocols for the intervention that have yet to be widely agreed and standardised despite the availability of specialist group position statements. However, this data also indicates that more specialists have knowledge of regenerative endodontic procedures than have had the opportunity to put their knowledge into practice to date.

Approximately one in five paediatric dentistry specialists, and one in twenty endodontic specialists, have not completed a root end closure procedure with an apical plug. A variety of apical plug materials are employed by those who have experience in this intervention. Mineral trioxide aggregate is the most commonly used material, in line with the current best available evidence and accepted standards for the management of non-vital immature teeth.

Likewise, most specialists would currently choose to carry out a root end closure procedure via apexification with mineral trioxide aggregate than with any other intervention. Interestingly, endodontists appear to be more prepared to plan a regenerative endodontic procedure than paediatric dentists, despite paediatric dentists managing significantly more immature teeth than endodontists. Some 16% (n=23) of endodontists would refer a child presenting for the endodontic management of an immature tooth to a paediatric dentist, highlighting a need for close collaboration of the specialities and commissioners of healthcare, couple with the establishment of care pathways for affected children.

On reflection, it may have been appropriate to determine whether responding specialists had continued to gain experience in the management of non-vital, immature teeth following registration as specialists, or whether their experience was limited to that gained during their specialist training.

As the questionnaire sought only to extract data in response to any previous experience of root end closure procedures with MTA and with regenerative endodontics, it is possible that some responders did not have the opportunity to highlight that there is a discrepancy between the number of non-vital, immature teeth they manage, their experience of interventions, and their chosen procedure.

Qualitative data analysis revealed interesting differences and similarities between the groups that may be considered appropriate reflection of their remit and working environments. The most frequent topics of discussion for paediatric dentists were mineral trioxide aggregate, antibiotic paste, and clinician access to materials, equipment and training required to deliver the interventions. Similar concerns were raised in a survey of endodontists and paediatric dentists discussed previously (Seale and Glickman, 2008, Mooney and North, 2008, Ha et al., 2016).

Conversely, for endodontists regenerative endodontic procedures, antibiotic paste and restrictions of the practice environment were most common. The specialties share concerns in relation to the availability, effectiveness and appropriateness of antibiotic paste. Paediatric dentists recognise limitations to their practice imposed by local protocol and financial restrictions that endodontists do not appear to experience.

It is possible that some paediatric dentists have a greater interest in non-endodontic aspects of the comprehensive care that paediatric dentistry offers to children. Endodontists are perhaps better informed about emerging options for root canal therapy. The working practice environment of many endodontists, perhaps affords them a greater degree of autonomy than that experienced by some paediatric dentists. Endodontists frequently discussed patient selection in terms of limitations of cooperation and compliance, whereas paediatric dentists discussed the requirement of sufficient time to successfully deliver the interventions to young anxious patients.

7.6.4 Designing an Appropriate Survey

This research was appropriately designed to describe, explore and consider how various factors might affect the specialist approach to the management of non-vital, immature teeth. Employing a self-administered, postal survey was an appropriate way in which to investigate the experience, knowledge, opinions, and practices of the target population in order to address this research question (Burns et al., 2008). The results of this study support the need for experimental research to establish cause and effect of the various independent variables at play in specialist practice environments and training programmes.

Participants are perhaps more likely to be truthful and accurate in their given answers when completing an anonymous, self-administered postal questionnaire which is completed in the absence of the researcher. It is, however, noted that a researcher cannot ascertain if a responder has understood the survey questions in their absence.

A disadvantage of using a self-administered postal questionnaire has been the encountered difficulty in examining complex issues which cannot be discussed with the responder in the absence of the researcher, limiting the validity of the study and necessitating careful construct of an appropriate research question. The answers provided to both open and closed-ended questions may be unlikely to be detailed when using a self-administered postal questionnaire such as this one. Although it is noted that succinct, and well-defined item format is perhaps appropriate in case of misinterpretation of the researcher's intentions.

Whilst both postal and online surveys allow the study cohort to be contacted directly providing accurate contact information has been sourced, researchers cannot be entirely sure that the intended recipient with either mode of contact completes the questionnaire, or that they will do so in a suitable environment in which they are compelled to devote sufficient time and attention to the task.

7.6.4.1 *Item Generation and Reduction, Pretesting and Piloting*

In this survey, 13 items were included in the final questionnaire design following item generation and item reduction as previously described (Abbott and McKinney, 2013, Saris and Gallhofer, 2014). Following review of the dental survey literature, this survey was considered to pose moderate time burden to responders (as discussed in chapter 6).

The inclusion of 13 items is within the suggested number of 25 items used to address a research question (Passmore et al., 2002), hence it is possible that an additional item could be incorporated to address whether specialists had continued to gain experience in the management of non-vital, immature teeth following registration as specialists or whether their experience was limited to that gained during their specialist training. Items were designed to capture data in relation to the demographics, experience, knowledge, opinion, and practices of responders.

Completion rate of the returned questionnaires was good (2.03%, n=6 of responses were incomplete and discarded). Incomplete responses in six cases were in section E (influences on the decision-making practices of responders). It is possible that incomplete responses in this section were due to a lack of participant certainty or knowledge in relation to the way in which the factors suggested might impose an influence on clinical choice. It is also possible that these responders were experiencing a degree of survey fatigue towards the end of the questionnaire, or that the question was not posed in a way which was easily understood by this minority of responders.

Question stems in 4 items were in excess of 20 words. It is possible that a number of non-responders were deterred from completing the survey as a consequence (Stone, 1993, Burns et al., 2008).

In this survey, data was gathered in section B in relation to responder agreement via a Likert scale. On reflection, this item could be unbalanced and unintentionally leading responders to agree with the researchers that young people have difficulty accessing good quality management of non-vital, immature apices in general dental practice (Dillman et al., 2014).

Preferable phrasing of the question stem with a closed-ended question might be: 'in my experience, access of young people to good quality management of non-vital, immature apices in general dental practice is excellent / good / fair / poor / dreadful'. This phrasing also meets the earlier discussed suggestion that question stems should be a maximum of 20 words in length.

Pre-testing was completed and served to improve clarity, and that the intention of the investigator was correctly understood. Pilot testing was also completed and served to edit the content of questionnaire items to the agreed preferences of the pilot participants. Content and face validity were assessed during these pre-test and pilot phases. Efforts were also made to evaluate whether the questionnaire measured what it was intended to measure during these processes. However, the comprehensiveness, reliability and validity of this questionnaire would be further enhanced by clinical sensibility testing. Clinical sensibility testing would serve to determine that this novel questionnaire answers the research question and the objectives of the survey.

Reliability testing of this questionnaire for future use might incorporate test-retest reliability to provide statistical analysis of whether the same question posed to the same individual yields consistent results at a four-week interval, providing intra-rater reliability. Inter-rater reliability would test that individuals expected to give the same response to a question, such as those working within the same geographical region, provide the same answers as one another. Inter-rater reliability is perhaps of lesser importance than test-retest reliability in the case of this survey.

Assessment of internal consistency would enable understanding of whether or not different question items that tap in to the same domains or constructs are correlated. In this survey, this might have been particularly useful in relation to the construct of clinical decision-making practice which was investigated by several items.

7.6.4.2 *Design Features*

Dillman's principles for survey research were followed in respect of questionnaire design, cover letter format, the inclusion of stamped, preaddressed return envelopes and a return postcard, and the reminder and repeat contact schedule (Dillman, 1978, Dillman et al., 2014).

The decision of whether to respond may be made almost immediately, hence the sincerity, importance, appearance and length of the cover letter and questionnaire were prioritised. University of Liverpool headed paper, incorporating the institutional logo, was utilised in order to emphasise the legitimacy of the research, and to inspire trust (Edwards et al., 2002).

Multiple-mode contact details for the principal investigator were provided in order that participants could ask questions about the research protocol in order to further inspire trust. The inclusion of stamped, preaddressed return envelopes ensures that any financial costs of participation were negligible, and that the burden of returning the questionnaire was minimal. The questionnaire was succinct and commenced with non-sensitive demographic data collection in order to encourage an early decision to respond (Burns et al., 2008).

Responders were assured of confidentiality without anonymity (Sierles, 2003). Confidentiality without anonymity was chosen in order to be able to track responders and reduce the burden to participants, and investigator costs, associated with repeat contact to previous responders. This method also enabled the calculation of response rate per specialty. However, the lack of anonymity may have affected the response rate as there may have been a degree of social desirability for responders, particularly in relation to comparison of the specialties if such a comparison is deemed by responders to be sensitive in nature (Sierles, 2003, Marsden and Wright, 2010).

There is advantage in identifying non-responders in order that targeted reminders can be employed to reduce the financial costs of mailing reminders to those who have already replied and to avoid burdening previous responders who may conclude that their reply was not valuable.

As previously noted (6.2, Methodological factors that may influence response rate), 65% of survey researchers make repeat contact with non-responders, or with the entire study population, either via reminders or with a second copy of the questionnaire. Some 68% of survey researchers track non-responders, hence the majority of responses may not be truly anonymous. The opportunity to contact non-responders without placing additional response burden on those who have already responded appears to be preferable to researchers.

In light of this, and the previously discussed lack of agreement regarding the benefit of reminders of participate in survey research, (Dillman, 1978, Sierles, 2003, Glidewell et al., 2012), it was considered appropriate in design of this survey that responders were tracked and repeat contact made with non-responders at predefined intervals. It is accepted some registrants may have declined to participate as a result of the confidentiality with anonymity approach, despite reassurance in relation to the process in the cover letter that accompanied the questionnaire.

The cover letter and questionnaire were designed to be limited in length to a double-sided, single sheet of A4 sized paper. The weight, and in effect the thickness and quality, of paper is measured in gsm (grams per square metre). High quality paper of 120gsm was chosen, and colour was incorporated in to both the cover letter and the questionnaire design to increase their attractiveness. It was suspected that an onerous and unattractive survey may deter responders who have demanding commitments on their time, and it was noted that the style, appearance and layout of a self-administered survey may be as important as a topical and interesting research question in generating a response (Edwards, 2010).

Inclusion in the cover letter to non-responders was a statement that reinforced the importance of each individual's contribution, and which acknowledged that a response was yet to be received, in order to produce behavioural intentions that encourage a response (Ajzen and Fishbein, 1980). This inclusion conveyed that others had responded and may have encouraged late responders to be consistent with their peers.

A self-administered survey approach was the most practicable with respect to financial costs, and the feasibility of conducting structured interviews for a large cohort of clinicians practicing across the United Kingdom. A postal approach allowed the entire study population to be invited to participate. An all-inclusive approach may encourage a 'team' response and suggests that responders need not feel individually targeted for inclusion. Repeat follow-up and personalisation of the cover letter are noted to increase response rate (Dillman, 1978, Dillman et al., 2014).

Due to financial constraints, recorded mail delivery was not utilised and a third contact was not made due to the prespecified research protocol that a third mailing of the questionnaire to responders would take place only if a response rate of 60% had not been achieved following the second mailing.

Cover letters were not personalised or hand signed in blue ink, as their design included a scanned copy of the principal investigator's signature. It is possible that if the total design method had been adhered to in its entirety that a greater response rate as predicted by Dillman would have been achieved.

The financial cost of survey administration in this research included provision of stamped, preaddressed return envelope to ensure that any financial costs of participation were negligible. A non-response postcard was designed for distribution to those who failed to reply to the first mailing. It was hoped that inclusion of the non-response postcard may capture non-responders' reasons for opting out of participation and encourage those who had little time to respond to take part (Locker, 2000). A small percentage (2.7%) of the eligible cohort chose to return the non-response card, hence the financial and resource costs of its inclusion is difficult to justify.

Conversely, the decision to include a prize draw incentive for participation may have had a positive, with almost a third (30.0%) of responders engaging. The financial cost associated with this prize draw could be worthwhile in relation to the costs of administration of this postal survey.

It was noted that the literature is mostly supportive of the effective use of small, financial incentives that appeal to the study cohort (Stephen et al., 2007, Wren and Showers, 2010, Singer, 2011, Buck et al., 2012, Olsen et al., 2012, Sánchez-Fernández et al., 2012).

Review of the literature revealed that only 6% of recent surveys of UK dentists incorporated an incentive for participation, despite the evidence base that favours the use of an incentive. Of these surveys, two were in the field of endodontics, and none were in paediatric dentistry. There was no significant effect of inclusion of an incentive in relation to response rate. However, the relatively low cost of including a small prize draw incentive in this survey appears to have been indicative of a perceived benefit for some responders, as 30% opted in and chose to provide their email address. Hence, this survey supports the use of incentives in survey research, and reports the first use of an incentive in survey of paediatric dentists.

Table 42 Financial cost of survey administration

| Item | Cost (£) |
|-------------------------------------|----------|
| Royal Mail stamps (2 mailings) | 925.20 |
| Envelopes | 30.88 |
| Printing and non-response postcards | 288.87 |
| Preadressed return labels | 15.08 |
| Prize draw incentive | 90.00 |
| TOTAL | 1350.03 |

7.6.5 Interpreting Response Rate in this Study

Following review of the literature, a mean response rate of approximately 60% was predicted, and deemed acceptable, in this self-administered postal survey of UK dentists that adhered to principles associated with encouraging optimal response rates (chapter 6).

Hence, it was planned that the research question would be appropriately addressed with a self-administered, postal questionnaire methodology, with responder tracking and repeat contact until 60% of the invited cohort responded.

Analysis of response rate revealed that almost 50% of the eligible cohort responded to the first mailing of the questionnaire, followed by response of a further 9.5% of endodontists and 17.2% of paediatric dentists. The final response rate was 61.8% of the total eligible population.

A response rate of 67.0% for paediatric dentists is comparable to those achieved in UK survey research, and notably better than in USA survey research, as discussed in chapter 6. The most recently published survey of UK paediatric dentists achieved a response rate of 45%, despite adhering to Dillman's principles (Coxon et al., 2017). As the authors of that study concluded, it is possible that lack of response indicates poor knowledge or experience in behavioural management techniques. It is possible that in the case of this survey, improved response rate was achieved due to inclusion of an incentive for completion, an interest in a novel intervention, and due to a perceived need to represent the opinion of paediatric dentists in comparison to endodontists.

Response rate was, however, not as good as that achieved in a previously mentioned online survey of a smaller group of paediatric dentistry trainees, which yielded a response rate of 71% (Kalkani et al., 2016). This survey may have enticed more participants due to its online format and its true anonymity, despite contacting the study cohort just once. It is noted that trainees may be more inclined to participate in survey research that may be beneficial for their specialist training if the subject matter is important for their learning, and if it is administered by a fellow trainee.

A response rate of 57.1% for endodontists is within acceptable realms for surveys of UK dentists, and notably better than surveys of USA endodontists, as discussed. However, it is somewhat disappointing in comparison to previous postal surveys of UK endodontists that yielded response rates of 83% and 79% (Madarati et al., 2008, Orafi and Rushton, 2013). These surveys may have had subject matters (fractured instruments and length determination) that appealed to a greater number of the invited cohort than that of non-vital, immature teeth.

Many responding endodontists in this survey stated that they infrequently provide treatment for children, and 16% reported that they would refer to a paediatric dentist if a child presented tomorrow with a non-vital, immature tooth. It is possible that non-responding endodontists simply do not manage immature apices, and unfortunately elected not to use the non-response postcard to indicate this, possibly as a result of distrust in the tracking process and the influence of social desirability bias.

The analysable response rate for paediatric dentists was greater than that of endodontists. It is possible that paediatric dentists are more likely to engage in survey research conducted primarily by a specialist in paediatric dentistry, despite the multidisciplinary profile of the research team. It is also possible that paediatric dentists were more compelled to respond to raise the profile of the specialty in comparison to endodontics if paediatric dentists consider the management of immature teeth to rest primarily within their domain.

The number of paediatric dentists with a primary role in academia was greater than that of endodontists, and it is possible that academic dentists are more likely to participate in research conducted as part of a postgraduate degree than dentists without a formal academic interest. It is noted that there were 98 consultants in paediatric dentistry at the time of survey, and that 53.1% (n=52) of those consultants responded. Paediatric dentists had significantly more frequent concerns than endodontists in relation to material cost and the limitations imposed on their practice by local protocols, and it is therefore possible that paediatric dentists were more likely to respond to a survey that provided them with a platform on which to raise their concerns than endodontists who perhaps feel that they have more autonomy and a lesser financial burden in administering interventions.

Lastly, it is also possible that paediatric dentists have different attitudes and behaviours in relation to survey research than endodontists. It could, therefore, be suggested that paediatric dentists are perhaps more likely to avoid dissonance by responding to survey research carried out by colleagues.

It has been discussed that response enhancement strategies, and the handling of the direction and extent of non-response, are taken in to account when determining the validity and generalisability of survey research (Locker, 2000). In order to assess the effect of non-response bias in this survey, a follow-up study of a sample of the non-responders is proposed to determine their characteristics and values in relation to non-vital, immature, traumatised teeth. However, unless all non-responders are successfully contacted it is difficult to estimate how representative a sample of non-responders would be of the entire population of those who did not respond. Information regarding the name, specialty and regional location of non-responders can be derived from the sampling frame available from the General Dental Council. However, demographic information that may be of interest to non-response analysis is not readily available.

Additional information of interest in relation to non-response in this survey may be non-responder gender, period on the specialist register, practice environment and number of immature teeth managed per month. Non-responder gender, geographic location, year of graduation, and university of graduation may be associated with practice patterns of dentists and may provide a basis for non-response analysis (Murray et al., 1996).

An alternative approach to analysis of non-responders might involve logistic regression and acknowledges the theory that non-responders tend to be more similar to late than early responders (Hochstim, 1967). However, it is noted that if successive staged response rates at each repeat contact were to be utilised in this way, three or more phases of data collection are preferred, and only two stages of data collection took place in this survey.

7.6.6 Survey Administration

7.6.6.1 *Method of distribution*

Employment of an online survey was considered and rejected. The General Dental Council does not provide email addresses for its registrants; therefore, in order to invite the entire target population to participate, it would have been necessary to request that the executive boards of relevant specialist societies, the British Society of Paediatric Dentistry and the British Endodontic Society, distribute an email to all specialists who were members of their respective societies containing a link to an online survey. It is possible that this permission would not have been granted, and it is likely that not all specialists are members of their specialty society.

Additionally, there may have been responses received from members of the specialty societies who were not registered specialists. A further disadvantage of this approach is that it would not have been possible for the researcher to have direct contact with the responders or to allocate potential responders with identifier codes, precluding the ability to contact non-responders with a reminder, or repeat distribution, of the survey.

Participants were mailed utilising name and address information provided annually on 31st December by all dental registrants to the General Dental Council for public access at the time the research was conducted. Contact information was requested from the General Dental Council in the first week of the New Year in order that it was up to date. Despite this, it is noted that a number of registrants were not contactable at the address that they had provided to the General Dental Council.

The timeframe for distribution of questionnaires was deliberately chosen to include a second mailing that was received shortly prior to the Easter holidays. It was suspected that a number of registrants, who provided contact details for a residential rather than a business address, may not be in a position to receive post to the address that they had provided outside of holiday periods if the address provided was a parental home address.

It was noted that the evidence is conflicting in relation to multimodal contact; it is reported that multimodal contact may decrease response rates (Smyth et al., 2010, Millar and Dillman, 2011, Medway and Fulton, 2012) but that sequential mixed-mode contact may increase response rates (Scott et al., 2011). Tracking of responders would have been complex, and possibly impracticable, with mixed-mode contact, hence survey administration via both post and email was therefore rejected. However, in light of the evidence that electronic prompts may increase response rates for postal questionnaires and reduce the overall time taken to receive responses (Clark et al., 2015), personification and reminders were distributed to all members of the specialist societies via email following permission from the chairs of the specialist bodies.

7.6.7 Sources of Error and Bias in this Study

Appropriate identification of a sampling frame for the target population in order that the results are generalisable to the entire population was not necessary in this survey as the entire subject population was invited to participate, hence, estimation of sample size was unnecessary, and selection bias was not applicable.

It is noted that if incomplete responses account for greater than 5% of responses received, missing data can be managed with multivariate imputation by chained equations (MICE) (Raghunathan et al., 2001, Azur et al., 2011), as was planned, but unnecessary, in this survey.

Alternatively, item non-response may be managed with imputation if item non-response is greater than 10%, hence it was unnecessary in this survey (Aday, 1996). Only six incomplete responses were received and there is no statistical difference between the actual and analysable response rates. These responses accounted for 2.03% of all responders, therefore these surveys were discarded as per protocol. As incomplete questionnaires accounted for less than 5% of responses, complete case analysis was accepted as a method of addressing missing data (Graham and Schafer, 2009). Hence, multivariate imputation by chained equations was unnecessary, and complete case analysis was carried out.

It was considered unlikely that recall bias would affect the data gathered in this survey, as participants were asked questions about their individual profile and practice. However, it is noted that participants may not be truthful in their responses. Survey responders may wish to answer questions in a manner that will be viewed favourably by others, and therefore social desirability bias may be expected (Kreuter et al., 2008). In this survey, it is possible that the confidentiality without anonymity approach may have introduced a degree of susceptibility to social desirability bias if the researchers were known to the responders.

Survey participation was voluntary although it was recognised that response rates may decrease if participants are offered the opportunity to opt out (Edwards et al., 2009). Those who chose not to participate may introduce non-response bias, limiting the generalisability of the results.

It is noted that whilst probability sampling requires a 100 percent response rate to guarantee unbiased estimates, a low response rate does not necessarily imply a high level of non-response bias. In this survey, a predefined anticipated response rate of 60% was chosen as acceptable following review of the literature (Sierles, 2003, Burns et al., 2008). Whilst this was achieved, it is recalled that appropriate, representative, random sampling of the population to reduce the size of study cohort, and focusing subsequent efforts on achieving as high a response rate as possible may be preferable to surveying the entire population (Parashos et al., 2005). This 'quality over quantity' approach to survey of the population may have achieved a greater response rate in this survey within the same timeframe and financial costs.

However, as previously concluded in light of the available literature, this survey's response rate of 57.1% for endodontists is satisfactory, and of 66.9% for paediatric dentists is acceptable but disappointing. The actual response rate of 62% is also acceptable, however following rejection of 2% incomplete responses, the analysable response rate of 60% lies on the threshold of acceptability of survey validity.

It is possible that responders differed to non-responders in relation to their positive attitude towards completion of surveys to help others. It is possible that some responders consider a survey a request for their individual help in determining group practice and future clinical guideline development and this belief in their contribution may be valuable in achieving a greater response rate, hence the understanding that personalized cover letters may increase response rate. A highly specialised study population may be well placed to voice an experience-based contribution and this may be a motivating factor for participation.

As discussed previously, non-responders may be less interested or less aware of the clinical problem that this study aims to address (6.2 The Significance of Response Rate). Non-response bias may lead to disparity and uncertainty in the generalisability of the results. Assuming an extreme response from the non-responders indicates an uncertainty in the estimate of prevalence due to the response rate of 62%. For example, 88.9% of all responders in this survey either strongly agreed (61.0%) or agreed (27.9%) that young people have difficulty accessing good quality management of non-vital, immature apices in general dental practice. If the opinion of the non-responding 38% of the study population does not agree then the true prevalence of disagreement has been underestimated.

7.6.8 Generalisability

The ability to invite the entire population of interest to address the study's objectives, negated the need to assess the sampling frame. Self-selection of voluntary participants has possibly introduced a non-response bias. Non-response bias may lead to disparity and uncertainty in the external validity of the results. It is therefore difficult to determine with certainty how representative this study's participants are of the population of interest.

The results of this survey also support the findings of previous surveys as discussed earlier (Designing a Survey of Multidisciplinary Specialists). Concerns raised by responders in relation to regenerative endodontic procedures included a lack of evidence, unpredictability and the availability of an antibiotic intracanal medicament. These concerns are similar to those raised by paediatric dentists and endodontists, attending a symposium of the American Association of Endodontists and the American Academy of Pediatric Dentistry.

The financial costs associated with mineral trioxide aggregate were previously cited by paediatric dentists as disadvantageous when treatment planning endodontic intervention. In this survey 59.7% of paediatric dentistry specialists use mineral trioxide aggregate as first line management for apical closure, compared to 54.5% of paediatric dentistry consultants practicing in 2008.

This survey provides evidence that approximately 54.6% of endodontic specialists would also plan mineral trioxide aggregate as first line management for apical closure. A majority, 77.2% of Australian endodontists, reported that they had experience in carrying out a regenerative endodontic procedure (Ha et al., 2016), compared to 33.3% of UK endodontists in this study. It is possible that UK specialist practice is more resistant to emerging treatment modalities, or that the availability of a more robust evidence based literature is preferred prior to change in clinical practice. As previously mentioned, 96.3% of the same cohort of Australian endodontists would chose mineral trioxide aggregate as first line management for apical closure despite their relative experience in the delivery of regenerative endodontic procedures.

7.7 Future Work

It would be of great interest to determine the diagnosis and intervention rates for non-vital, immature permanent teeth, managed in both primary and specialist dental care environments. Collection of outcome data for the total population treated via apexification with calcium hydroxide, mineral trioxide aggregate or regenerative endodontic procedures would enable clinical and patient reported outcome and experience measures to be benchmarked, whilst serving to estimate the unmet need of the population who experience dental trauma in light of prevalence data recorded by the Child Dental Health Survey (Steele J et al., 2015).

Furthermore, access to the population who suffer traumatic dental injuries and who fail to present for treatment, or who present but remain untreated, would be of considerable interest. If such a population could be identified and surveyed it might be possible to develop a better understanding of barriers to access and provision of emergency care for dental trauma. Examination of this population would enable evaluation of the impact and burden of untreated traumatic dental injuries on oral health and development.

Likewise, insight in to the decision-making practices of dental practitioners who fail to manage traumatic dental injuries would be valuable and may support wider access to postgraduate training and continued professional development.

Data collection on this scale would be complex, and is perhaps currently only within the remit of collaborating health care providers, although opportunity may arise to participate in nationwide data collection on this scale if the plight of children affected by traumatic dental injuries is raised. Analysis of the self-reported, clinical decision-making practice of specialists was more achievable and will serve to support the guidance of future clinical practice for all dental practitioners.

It has been recognised that trauma related teaching needs to be enhanced within the undergraduate curriculum (Rodd et al., 2010b). Appropriate intervention for children with incisor injuries may increase tooth survival and may also yield important psychosocial benefits (Rodd et al., 2010a). The consequences of unmet need for affected children may include dental morbidity, hospital admission and tooth loss, hence clinician knowledge and behaviour in responding to traumatic dental injuries is of importance to the child population. Dissemination of the results of this survey may encourage the relevant specialties to reflect upon undergraduate and postgraduate teaching needs, and to incorporate in to curricula the importance of shared, comprehensive care and emerging treatment modalities for children.

It was not appropriate within the scope of this work to estimate the number of affected children presenting to specialist services on an annual basis within the United Kingdom. An analysable response rate of 61.8% and difficulties assessing the likely magnitude and extent of non-response bias with the limited non-responder data available preclude the possibility of approximating such data. It was, however, established that 75% (n=218) of responders are managing between 1-5 or more than 5 non-vital, immature teeth per month. It can, therefore, be estimated that this population of responders is managing up to approximately 1090 cases per month (218 x 5).

If it is assumed that responders have an active interest in the subject field, and that non-responders do not routinely manage this clinical problem, then it is suggested that at least 13,080 (1090 x 12) non-vital, immature teeth are managed by specialists in paediatric dentistry and endodontics alone per year in the UK.

It is of course likely that an unknown number of non-responders do manage this clinical problem and have chosen not to respond for a variety of other reasons that have been discussed. Furthermore, many such cases are successfully managed in primary and secondary care by dentists with a special interest in endodontics or paediatric dentistry. Nevertheless, this survey has supported the role of specialists in the endodontic management of immature teeth, and provides data on which to reflect on trends of prevalence and access if it is repeated in the future, with further efforts to improve response rate.

Replicating this survey in the future may detect changes in clinical practice in this rapidly evolving field of interventional dentistry. A longitudinal study of the study population and the factors that influence parameters affecting their decision-making practices may have considerable analytical advantages over survey research, however this can be challenging to implement successfully.

A longitudinal study may allow better detection of changes in clinical practice, as the evidence base and material science develop, than repetition of this survey in the future. Predictable difficulties in designing a longitudinal survey to answer the study question include practical complexities in tracking participants over time and keeping those participants motivated to continue with limited individual benefit. If this survey were to be replicated, optimising the response rate of a representative random sample may be more appropriate than achieving a less than optimal response rate from an invited entire population of interest (Edwards, 2010).

This survey was not designed to investigate the relationship of specialists with primary care clinicians in relation to shared care, nor to address the management of non-vital, immature teeth by primary care clinicians. Expanding the field of interest to incorporate these aspects of care for young children who have suffered dental trauma may be of interest for future work. However, the practice of primary care clinicians is not appropriate for inclusions in the objectives of this survey, which instead set about to investigate the practices of those who have been trained in the specialist management of complex endodontic presentations.

Investigation of the practice of primary care clinicians would warrant complete survey redesign and administration, to be appropriate for the target participants. A similar survey designed to assess knowledge of the emergency management of traumatic injuries in children by primary care clinicians yielded a response rate of 68% following a single request for participation, suggesting that primary care clinicians may respond favourably if invited to participate (Kostopoulou and Duggal, 2005). Hence, redesign of this survey for administration to an appropriate sample of primary care clinicians may yield a response rate that provides insight to the management of this clinical problem in primary care.

As a result of this survey, a research question has emerged in relation to the management of non-vital, immature teeth by primary care clinicians. Redesign of this survey, and its administration, to address this question may help to inform both the general and specialist dental professions of the access of young people to appropriate endodontic care. It is likely that a large target population would be required to gather sufficient data analysis for interpretation, unless a group of primary care clinicians with a special interest in endodontics can be identified. It is noted that such clinicians may be identifiable through specialist societies, yet it is not known how variable their approach might be to those primary care clinicians who are carrying out apexification procedures, within their remit as dentists, without a declared specialist interest. Such a survey might provide the opportunity for primary care clinicians to respond to the 88.9% of responders in this survey who agreed that young people have difficulty accessing good quality management of non-vital, immature apices in general dental practice.

Dissemination of the results of this survey may aid service planning, training provision and future guideline development in relation to the management of non-vital, immature teeth. Sharing of the results may affect individual and group practice, and may serve to unify the specialities in their approach towards this common and complex clinical problem. Paediatric dentists and endodontists will be encouraged to collaborate across the boundaries of speciality to share knowledge and experience with the purpose of improving clinical outcomes for children who have suffered traumatic dental injuries.

7.8 Conclusion

An overall response rate of 62% of UK specialists in paediatric dentistry and endodontics provides a representative sample of the study population from which to draw conclusions. This survey has appropriately addressed the research question: *How do Specialists in Paediatric Dentistry and Endodontics Manage Necrotic, Immature, Permanent Teeth?* The objectives of the study have been individually addressed as follows:

Primary Objective

- The majority of UK specialists in paediatric dentistry and endodontics manage non-vital, immature incisors in their everyday practice. Paediatric dentists are significantly more likely than endodontists to manage non-vital, immature teeth. There is variation in practice between and within the specialities.

Secondary Objectives

- Demographic data has been gathered and reflects disparities in access to specialist management of non-vital immature teeth between and within the specialties in terms of geographic location and practice environment.
- Good agreement exists both between and within the specialties in relation to the availability of access to good quality management of non-vital, immature teeth within primary care.
- The decision-making practices of specialists may be affected by specialty, role, practice environment, geographical location, and experience.

There is a need for facilitation of continued professional development for specialists who do not routinely manage this clinical problem.

A united call has been made by responding specialists for review of the evidence based literature, and guidance in relation to the optimal management of non-vital, immature permanent teeth.

The results will be made available to inform the provision of oral health care for children who have suffered traumatic dental injuries.

8 Interventions for the Management of Necrotic Immature Permanent Teeth: A Systematic Review

8.1 Research Question

Does the literature provide evidence for an optimal intervention for the endodontic management of necrotic, immature permanent teeth in a young population?

8.2 Clarification of Research Question and Scope

8.2.1 Introduction

As previously discussed (chapter 5), there are three recognised intervention strategies for the management of necrotic, immature, permanent teeth. Review of the literature has suggested that each of these interventions has a role in the management of open apices that is not without its limitations. The literature in relation to immature apices is vast, yet it appears to be comprised primarily of case reports and observational studies. Such studies have a valid and key role in the development and reporting of novel interventions, however, they are considered to be relatively low in study quality (Khan, 2011, Gosall and Gosall, 2015).

Likewise, few randomised controlled trials appear to have been reported that compare the interventions. It has been suggested that the lack of quality controlled, comparative randomised controlled trials to support the decision-making practices of clinicians constitutes a significant knowledge gap in the endodontic literature (Kontakiotis, Filippatos, and Agrafioti 2014).

As previously described, four existing systematic reviews have previously addressed the interventions (Chala et al., 2011, Kontakiotis et al., 2014, Lin et al., 2016b, Antunes et al., 2016). No existing systematic reviews have sought to compare all the interventions, nor have they reviewed the literature for alternative approaches to the management of immature apices, despite the prevalent, and challenging, problem of non-vital, immature teeth, and the complexities of decision-making that clinicians face.

8.2.2 Rationale for a Systematic Review

A scoping search was conducted (chapter 5) that revealed that a large amount of information has been generated by dental researchers to date, in relation to interventions for managing necrotic, immature teeth. Existing systematic reviews have previously attempted to summarise the available evidence. However, the quality of those reviews is compromised to varying extents. The authors of those reviews have each concluded that the quality, and number, of included studies was limited.

In order to address the endodontic knowledge gap, and to robustly support the evidence-based decision-making practices of clinicians, it is imperative that high quality studies are carried out, appropriately reported, and available for systematic review. Review of the literature has confirmed that material science and intervention developments are rapidly advancing. Thus, it might be expected that high quality comparative studies of the interventions continue to be published.

As a result of the identified limitations of previous reviews (chapter 5), and in the absence of a review that compared all of the interventions, the research question could not be adequately addressed to answer whether the current literature provides a reliable evidence base for the optimal management of non-vital, immature, permanent teeth.

Survey of the specialist paediatric dentistry and endodontic professions has manifested a united call for review of the evidence-based literature, and guidance in relation to the optimal management of non-vital, immature permanent teeth (chapter 7).

In light of this accumulated evidence, the magnitude of the clinical problem, and in the wake of rapid development of intervention protocols for regenerative endodontic procedures, it was felt that a full and contemporaneous systematic review of the interventions was justified.

The aim of this systematic review was to assess the clinical and radiographic effectiveness of the three recognised interventions for the endodontic management of necrotic, immature, permanent teeth. The interventions considered were apexification with calcium hydroxide (CaOH), apexification with mineral trioxide aggregate (MTA), and regenerative endodontic procedures (REP).

8.2.3 Primary Objective

- This systematic review aimed to produce a thorough and explicit review of the relevant literature for the management of non-vital, immature permanent incisors, and in doing so, aimed to address the call for evidence synthesis for the clinical dilemma posed.

8.2.4 Secondary Objectives

- To compare the effectiveness and limitations of three treatment approaches calcium hydroxide apexification (CaOH), mineral trioxide aggregate apexification (MTA), and regenerative endodontic procedures (REP), for root end closure in managing non-vital, immature, permanent teeth.
- To identify the methodological limitations of the current approaches to investigating the management of non-vital immature permanent teeth.
- Examine the case for undertaking a randomised controlled trial by providing an explicit evaluation of the weaknesses of the available studies.
- To provide recommendations to guide future research and inform the design of a future randomised controlled trial.

8.3 Method

The review was conducted according to accepted procedures for conducting and reporting systematic reviews (Moher et al., 2009).

8.3.1 Registration

The protocol for this systematic review was published on the PROSPERO register CRD42014004096.

8.3.2 Eligibility Criteria

Eligibility criteria are listed in Table 43, and discussed below.

Population: No age limitations were imposed on participants. Whilst it was expected that the majority of endodontic interventions for non-vital, immature teeth are delivered to children, the effect of the interventions in older participants is of interest, particularly in respect of regenerative endodontic procedures that may harness the regenerative potential of stem cells. There were no limitations imposed in relation to the aetiology of necrosis (i.e. trauma, caries, dental anomaly), nor tooth type.

Interventions: Comparative studies of three recognised interventions (CaOH, MTA and REP) for the management of necrotic immature, permanent teeth. Few limitations were imposed in relation to delivery of the interventions, on condition that a clear description of the intervention protocols was described.

Comparators: It was considered likely that the control would be one of the three interventions, as failure to provide treatment or placebo treatments would lead to probable tooth loss, and therefore, ethical approval is unlikely to be granted for comparative studies that do not include an intervention as a comparator.

Outcomes: A scoping review confirmed that outcome reporting is diverse, and that assessment tools may record subjective judgements or objective data, with varying construct validity. It was therefore decided that the primary outcome would encompass a shared patient and clinician based-outcome, of any adequate description of tooth survival, with clinical and radiographic signs of healing. Tooth development, apical barrier formation, and sensibility testing were included as secondary outcome measures due to debate in the literature in relation to the

occurrence and the importance of these clinician-based outcomes (Torabinejad, 2016).

Tooth discolouration was included due to its importance to young patients, and due to suggestions within the literature that the interventions are associated with iatrogenically induced colour change. The incidence of reported complications was included to confirm the safety of the interventions and to inform the appropriate design of a future randomised controlled trial.

8.3.3 Study Selection

Evidence was derived from experimental comparative studies and randomised controlled trials. Also accepted were pseudo-randomised controlled trials with appropriate application of sufficient quality assessment. Non-comparative studies, cohort studies, case-control series, case series, and case reports were excluded due to the inherently biased nature of these study types, and due to the existence of non-systematic review papers that have described these studies, as discussed in chapter 5. In-vitro, ex-vivo, and animal studies, review articles, letters, and opinion articles were also excluded.

8.3.4 Information Sources and Search Strategy

A literature search was conducted of the major electronic databases including: The Cochrane Library (CENTRAL, Cochrane Database of Systematic Reviews, Cochrane Methodology Register), MEDLINE, EMBASE, Scopus, EBSCO Dentistry and Oral Sciences Source and PubMed. Unpublished literature was searched for on the UK Clinical Research Network Portfolio Database, Current Controlled Trials, ClinicalTrials.gov and the TRIP Database. A search strategy was devised and was adapted as appropriate for the listed databases (Table 44). Additionally, a lateral approach involving a review of reference lists in papers was undertaken. Additional studies were identified by hand searching, contacting clinical experts and searching the grey literature. It was planned that authors would be contacted for further clarification when necessary. The database was held in an Endnote software package. The original search dates were: 1946 – 30th April 2014. An update search was conducted to ensure that the review was contemporaneous, the dates of which were: 30th April 2014 – 31st October 2016.

Table 43 Inclusion criteria

| | |
|---------------------------|---|
| Question | Does the literature provide evidence for an optimal intervention for the endodontic management of non-vital, immature teeth in a young population? |
| Population | Patients with a non-vital, immature permanent tooth (diagnosed clinically and/or radiographically) for which endodontic treatment is indicated |
| Interventions | Endodontic treatment including apexification with calcium hydroxide or apexification with MTA or regenerative endodontic procedures (also known as pulp revascularisation or revitalisation) for a tooth with a diagnosis of pulp necrosis / loss of vitality / irreversible pulp disease / periapical periodontitis Clear description of the intervention protocols |
| Comparators | All variations of the interventions will be included Variations in protocol will be described Each of the interventions will be compared to the other two interventions / placebo / no treatment as applicable Studies involving only part of one of the interventions as accepted by current protocol, or combining interventions, will be excluded Studies will be included of interventions administered over any time period Co-interventions will be noted and these studies will be included unless the co-intervention represents a significant default from the recognised protocol for the intervention |
| Primary Outcome | Tooth survival with clinical and radiographic signs of healing <ul style="list-style-type: none"> • Absence of signs and symptoms of pulpal or periapical inflammation • Radiographic signs of healing including resolution of periapical radiolucency, absence of root resorption |
| Secondary Outcomes | Tooth development recorded objectively or subjectively with plain film or digital image standardisation software Formation of an apical barrier Tooth discolouration Positive response to sensibility testing |
| Setting | All dental care settings Outcomes evaluated clinically and radiographically with a follow-up period of not less than 6 months |
| Study design | Randomised controlled trials Pseudo-randomised controlled trials |
| Language | Limited to English |

Table 44 Sample search strategy

| Database: Ovid MEDLINE(R) <1946 to April Week 4 2014> Search Strategy: |
|--|
| 1. ((open or unformed or immature or pulpless or incomplete or blunderbuss or non-blunderbuss or non-blunderbuss or non-vital or nonvital or adult or permanent or necrotic) adj (tooth or teeth or apex or apices or anterior\$ or incisor\$ or canal\$)).tw. (7099) |
| 2. exp Tooth, Nonvital/ (1381) |
| 3. (dental adj (tissue\$ or pulp)).ti,ab. (5292) |
| 4. (root end closure or root end induction or apexification or barrier formation or root canal treatment or apexogenesis).tw. (1869) |
| 5. (calcium hydroxide or CaOH or mineral trioxide aggregate or MTA or tricalcium silicate or portland cement or biodentine or revasculari?ation or revitali?ation or regenerative endodontic\$ or regenerative pulp therapy or pulp regeneration or regenerat\$ or maturogenesis).tw. (147082) |
| 6. exp Apexification/ (111) |
| 7. (or/1-3) and (or/4-6) (1328) |
| 8. limit 7 to humans (1057) |
| 9. limit 8 to English language (987) |

8.3.5 Identification of Eligible Studies

The titles and abstracts of studies retrieved using the search strategy were stored in EndNote X8, and were independently screened by two reviewers, in order to identify all of the studies that potentially met the inclusion criteria. The full text of the potentially eligible studies, and those where there was insufficient data available in the title and abstract to make a decision, were retrieved and independently assessed for eligibility by two reviewers. The full texts of all eligible studies were sourced from a university library and an inter-library loans system. Discrepancies in opinion regarding eligibility were identified and resolved through discussion with a third reviewer where necessary. Inclusion criteria were applied as previously described to determine the number of studies for data extraction.

8.3.6 Data Extraction Strategy

A standardised, pre-piloted form was used to extract data from the included studies for quality assessment (risk of bias) and evidence synthesis. Data was extracted independently by two reviewers and included:

- Author, year of publication, country of origin, journal of publication
- Study type
- Aim
- Tooth type
- Sample size
- Age range
- Aetiology
- Observation period
- Assessment tool
- Tooth loss
- Feasibility / acceptability
- Details of the interventions, techniques and controls
- Outcomes assessments
- Methodological limitations of the study

It was planned that if data extraction issues arose they would be resolved according to a predetermined approach (Table 45).

Table 45 Predicted data extraction issues and proposed resolutions

| Data extraction issues | Resolution |
|--|--|
| Studies where there was any difficulty in determining the methodology or data | The author of the study was contacted for clarification using open-ended questions to avoid overly positive answers (Higgins et al., 2011) |
| Data from multiple publications | The primary referenced or most recently published paper was chosen and adjoining publications were listed |
| Studies that did not meet the inclusion criteria | Studies were excluded with reasons for exclusion |
| Ongoing studies that did not report relevant outcomes but met the inclusion criteria | Studies were listed for future use |
| Studies involving only a subset of the participants | Data were requested from study authors |
| Missing data | Data were requested from study authors |

8.3.7 Quality Assessment Strategy

As previously discussed, The Centre for Reviews and Dissemination (CRD) Checklist for quality assessment is accompanied by detailed guidance for its appropriate use (Centre for Reviews and Dissemination, 2009), and the tool is adaptable to suit the needs of individual systematic reviewers (Boland, Cherry, and Dickson 2014).

The CRD quality assessment tool was adapted as detailed below (Table 46), for included studies. The quality of the individual studies was assessed by one reviewer and independently checked for agreement by a second. Disagreements were resolved through discussion with a third reviewer if necessary. Judgements were limited to: yes/no/partially/not reported. If authors did not report, or provided inadequate detail for a quality judgement to be made, it was assumed that bias was present. Criteria for judging risk of bias in the assessment tool were used as detailed below and adapted from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011).

An overall judgement of risk of bias was given as follows:

- Low risk of bias if all criteria defined were met as might reasonably be expected
- Moderate risk of bias if participants were randomised and the remaining criteria were mainly met
- High risk of bias if participants were not randomised and the remaining criteria were mainly not met

Table 46 Quality assessment tool for risk of bias

| |
|--|
| Randomisation (allocation bias) |
| Was the method used to assign participants to groups truly random? (Such as a random number table, a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots) |
| Was the allocation of treatment concealed? Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation central allocation, sequentially numbered, opaque, sealed envelopes. |
| Was the number of participants randomised stated? |
| Comparability (confounding) |
| Were participant demographics presented for baseline comparability? |
| Were the groups comparable at baseline? |
| Eligibility (selection bias) |
| Were eligibility criteria specified? |
| Were there any co-interventions that might influence the outcomes for one group? |
| Blinding (detection bias) |
| Were outcome assessors blinded to treatment allocation when possible? e.g. for clinical outcomes (or if no blinding or incomplete blinding, but the outcome is not likely to be influenced by lack of blinding) |
| Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. |
| Were participants blinded to treatment allocation? |
| Were the intervention administrators blinded to treatment allocation? |
| Participant Dropouts (attrition bias) |
| Were >80% of randomised participants included in the final analysis? |
| Were participant dropout reasons stated and balanced in numbers across groups, with similar reasons for missing data across groups? |
| Was an intention to treat analysis included? |
| Outcomes (reporting bias) |
| Is there evidence more outcomes were measured than reported? |
| Is there evidence of registration on a trial database? |

8.3.8 Data Synthesis Strategy

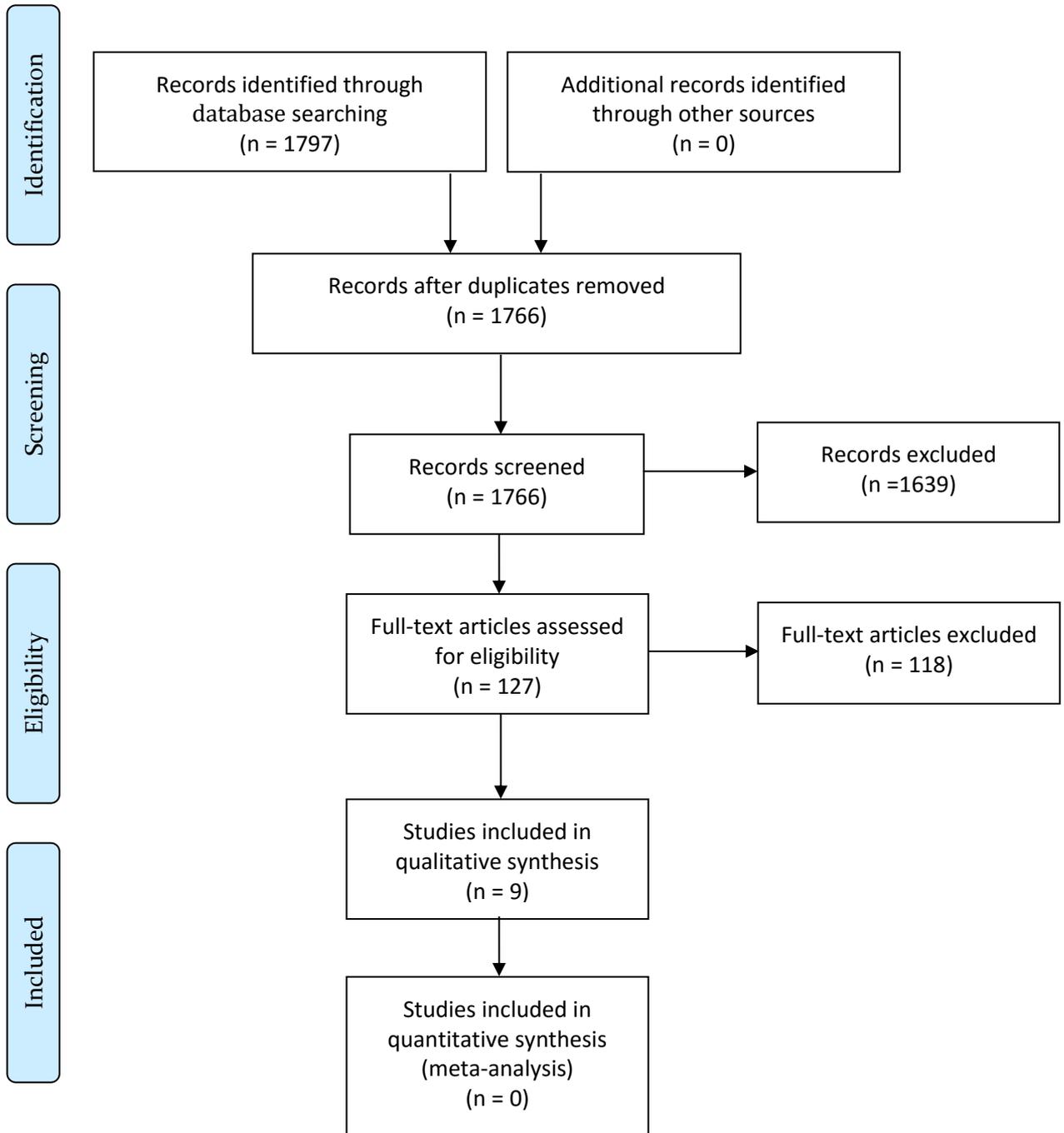
A narrative description of the data extraction and quality assessment was planned, with presentation of the results in structured summary tables, coupled with a discussion of the studies' characteristics and findings, and the possible effects of bias on the effectiveness data.

It was recognised that outcome data would be extracted from studies with reported heterogeneous intervention protocols, assessment tools, and outcome observation periods. If data were available, determination was planned of the direction of the intervention effects, the size of the effects, whether the effects were consistent across studies, differences in the effects, and the strength of evidence for the effects.

It was anticipated that there would be limited scope for meta-analysis as a result of diverse study methodology, heterogeneous intervention and reporting protocols, and an expected small number of existing comparative randomised controlled trials. However, a random-effects meta-analysis of studies with a low risk of bias that described the same type of intervention and comparator, and the same validated, reliable outcome assessments was planned for if these criteria were met, in order to increase power, to improve precision, and to explore reasons for differences in effect. Intention-to-treat (ITT) analysis was planned to include all participants randomised into a trial within the groups to which they were randomised, regardless of which treatment they received.

If meta-analysis was possible it was expected that included studies would have a substantial degree of heterogeneity due to likely clinical and methodological diversity. Heterogeneity of intervention effects was planned with a chi-squared test (χ^2) and inconsistency with the I^2 statistic. An I^2 value greater than 50% was determined to be indicative of substantial heterogeneity and χ^2 with $p < 0.1$. It was predicted that dichotomous outcome data would arise and that the effect measures likely to be encountered were risk ratio (RR), odds ratio (OR), risk difference (RD) and number needed to treat (NNT). When calculations were based on odds ratios, the findings were to be transformed to describe the results as changes in the concept of risk. If a combination of dichotomous and continuous data arose, the mean differences and standard deviations would be extracted as continuous outcomes, the counts as dichotomous outcomes and all the data in text form as 'other data' outcomes. Sensitivity analyses would be conducted where appropriate.

Figure 21 PRISMA 2009 Flow diagram



8.4 Results

Following the removal of duplicates, 1766 studies were identified by the combined searches (1243 in the original search, 523 in the update search). The titles and abstracts of 1766 studies were reviewed, and the full text of 127 potentially eligible studies were retrieved (109 in the original search, 18 in the update search).

118 full text articles were excluded as follows:

- 32.2% (n=38) individual case reports
- 19.5% (n=23) case series / non-comparative / retrospective studies
- 18.6% (n=22) non-comparative prospective studies
- 12.7% (n=15) review articles / opinions / letters to the editor
- 9.3% (n=11) in-vitro, ex-vivo, animal studies
- 7.7% (n=9) study protocols

9 full text articles were included as follows (Tables 47-50):

Author (year of publication), country of origin, journal of publication

- Roberts and Brilliant (1975), USA, Journal of Endodontics
- Bal et al. (1993), India, Indian Journal of Dental Research
- El-Meligy and Avery (2006), Egypt, Pediatric Dentistry
- Pradhan et al. (2006), India, Journal of Dentistry for Children
- Bonte et al. (2015), France, Clinical Oral Investigations
- Damle et al. (2016), India, Dental Research Journal
- Nagy et al. (2014), Egypt, Journal of Endodontics
- Lee et al. (2015), Taiwan, Journal of Formosan Medical Association
- Narang et al. (2015), India, Contemporary Clinical Dentistry

Table 47 Study characteristics

| | Roberts | Bal | El-Meligy | Pradhan | Bonte | Damle | Nagy | Lee | Narang |
|-----------------------------|---------------------------------|----------------------------------|---------------------------------|----------------------------|---------------------|---------------------------------|---|------------------------|----------------------------------|
| Study type | Pseudo | Pseudo | Split mouth | Pseudo | RCT | RCT | Pseudo | Pseudo | Pilot RCT |
| Aim | Apical barrier | Healing | Apical barrier | Apical barrier and healing | Apical barrier | Apical barrier and healing | Assess regenerative potential | Clinical healing | Assess regenerative potential |
| Tooth type | 15 incisors 1 premolar | Incisors | Incisors | Incisors | Incisors | Incisors | Anterior teeth | Incisors | NR |
| Sample size | 16 | 30 | 30 | 20 | 34 | 22 | 36 | 40 | 20 |
| Age range | 8-23 | NR | 6-12 | 8-15 | 6-18 | 8-13 | 9-13 | 6.5-10 | < 20 years |
| Aetiology | 7 crown fractures | NR | Trauma or caries | Trauma | NR | Trauma | NR | NR | NR |
| Observation period | 5-11 months | 6 months | 12 months | 11 months | 12 months | 9 months | 18 months | Not reported | 18 months |
| Assessment tool | Parallel plain film radiographs | Bisecting plain film radiographs | Parallel plain film radiographs | Plain film radiographs | Digital radiographs | Parallel plain film radiographs | Digitised parallel plain film radiographs and ImageJ software | Plain film radiographs | Digitised plain film radiographs |
| Tooth loss | No | No | No | No | Yes | No | No | No | No |
| Feasibility / acceptability | NR | NR | NR | NR | NR | NR | Compliance issues but not allocated | NR | NR |

Pseudo = pseudorandomised comparative study

NR = not reported

PRF = platelet rich fibrin

PRP = platelet rich plasma

Table 48 Study interventions: healing and apical barrier outcomes

| | Roberts | Bal | El-Meligy | Pradhan | Bonte | Damle | Nagy | Lee | Narang |
|----------------------|---------------------|--|----------------------|--|-----------------------|-------------------------|---|--|---|
| Interventions | CaOH TCP | CaOH TCP GP & ZOE | CaOH MTA | CaOH MTA | CaOH MTA | CaOH MTA | MTA REP FGF | Ultrasonic vs hand placement CaOH vs MTA | MTA REP PRP PRF |
| Clinical healing | NR | 100% all participants | 100% MTA 87% CaOH | NR | 100% MTA 73% CaOH | 91% MTA 82% CaOH | NR | 100% | 100% |
| Radiographic healing | 63% TCP 63% CaOH | Mean decrease size radiolucency CaOH 4.14mm TCP 3.63mm | 100% MTA 87% CaOH | 4.6 months (SD1.5) MTA 4.4 months (SD 1.3) CaOH | 82% MTA 75% CaOH | 91% MTA 82% CaOH | Improved bone density for all groups | 100% | MTA NR 98% PRF excellent 60% REP good 80% PRP good |
| Apical barrier | 75% CaOH 75% TCP | NR | 100% MTA 87% CaOH | 70% MTA 100% CaOH | 76.5% MTA 50% CaOH | 90.9% MTA 81.8% CaOH | Decrease apical diameter 0.8 (SD 0.3) REP 0.9 (SD 0.2) FGF 0.0 MTA | 100% | 0% MTA 66.7% REP good 40% PRF good 60% PRP good |

Table 49 Tooth development outcomes

| | Nagy | Lee | Narang |
|-------------------|--|--|---|
| Tooth development | <p>Increased root length: 1.2mm (SD 0.5) REP 1.3 (SD 0.5) FGF</p> <p>Percentage increase root thickness at the apical third of the root canal: 12.7% (SD 4.7) REP 11.6% (SD 3.6) FGF</p> | <p>Increased root length: 2.1 (SD 0.2) MTA 3.6 (SD 0.3) CaOH</p> | <p>Increased root length: 99% PRF excellent 40% REP good 40% PRP good Dentinal wall thickening: 60% PRF excellent 50% REP good 20% PRP good</p> |

Table 50 Quality assessment of included studies

| | Roberts | Bal | Pradhan | Bonte | Damle | El-Meligy | Nagy | Lee | Narang |
|--------------------------|---------|------|---------|-------|----------|-----------|-----------|---------|---------|
| Random allocation | No | No | No | Yes | Yes | No | No | No | Yes |
| Allocation concealment | No | No | No | Yes | No | No | No | No | No |
| Participant demographics | Yes | No | No | Yes | No | No | Yes | Yes | No |
| Comparable groups | Yes | No | Yes | Yes | Yes | No | Yes | Yes | No |
| Eligibility criteria | No | No | Yes | Yes | Yes | No | Yes | Yes | Partial |
| Blinded participants | No | No | No | No | No | No | No | No | No |
| Blinded clinicians | Yes | No | No | No | No | No | No | No | No |
| Blinded assessors | No | No | No | Yes | No | Yes | No | Partial | Partial |
| >80% reported | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Dropouts described | Yes | NR | NA | Yes | NA | NA | Partially | NA | NA |
| All outcomes reported | Yes | Yes | Yes | Yes | No | No | Yes | Partial | Yes |
| Registered | No | No | No | Yes | No | No | No | No | No |
| Overall risk of bias | High | High | High | Low | Moderate | High | High | High | High |

8.5 Discussion

8.5.1 Review of the Included Studies

The earlier studies compared calcium hydroxide apexification with tricalcium phosphate (employed for apical closure prior to the commercial availability of MTA). These studies either reported no difference between the interventions (Roberts and Brilliant, 1975) or favoured the use of calcium hydroxide apexification (Bal et al., 1993).

Later studies compared calcium hydroxide with MTA, and reported that MTA was superior in terms of clinical and radiographic periapical healing, and in providing an apical barrier. These studies proposed that MTA replace calcium hydroxide apexification (El-Meligy and Avery, 2006, Pradhan et al., 2006, Damle et al., 2016).

The aim of studies comparing regenerative endodontic procedures was to assess the regenerative potential of teeth treated via different protocols (Nagy et al., 2014, Narang et al., 2015). These studies compared regenerative endodontic procedures as previously described, with the use of injectable scaffolds (PRP and PRF), and with MTA. Nagy (Nagy et al. 2014) reported that MTA and REP were both successful interventions, and that the use of a scaffold (FGF) for regenerative endodontic procedures was not necessary. A statistically significant effect of regenerative endodontic procedures on tooth development was reported. This study reported a high dropout rate, and was probably underpowered. Conversely, Narang (Narang, Mittal, and Mishra 2015) reported that teeth managed with PRF exhibited significantly improved periapical healing and tooth development compared to REP or PRP. Unfortunately, this study was certainly underpowered.

Reporting of patient demographics across the studies was variable. Included participants were aged 6 to 23 years, however it was not possible to extract data for different ages for subgroup analysis due to varied standards of reporting of demographic data. The majority of studies described eligibility criteria to some degree. The majority of studies described comparable groups with similar baseline characteristics, although these were better described in some studies than others.

Intervention protocols varied in relation to dressing period, and the disinfection regime. Studies involving regenerative endodontic procedures, described the irrigation of all root canals with either 2.6% or 2.5% sodium hypochlorite. Studies of CaOH vs MTA, used a variety of irrigants including 5.25%, 3% and 2.5% sodium hypochlorite, 7.5% chlorhexidine, and 0.9% saline.

Comparison of the disinfection protocols in relation to clinical or radiographic healing was hampered by a non-standardised approach to reporting. Clinical healing was reported across those studies that included it as an outcome, at a rate of 91%-100% for MTA, and 73%-100% for CaOH. The study reporting the lowest rate of clinical healing for calcium hydroxide apexification (73%), described irrigation of root canals with 3% NaOCl (Bonte et al., 2015). The concentration of sodium hypochlorite was not described for a study that reported 100% healing (Bal, Padda, and Bala 1993). Clinical healing was not reported by studies that described an irrigation regime of 5.25% NaOCl (Roberts and Brilliant 1975) and 2.5% (Pradhan et al. 2006).

Surprisingly few studies reported the detailed assessment of clinical healing. For example, the objective of one study was to describe clinical outcomes for the interventions, however, the data presented were for apical barrier formation and increase in root length (Lee et al., 2015). The Pradhan study (Pradhan et al. 2006) was the first to generate evidence from a comparative study that MTA has comparable healing to CaOH. Unfortunately, this study exhibited methodological errors, including a lack of standardisation of the outcome measurement, that compromise its internal validity. Periapical healing was assessed by a variety of means. Healing reported within the limitations of the outcome assessment periods may, or may not, be clinically important. For example, in the Bal study (Bal, Padda, and Bala 1993) there was a mean reduction in periapical radiolucency of approximately 3mm reported for both groups.

The primary aim of the majority of studies was to assess apical barrier formation following apexification procedures. This outcome is arguably one of clinician-based interest as previously discussed, despite the importance of achieving apical closure before endodontic treatment can be completed. These studies also tended to describe the outcome assessment periods required to achieve apical barrier formation, with each study reporting a preference for MTA.

Time taken for apical barrier formation was variable and variably reported:

- Lee et al. 2015, 100% success, CaOH at 12.2 weeks (SD 1.6), MTA at 6.6 weeks (SD 1.9)
- Pradhan et al. 2006, 100% success CaOH at 7 months (SD 2.5), 70% success MTA at 3 months (SD 2.9) (30% failure of MTA attributable to extrusion of MTA through the immature apex)
- Bonte et al. 2015, present at 12 months for 50% of CaOH and 82% of MTA

No studies reported change in tooth colour, nor response to sensibility testing. No studies reported assessment of the feasibility or the acceptability of the interventions for participants or clinicians. One study reported a dropout rate of 19% (n=7) as a result of compliance and failure to attend for follow-up, however no further information was reported in order that issues with compliance could be further considered in relation to the intervention protocol (Nagy et al. 2014).

Adverse events were reported in three studies. In the Bonte study (Bonte et al. 2015), there was a clinically important rate of tooth loss of 26% (n=4) in a 12-month period for participants in the CaOH group. In the Nagy study (Nagy et al. 2014), 25% (n=3) participants (1 in the REP group, 2 in the FGF group) experienced clinical and radiographic signs of failure of the intervention that necessitated their transfer to the MTA group. El-Meligy (El-Meligy and Avery 2006) reported two failures in the CaOH group attributable to the presence of persistent periradicular inflammation.

The Lee study (Lee et al. 2015) was the only study to compare different techniques of achieving CaOH and MTA apexification. It was also the only study to report an increase in root length for apexification interventions. A statistical difference was reported in relation to an increase in root length for CaOH compared to MTA, however, no statistically significant differences were found between ultrasonic vs hand placement of the materials into the root canal. CaOH apexification placed by hand exhibited the greatest increase in root length but also had the longest mean duration of hard tissue barrier formation 13.1 (SD 1.5 weeks). MTA placed with an ultrasonic device achieved apical barrier formation in the shortest time 5.4 (SD 1.1 weeks).

The focus of the two studies that included regenerative endodontic procedures was to compare different regenerative protocols, rather than to compare the effectiveness of the interventions with MTA (Nagy et al. 2014; Narang, Mittal, and Mishra 2015). However, both studies reported radiographic signs of tooth development for regenerative endodontic procedures, delivered according to the protocol previously described (Banchs and Trope 2004), which may offer benefits in relation to tooth survival.

The reporting of the methodological design of the included studies, and the subsequent statistical analyses, were variable. No studies described the reliability of the outcome assessment tools used, although the Nagy study (Nagy et al. 2014) used a valid and reliable method of radiographic assessment that has been discussed earlier in this thesis (Bose et al., 2009).

The majority of studies described the subjective assessment of outcomes, which were not always prespecified or defined. For example, Narang (Narang, Mittal, and Mishra 2015) described outcomes as 'good' or 'excellent', however, descriptors for these judgements were not provided. In studies with participant dropouts, the management of missing data was rarely discussed. For example, a participant in the CaOH group of the Roberts study (Roberts and Brilliant 1975) failed to attend for review, reducing the success rate for apical closure from 81% to 75% in this group with an intention to treat (ITT) analysis, which was not applied by the authors.

The 'random choosing' of participant group allocation was described by Nagy (Nagy et al. 2014). Likewise, Lee (Lee et al. 2015) described the 'even dividing' of teeth into four intervention groups in order to avoid bias by allocating participants into groups according to comparative baseline values. Interestingly, Damle published an earlier comparative study that appears to report the same cohort as that published in 2016 (Damle et al., 2012, Damle et al., 2016). Unfortunately, the earlier study was not referenced in the later study. The most recently reported study was chosen for inclusion, as per the systematic review protocol. The earlier study was discussed in chapter 5. Only one study estimated effect size in order to calculate sample size (Bonte et al. 2015). The authors calculated that a sample of 30 participants was required to compare apical barrier formation for CaOH and MTA with 80% power. The study achieved this following the dropout of four participants recruited from a sample of 34.

There was a high risk of bias across various domains including allocation, selection, detection, attrition and reporting bias for 7 of the included studies. One study was judged to have a moderate risk of bias (Damle et al. 2016), and one study a low risk of bias (Bonte et al. 2015). The Bonte study reported no statistical differences between calcium hydroxide and MTA apexification in relation to the assessed outcomes, however the authors report a preference for MTA due its ability to offer equal effectiveness, with reduced risk of adverse events attributable to cervical fracture of teeth managed with CaOH. The possibility of detection bias in the Bonte study remains, however, it is noted that outcome assessment was blinded, and that blinding of investigators for comparative studies of CaOH and MTA is not possible at the second intervention visit. It is unlikely that blinding of participants would have a significant impact on the intervention, unless the participants choose to attend another dentist for an alternative intervention at any time throughout the study period.

8.5.1 Study Strengths and Limitations

The review question was clearly defined. All eligible studies that were identified for inclusion were located, and preventive steps were taken to minimise bias and errors in the study selection process. Practical limitations of access to a team of interpreters may have imposed language bias on the study design. It has been reported that studies with positive findings are more likely to be published in an English speaking journal than those with negative findings (Boland et al., 2014).

A large number of studies identified from the search were irrelevant to the research question, thus, it might be possible in a repeat of this systematic review for the sensitivity of the search terms to be reviewed in order that too many studies are not identified for screening for eligibility. However, this is balanced with the excellent specificity of the search, which led to identification of all known relevant studies, and those reported in existing systematic reviews. Handsearching did not identify any additional studies, indicating that the search was appropriately inclusive. Thus, it is concluded that the search was balanced in terms of sensitivity and specificity, and allowed for a pragmatic, logical, and systematic approach. Pre-specified quality assessment criteria were defined and appropriate. Preventive steps were taken to minimise bias and errors in the quality assessment process.

Meta-analysis of the included studies was considered to be inappropriate due to diverse study methodology, heterogeneous intervention protocols, assessment tools, and outcome reporting. The majority of the included studies were published following wide acceptance of the CONSORT statement, which aims to standardise and improve the transparent reporting of trials, in a bid to improve validity (Plint et al., 2006). The heterogeneity, lack of power, and high risk of bias of the included studies justifies further investigation of the interventions. The results of this systematic review support that of existing reviews (Kontakiotis et al., 2014, Antunes et al., 2016); that high quality, truly randomised, controlled and comparative trials, are required in order to generate evidence in relation to the clinical, radiographic, and developmental effectiveness of regenerative endodontic procedures, in comparison with MTA apexification.

8.5.2 Summary

This systematic review has confirmed the findings of existing reviews, that both CaOH or MTA could be recommended for the apexification of immature teeth, however, MTA may be associated with reduced treatment times and improved tooth survival (Chala et al., 2011, Lin et al., 2016b). It is, therefore, suggested that there is sufficient evidence to recommend discontinuing the use of prolonged CaOH root canal dressings in necrotic, immature teeth, as a result of the suboptimal effectiveness of CaOH compared to MTA, in relation to healing, and an apparently increased risk of tooth loss.

At present, all of the included studies have methodological limitations, and a risk of bias that may undermine the trustworthiness of the results. MTA appears to offer predictable endodontic success for outcomes that are of both patient and clinician interest. The majority of studies report apical barrier formation as a primary outcome, however it is suggested that clinical and radiographic healing, coupled with signs of tooth development for regenerative procedures, may be more appropriate. There remains a lack of quality controlled, comparative randomised controlled trials to support the decision-making practices of clinicians, which constitutes a significant, continuing knowledge gap in the endodontic literature.

It is true to say that the dental profession appears to be somewhat hesitant to embrace regenerative endodontic procedures. This is understandable in the light of a weak evidence base, and in a healthcare culture of informed consent and complaint. Notably, it appears that the reported literature has mainly assessed tooth development outcomes using straight line measurements on plain film radiographs, without the use of digital alignment or standardisation software. It has been discussed throughout this thesis that this assessment technique lacks construct validity and reliability. Therefore, it is strongly suggested that published data of clinical studies using conventional radiographs should be interpreted with caution, and that future comparative studies of the interventions utilise the software available to enhance the trustworthiness of the data generated.

The majority of studies that describe assessment of tooth development following regenerative endodontic procedures appear to report wide standard deviations within their data, perhaps exacerbating clinicians' reluctance to expand the use of regenerative endodontic procedures.

It is conceivable that some immature teeth develop better, and more predictably, than others. The case report that first proposed regenerative endodontic procedures as a new intervention protocol was notably completed on a necrotic, immature premolar with dens evaginatus (Banchs and Trope, 2004). It is therefore suggested that future comparative studies of the interventions determine to investigate the effectiveness of regenerative endodontic procedures for various tooth types, and for teeth which have been rendered non-vital with diverse aetiologies.

High quality evidence to support any of the currently recognised interventions for managing non-vital, immature teeth has been lacking. Although disappointing, this is perhaps not surprising in light of the difficulties encountered in establishing a suitable research environment for the effective management of acute injuries in children. Dental trauma data can only be gathered following an unexpected, and often distressing, occurrence.

Establishing a research basis for the investigation of immature apices is challenging, yet important. The lack of randomised controlled trials may be due in part to predictable difficulties in the methodological processes involved in successfully establishing a high quality, experimental study for the population in question.

Securing sufficient participants to comparative randomised controlled trials, with a prerequisite for statistical power to detect difference and independence between the intervention groups, may be a lengthy process, and must be considered together with the need to avoid an ethically undesirable situation in which children are unnecessarily recruited to multiple, underpowered studies at distant sites. Moreover, the necessity for an acceptable outcome observation period, and for the subsequent reporting of that study in a peer reviewed journal, might be expected to further prolong the process.

The role of systematic reviewers is to describe data from relevant, homogeneous, randomised controlled trials, and to combine that data for meta-analysis for the purpose of clarifying intervention effectiveness and guiding healthcare when it is appropriate. Unfortunately, in the case of necrotic, immature teeth, insufficient evidence exists to date to enable meta-analysis. However, this systematic review has addressed the call for evidence synthesis for the clinical problem, and has examined the case for undertaking a randomised controlled trial by providing an explicit evaluation of the weaknesses of the available studies.

This systematic review reinforces the call for action for dental research in respect of the recognised gold standard and novel interventions, as discussed in chapter 5.

8.6 Collaboration with Cochrane

It is recognised that non-randomised studies of the effects of interventions may be important in healthcare, but that they are inherently biased and subject to confounding (Higgins and Green, 2011). The results of non-randomised studies should, therefore, be interpreted with caution. Data arising from randomised and non-randomised studies should not be combined for meta-analysis. Quality assessment and risk of bias for non-randomised studies is somewhat complex and of limited usefulness (Boland et al., 2014).

In designing the methodology of study selection for this systematic review, following competitive application, the author was invited to join a small developmental group of systematic reviewers at the Cochrane Collaboration, in the piloting of their novel tool, developed for the assessment of risk of bias in non-randomised studies of interventions (Sterne et al., 2014).

The ROBINS-I tool (Risk Of Bias In Non-Randomized Studies - of Interventions) is designed to assess seven domains of bias (confounding, selection, classification of the interventions, deviations from the intended interventions, missing data, measurement, reporting). The tool was later substantially revised following extensive piloting and user feedback; thus, it was not publicly available for use at the time that this systematic review was conducted (Sterne et al., 2016). The tool is primarily designed for use by large review groups, such as those involved in Cochrane reviews, that include members with substantial methodological expertise. The tool may be limited in reliability as a result of the requirement for reviewers to make subjective judgements. The tool is designed to assess risk of bias alone, and does not account for imprecision in reported results or statistical analyses.

It is good practice to update systematic reviews (Higgins and Green, 2011), and it is therefore appropriate that the systematic review completed as part of this research is repeated in the future, as comparative trials involving regenerative endodontic procedures with developing protocols begin to emerge. If at that time, an insufficient number of newly published randomised studies remains, consideration will be given to including a second phase of data extraction in which non-randomised studies could be included. It is noted from the search results reported in this review, that the number of studies eligible for data extraction will be vast, and that exclusion criteria will need to be carefully prespecified and applied.

8.7 Conclusion

This systematic review has appropriately addressed the research question: *Does the literature provide evidence for an optimal intervention for the endodontic management of necrotic, immature permanent teeth in a young population?*

Primary Objective

- This systematic review has produced a thorough and explicit review of the relevant literature for the management of non-vital, immature permanent incisors, and in doing so, has addressed the call for evidence synthesis for the clinical dilemma posed.

Secondary Objectives

- The effectiveness and limitations of three treatment approaches (CaOH, MTA, and REP) for root end closure in managing non-vital, immature, permanent teeth have been compared. Variations in intervention protocol have been described. No alternative approaches to the management of immature apices have been found.
- The methodological limitations of the current approaches to investigating the management of non-vital immature permanent teeth have been identified.
- The case for undertaking a randomised controlled trial has been examined and justified by providing an explicit evaluation of the weaknesses of the available studies.
- Recommendations have been made to guide future research and inform the design of a future randomised controlled trial (as discussed in chapter 9).

9 Regenerative Endodontic Procedures Versus Mineral Trioxide Aggregate Apexification: A Randomised Controlled Trial

9.1 Research Question

- 9.1.1 Are regenerative endodontic procedures (REP) superior to mineral trioxide aggregate apexification (MTA) in the management of necrotic, immature, permanent incisors?

9.2 Clarification of Research Question and Scope

9.2.1 Introduction

As previously discussed (chapter 5), mineral trioxide aggregate has established a leading role in management of the open apex, surpassing that of calcium hydroxide apexification. Nevertheless, mineral trioxide aggregate apexification procedures remain primarily the domain of specialists in paediatric dentistry and endodontics, because undergraduate curricula do not describe any requirement for competency with apexification procedures (De Moor et al., 2013). There is confusion, and doubt, about how, and whether, regenerative endodontic procedures may offer a viable alternative to apexification techniques (Geisler, 2012, Galler, 2016).

If regenerative endodontic procedures present a viable alternative for routine practice, it can be envisioned that the materials and skills required to introduce the intervention to undergraduate teaching, and therefore to primary care, may be more realistic than for mineral trioxide aggregate apexification, and therefore, may improve access to the trained workforce for children who suffer traumatic dental injuries.

9.2.2 Defining Endodontic Success for an Immature Tooth

Review of the literature (chapters 5 and 8) has revealed that there is agreement in the definition of endodontic success in relation to resolution of clinical signs and symptoms of inflammation, radiographic signs of healing, and tooth development. However, the common presentation of this outcome data is via a checklist approach. The literature does not define a single primary outcome that is applicable to the endodontic success of immature teeth, and which might be included in studies that seek to compare the interventions in order to standardise the reporting of outcome measures.

As previously mentioned, it has been reported that there is significant heterogeneity in outcomes reported for traumatic dental injuries, precluding meaningful meta-analysis between studies (Sharif et al., 2015). Therefore, a newly defined, single primary outcome measure for the endodontic success of non-vital, immature permanent teeth that incorporates clinical and radiographic signs of healing, plus radiographic signs of tooth development is proposed (Table 51). Response to vitality testing has been classified as a tertiary outcome to healing and root development, and was therefore classified as a secondary outcome in this study (Diogenes and Ruparel, 2017).

To satisfy a positive recording of endodontic success, it is proposed that all descriptive criteria, in each of the three domains, are met. Consistent and transparent reporting of this primary outcome measure might aid the reporting of randomised controlled trials for the investigation of non-vital, immature teeth, with subgroup analyses of the domains as chosen by investigators.

Table 51 Primary outcome measure for endodontic success of an immature tooth

| Domain | Definition | Descriptive Criteria |
|-------------------------------|---|--|
| Clinical signs of healing | A retained, satisfactorily restored tooth with absence of signs and symptoms of pulpal or periapical inflammation | Retained, satisfactorily restored tooth Absence of pain Absence of soft tissue pathology Absence of tooth mobility Absence of tenderness to percussion |
| Radiographic signs of healing | Radiographic signs of healing as per the Strindberg index | Normal periodontal ligament space around the root Decrease in the size of an existing periapical lesion Absence of root resorption |
| Tooth Development | Radiographic signs of continued tooth development | Increase in root length and/or radiographic root area measured with digital image standardisation software |

This newly defined primary outcome measure can be translated for use in clinical practice, and to aid in the dissemination of clinical guidelines. It is noted that for the purpose of current clinical practice the omission of digital image standardisation software would be recommended to facilitate clinicians who lack the facilities, and time, required to use this software at the chairside. It is further noted that as a result of omitting this software requirement, clinicians may underestimate radiographic signs of tooth development, hence making fewer positive recordings of endodontic success. However, as endodontic retreatment is not indicated in the presence of clinical and radiographic signs of healing, a cautionary approach to follow-up might be indicated in the absence of detection of tooth development.

As discussed in chapter 7, treatment planning varies significantly between the specialties. Endodontists are more likely than paediatric dentists to plan a regenerative endodontic procedure, and less likely to plan calcium hydroxide apexification. There is also uncertainty amongst specialists in relation to the efficacy of various root canal dressing materials in regenerative endodontic procedures, with paediatric dentists most likely to employ an antibiotic paste, and endodontists most likely to use calcium hydroxide.

In addition, UK specialists in paediatric dentistry and endodontics were reported to be managing the clinical problem of non-vital, immature incisors in their everyday practice, obligated to treatment plan interventions in the absence of evidence to support them (chapter 8).

There is a lack of quality controlled, comparative randomised controlled trials to support the decision-making practices of clinicians, thus, a research question arose in relation to the optimal management of non-vital, immature incisors.

A randomised controlled trial was designed to answer a call for action for evidence that seeks to compare the gold standard intervention, mineral trioxide aggregate apexification, with regenerative endodontic procedures, and to guide clinical practice (Murray et al., 2007). As this was the first randomised controlled trial completed of its kind, this study also sought to assess the feasibility of investigating this clinical problem, and to determine effect size in respect of a newly defined primary outcome of endodontic success for an immature tooth.

9.2.3 Null Hypothesis

The null hypothesis was that there would be no difference in the success rate of regenerative endodontic procedures versus mineral trioxide aggregate apexification in achieving endodontic success for an immature tooth.

9.2.4 Primary Objective

- Assess endodontic success for an immature tooth, following mineral trioxide aggregate apexification and regenerative endodontic procedures, incorporating both clinical and radiographic signs of healing plus radiographic signs of tooth development.

9.2.5 Secondary Objectives

- Report clinical safety concerns for a novel intervention.
- Determine effect size, with 90% power, in respect of a newly defined primary outcome of endodontic success for an immature tooth.
- Assess the success of apical closure following mineral trioxide aggregate apexification and regenerative endodontic procedures.
- Assess change in tooth colour following mineral trioxide aggregate apexification and regenerative endodontic procedures.
- Determine whether teeth managed with regenerative endodontic procedures respond positively to sensibility testing.
- Describe the feasibility and acceptability of the study protocols, and delivery of the interventions, for use in a future, larger randomised-controlled trial, to be conducted if appropriate.

9.3 Method

9.3.1 Ethical Approval

Ethical approval was granted by the North West National Research Ethics Service (10/H1014/50) (Appendix 4) and was sponsored by the University of Liverpool (UoL000590) (Appendix 5) and the Royal Liverpool and Broadgreen University Hospitals Trust (RD&I 3968) (Appendix 6).

9.3.2 Registration

The trial was registered on the following databases:

- ISRCTN registry (ISRCTN 34934882)
- ClinicalTrials.gov registry (NCT 01817413)

9.3.3 Trial Design

This study was designed as a randomised, controlled, open-label, observer blinded, monocentric, superiority trial, with two parallel groups and a primary endpoint of endodontic success for an immature tooth at 12-month follow-up. There was a single operator who was trained and calibrated for delivery of the interventions prior to commencement of the study. All intervention and follow-up visits took place in a single clinical surgery which provides a similar setting to routine practice and a suitable environment in which to review the outcome data.

9.3.4 Sample Size

In the absence of previous trials to determine the effect size for 90% power, a review of endodontic studies was carried out, and advice sought from a statistician to establish a sample size of 30 participants.

9.3.5 Participants

Children and young adults who suffer traumatic dental injuries during the period of tooth formation are referred to the Paediatric Dentistry and Restorative Dentistry Departments of Liverpool University Dental Hospital from across the North West of England following referral by a range of dental service providers.

9.3.6 Eligibility Criteria

Patients who were referred to the Paediatric Dentistry and Restorative Dentistry Departments of Liverpool University Dental Hospital for the management of a non-vital, immature incisor, attended for consultation on the Paediatric Dentistry Consultation Clinic.

Patients underwent a comprehensive clinical examination in order to confirm the diagnosis of non-vital, immature permanent central incisor, and to establish eligibility for participation in the study. Teeth were subject to a pre-operative periapical radiograph using a paralleling technique in film holders with an alignment system (Rinn, Denstply).

In order for loss of vitality to be diagnosed, patients were required to present with at least two clinical or radiographic, signs or symptoms, that indicated pulpal death including pain, soft tissue pathology, mobility, tenderness to percussion, and a periapical radiolucency.

Patients who met the inclusion criteria were invited to participate (Table 52). The eligibility criteria aimed to exclude those patients less likely to benefit from trial participation, and limit the impact of confounding factors, whilst maintaining generalisability and relevance.

Table 52 Eligibility Criteria

| Inclusion criteria | Exclusion criteria |
|--|---|
| Aged 7 to 21 years of age and able to provide valid consent for participation in the study. | Medical or dental history that may complicate treatment delivery |
| No significant medical history (ASA 1 or 2) | Medical history that may be compromised by recruitment to the study or by the proposed study interventions |
| History of traumatic dental injury with diagnosis of a non-vital, permanent maxillary central incisor with incomplete root development (divergent apical morphology) | For the non-vital, immature, permanent maxillary central incisor to be treated: Diagnosis of avulsion or severe intrusion Diagnosis of root fracture Diagnosis of caries or evidence of previous restoration of caries Diagnosis of root resorption |
| Cooperative in the dental chair | Root is less than half formed Presence of anatomical complexity or anomaly |
| Able to commit to the recall schedules prescribed by the study | Previously root treated (other than for extirpation and dressing with calcium hydroxide for a period of up to 3 months) |

9.3.7 Information and Consent for participation

Information leaflets and consent forms were designed (Appendices 7-10). Piloting was conducted to ensure that the information contained was easily understood, correctly interpreted, and addressed the queries of children and their caregivers. Piloting incorporated a face-to-face feedback discussion between the principal investigator and the pilot participants following their reading of the information leaflets and completion of the consent forms. Pilot participants were children and their caregivers who were scheduled to attend trauma clinics with the chief investigator, prior to application for ethical approval. The information and leaflets and consent forms underwent peer review following piloting as part of the ethical approval process. Information leaflets and consent forms were distributed at the consultation appointment. Patients and their caregivers were asked to consider the information provided for a period of two weeks before written consent was given by those wished to participate. Those who decided not to participate in the study were offered treatment on an appropriate clinic.

Participants were given the opportunity to discuss any queries and concerns that arose throughout the course of the study and were free to withdraw at any time. General dental practitioners who had referred participants to the hospital were informed that their patient had been recruited to a randomised controlled trial, and were asked to avoid intervention of the tooth in question during the study period, except in the case of a dental emergency (Appendix 11). Participants were informed that emergency dental appointments would be made available for them at the dental hospital if required.

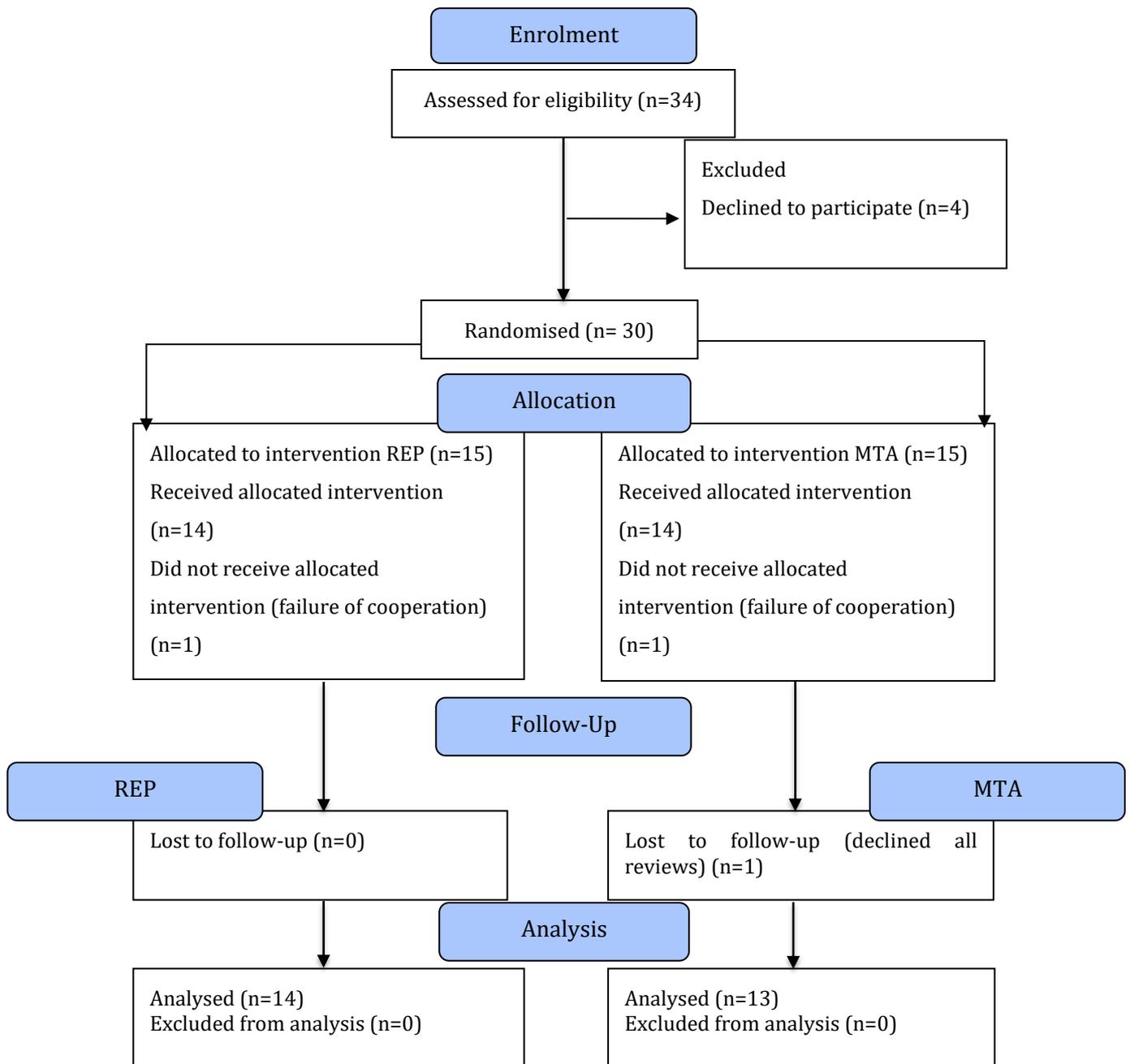
9.3.8 Recruitment

Recruitment took place over 36 months between 2011 and 2014. Thirty participants were recruited and randomised, with fifteen allocated to each intervention arm. One participant from each arm discontinued trial between the first and second intervention visits due to being unable to fully cooperate with the trial protocol. A further participant was lost to follow-up. The participant lost to follow-up was allocated to the MTA arm. Data for twenty seven participants were therefore available for per protocol analysis (Figure 22).

9.3.9 Sequence Generation, Randomisation and Allocation Concealment

Simple randomisation was performed with a 1:1 allocation. Sequence generation was via a computerised random number generator conducted by a third-party statistician. Allocation concealment was with serially numbered opaque envelopes. Sequence allocation was determined by opening the next envelope in the randomised sequence for each recruited participant. Sequence implementation took place for each participant at the first intervention visit.

Figure 22 CONSORT Flow diagram of participants



9.4 Interventions

9.4.1 Intervention Schedule

A triple antibiotic root canal dressing paste (TAP) was prescribed as per a locally agreed hospital pharmacy protocol the day prior to the first intervention visit for each of the recruited 30 participants. TAP was prepared with ciprofloxacin 1000mg, metronidazole 1000mg, and minocycline 1000mg, mixed with 2 mL of sterile water. Once prepared, TAP was stored in the hospital pharmacy fridge until the time of collection, shortly prior to commencement of the first intervention visit.

UltraCal XS (Ultradent) is a radiopaque, aqueous paste of 35% calcium hydroxide, with a pH of 12.5 that was suitable for root canal dressing. Syringe tip dispensing allowed for controlled delivery short of the apex and avoided instrument separation.

All interventions were delivered over two treatment visits, two weeks apart, as per an accepted treatment protocol for regenerative endodontic procedures (Banchs and Trope, 2004). Intervention group 1 received a regenerative endodontic procedure. Intervention group 2 received a mineral trioxide aggregate apexification procedure, and acted as the control group. Interventions were delivered as per protocol (Table 53 and Table 54). Participants who presented with discoloured, but otherwise intact incisal edge restorations that provided adequate coronal seal, were advised that restoration replacement would take place following completion of 12-month follow-up, following periapical healing at a time when aesthetics of the traumatised tooth would be addressed. Participants who presented with incisal edge restorations that provided suboptimal seal underwent restoration replacement following obturation and outcome assessment at intervention visit 2.

9.4.2 Outcome Assessment Observation Period

Participants attended for three monthly follow-ups for one year. In case of suspected endodontic failure, two investigators were available to review participants to ensure that there was agreement, and offer alternative treatment if appropriate. Participants were provided with contact details for the investigators in case signs or symptoms that indicated failure of treatment arose, or in case of participant queries.

Table 53 Clinical technique: intervention visit 1

| | |
|--|--|
| 1. | A clinical photograph (anterior view of the dentition) was taken. |
| 2. | Tooth shade was recorded with an electronic shade matching system (VITA Easyshade® Panadent). |
| 3. | Local anaesthetic without vasoconstrictor was administered via a labial infiltration technique. |
| 4. | The tooth was isolated with dental dam. |
| 5. | A conventional access cavity was prepared. |
| 6. | Working length determination was carried out using an electronic apex locator. |
| 7. | Necrotic pulp was extirpated with hand instruments. |
| 8. | The tooth was irrigated carefully with 5mL of 5.25% sodium hypochlorite, followed by 5mL of 2.0% chlorhexidine gluconate, followed by a final wash-out with 20mL of normal saline. |
| 9. | The root canal was gently dried using absorbent paper points. |
| Introduction of dressing material: group 1 (REP): | |
| <ul style="list-style-type: none">• A 20G needle was set to 2mm short of the working length and used to introduce triple antibiotic paste (TAP) into the root canal using a backfill approach to the level of the cemento-enamel junction (CEJ). | |
| Introduction of dressing material: group 2 (MTA): | |
| <ul style="list-style-type: none">• Calcium hydroxide (CaOH) was introduced into the canal using a backfill approach from the working length up to the level of the cemento-enamel junction using the dispenser provided by the manufacturer (UltraCal XS, Ultradent). | |
| 10. | The tooth was temporarily sealed with a cotton pellet and temporary restorative material (Fuji IX, GC). |

Table 54 Clinical technique: intervention visit 2

| | |
|--|---|
| 1. | A clinical photograph (anterior view of the dentition) was taken. |
| 2. | Tooth shade was recorded with an electronic shade matching system (VITA Easyshade® Panadent). |
| 3. | Local anaesthetic without vasoconstrictor was administered via a labial infiltration technique. |
| 4. | The tooth was isolated with dental dam. |
| 5. | A conventional access cavity was prepared and the dressing was removed by irrigation of the root canal with saline. |
| Intervention: group 1 (REP): | |
| <ul style="list-style-type: none">• Following access to the root canal, a rubber stop was placed 2mm beyond the working length of an endodontic file (size 20). The file was pushed past the confines of the canal into the periapical tissues to induce bleeding.• Bleeding was encouraged to reach the level of the CEJ. Haemostasis was achieved with a cotton wool pellet at a depth of 3-4mm into the canal so that a blood clot could form and possibly provide a scaffold for the in-growth of new tissue.• A plug of MTA (ProRoot MTA Dentsply, USA) was placed in the cervical portion of the root canal to provide a seal. | |
| Intervention: group 2 (MTA): | |
| <ul style="list-style-type: none">• Following access to the root canal, a 5mm MTA (ProRoot MTA Dentsply, USA) apical plug was placed at the immature apex with an appropriately sized endodontic plugger and the aid of an endodontic operating microscope.• Radiographic examination of the apical plug was carried out followed by any necessary adjustments.• Obturation of the remaining root canal was completed using thermoplastic gutta-percha and a resin-based sealer. | |
| 6. | A post-operative periapical radiograph was taken using a paralleling technique in film holders with an alignment system (Rinn, Denstply). |
| 7. | The tooth was restored with a bonded resin coronal restoration. |

9.5 Data Collection and Analyses

Data collection sheets were designed to extract data for participant demographics and presenting characteristics (age, gender, incisor relationship, history of orthodontic treatment, aetiology of the injury, clinical presentation), and the primary and secondary outcomes, as described.

Data collection sheets were piloted by the operator trained to deliver the interventions, and by a supervising investigator. Pilot participants were children and their caregivers who were scheduled to attend trauma clinics with the chief investigator, prior to application for ethical approval. Piloting was conducted to ensure that the data collected in its entirety was suitable for extraction, and that it was correctly interpreted.

Reproducibility of Radiographic Outcomes

Two investigators assessed all radiographic outcomes according to the following protocol:

- Calibration was completed on ten reference teeth unrelated to the study.
- Investigators were blinded to the clinical outcome.
- To measure inter-rater agreement, both investigators independently assessed all radiographs taken preoperatively and at 12-month follow-up.
- To measure intra-rater agreement, both investigators reassessed twelve radiographs (pre-and postoperative images for three participants from each intervention group) 14 days after the initial assessment was carried out.
- Inter- and intra-rater agreement was calculated with kappa values for categorical variables, and with intraclass correlation (ICC) values for continuous variables, with an online calculator (StatsDirect Ltd. StatsDirect Statistical Software 2013). Substantial agreement was set at 0.61 - 0.80, and almost perfect agreement at 0.81 - 1.00.

9.6 Statistical analyses

The analyses were designed to be largely descriptive, to establish the feasibility of recruitment and participant flow, to estimate success rates, and to describe the appropriateness of the outcome measures. Coded data was entered into SPSS software (Statistics 24, IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) for statistical analysis.

An exploratory analysis of the primary efficacy outcome of success or failure was performed by calculating the difference in proportions between the two groups, with a 95% confidence interval. Continuous data were assessed for whether they were normally distributed by using a Shapiro-Wilks test. Non-normally distributed data were transformed for statistical analysis. Normally distributed data were analysed with independent t tests. Pearson chi-square, and Fisher's exact tests (for data frequencies <5 observations per cell), were used to determine independence for categorical variables.

9.6.1 Primary Outcome

This trial was designed to compare a gold standard intervention for root end closure, versus a more novel intervention which aims to engineer tooth development, therefore it was important to include tooth development in defining a novel primary outcome measure (chapter 9.2.2).

The primary outcome measure was, therefore, pre-specified and completely defined as that of endodontic success for an immature tooth, incorporating both clinical and radiographic signs of healing plus radiographic signs of tooth development. To satisfy a positive recording of endodontic success, all descriptive criteria, in each of the three domains, were met (Table 55).

Table 55 Primary outcome measure for endodontic success of an immature tooth (Recap)

| Domain | Definition | Descriptive Criteria |
|-------------------------------|---|--|
| Clinical signs of healing | A retained, satisfactorily restored tooth with absence of signs and symptoms of pulpal or periapical inflammation | Retained, satisfactorily restored tooth Absence of pain Absence of soft tissue pathology Absence of tooth mobility Absence of tenderness to percussion |
| Radiographic signs of healing | Radiographic signs of healing as per the Strindberg index | Normal periodontal ligament space around the root Decrease in the size of an existing periapical lesion Absence of root resorption |
| Tooth Development | Radiographic signs of continued tooth development | Increase in root length and/or radiographic root area measured with digital image standardisation software |

9.6.1.1 Clinical Signs of Healing

The presence or absence of descriptive criteria for clinical signs of healing were recorded by the operator at each intervention and follow-up visit (Table 55). Pre- and postoperative data were extracted for analysis.

9.6.1.2 Radiographic Signs of Healing

Intraoral, bidimensional, conventional, plain film periapical radiographs, of the same size film, were taken on a single radiography system, taken preoperatively and at 12-month follow-up, by a single operator, using a standardised exposure, and a paralleling technique with film holders and an alignment system (Rinn, Denstply).

Two investigators followed an agreed protocol for recording subjective, trichotomous outcomes of endodontic success as favourable, uncertain or unfavourable as defined in the Strindberg Index (Table 56). Both investigators had experience of performing the measure previously. Difficulties in obtaining reproducible images, for example, due to child cooperation, were noted.

Table 56 Strindberg index: trichotomous radiographic assessment criteria for periapical healing

| Favourable Outcome | Uncertain Outcome | Unfavourable Outcome |
|---|--|---|
| Radiological evidence of a normal periodontal ligament space around the root | Periapical lesion has remained the same size | Periapical lesion has appeared subsequent to treatment or a pre-existing lesion has increased in size |
| Decrease in the size of the periapical lesion as compared with preoperative radiographs | | A lesion has remained the same size or has only diminished in size |
| Absence of root resorption | | Signs of root resorption |

9.6.1.3 Radiographic Signs of Tooth Development

Pre- and postoperative (12-month review) radiographs were saved in JPEG format and transferred to ImageJ software for digital alignment of non-standardised radiographs, (ImageJ v 1.48, US National Institutes of Health, Bethesda, MD), with the plug-in application TurboReg, (Lausanne, VD, Switzerland).

Two investigators performed independent measurements and the mean was calculated. Root length, total root area and root canal space area were measured using a standardised and validated protocol (Flake et al., 2014) (Figure 23). This allowed percentage changes in root length and radiographic root area (RRA) to be calculated (Table 57) e.g. percentage of increase in length = (postoperative length – preoperative length/ preoperative length) x 100.

Figure 23 Measurement of root length and radiographic root area (RRA) on ImageJ software



Table 57 Protocol for assessment of tooth development

| |
|---|
| 1. JPEG images were imported for analysis to Image J software. |
| 2. Images were saved as RGB stack files and digitally aligned with TurboReg plugin software. |
| 3. A measuring scale was set (bite block of periapical holder 8.5mm, width of unrestored contralateral central incisor crown 9mm, unrestored adjacent lateral incisor crown 7mm). The same scale was used for each of the two images measured per participant in order to allow comparison. JPEG images were saved with the scale set. |
| 4. The cemento-enamel junction was identified and outlined on both images using the line drawing tool. |
| 5. Pre- and postoperative root length was measured in millimetres as a straight line from the cemento-enamel junction to the radiographic apex. Change in root length was calculated by subtracting the preoperative length from the postoperative length. |
| 6. The polygon tool was used to outline the total root area bordered on the occlusal aspect by the mesial and distal cemento-enamel junction and peripherally by the periodontal ligament space. To account for the space taken by the root canal system, the polygon tool was used to outline the root canal space and the measurement for the area was obtained. The radiographic root area (RRA) measurement was calculated as the difference between the total root area and the root canal space in each radiograph. |
| 7. Changes were measured in millimetres and converted to percentage change to assist evaluation of the clinical significance of any change. |
| 8. Data were collected, tabulated, and entered in to SPSS software (Statistics 24, IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) for statistical analysis. |

9.6.2 Secondary Outcome Measures

9.6.2.1 *Clinical Safety*

Predicted adverse effects of endodontic intervention included mild post-operative discomfort. It was planned, and required by ethics, that unexpected adverse effects would be recorded if they arose. Interim analysis and review of preliminary results took place following delivery of interventions to the first 15 participants of the study cohort. Stopping guidelines were to be affected if unpredictable tooth loss or adverse effect were recorded in either group at any time.

9.6.2.2 *Effect Size*

Effect size, with 90% power, was determined in respect of a newly defined primary outcome of endodontic success for an immature tooth.

9.6.2.3 *Apical Closure*

Intraoral, bidimensional, conventional, plain film periapical radiographs, of the same size film, were taken on a single radiography system, taken preoperatively and at 12-month follow-up, by a single operator, using a standardised exposure, and a paralleling technique with film holders and an alignment system (Rinn, Denstply). Radiographs were assessed for apical closure according to subjective dichotomous outcomes (closed, not closed) (Felippe et al., 2006). A positive recording of apical closure was made if there was a complete apical calcified tissue barrier present in the foramen (either within the interior of the canal, at the limit of the foramen or beyond the limits of the root canal walls).

9.6.2.4 *Colour Difference (Change in Tooth Colour)*

Subjective, dichotomous, perceptible colour change date, and objective CIE colour space (CIE L*a*b*) data were recorded for the assessment of colour difference prior to (first intervention visit), during (second intervention visit), and following (12-month follow-up) delivery of the interventions. A reference frame for analysing colour difference was established for perceptibility > 4 ΔE units, and acceptability > 8 ΔE units.

➤ *Subjective Clinical Assessment*

Visible colour difference was recorded following assessment of standardised clinical photographs taken preoperatively at the first intervention visit, following irrigation of the dressing material from the root canal at the second intervention visit, and at 12-month follow-up. In order to optimise the standardisation of clinical photography, photographic equipment (Fujifilm (Tokyo, Japan) Finepix S3 Pro camera with 105-mm Micro Nikon (Tokyo, Japan) f2.8 lens and sigma ring flash, EM-140DG), the clinical environment, participant and clinician positioning, and ambient lighting were consistent at each attendance.

Investigators followed an agreed protocol for recording subjective, dichotomous perceptible colour difference outcomes (difference, no difference). Both investigators had experience of performing the measure previously. Investigators were blinded to the intervention. A positive recording of colour difference was made if, in the clinical opinion of the investigator, there had been a perceptible change in tooth colour between the pre- and postoperative clinical photographs.

Reproducibility of Colour Difference Outcomes

- To measure inter-rater agreement, two investigators independently assessed all clinical photographs taken preoperatively and at 12-month follow-up.
- To measure intra-rater agreement, two investigators reassessed all photographs on a second occasion 14 days after the initial assessment was carried out.

➤ *Objective Electronic Assessment*

To assess change in tooth colour following the interventions, CIE colour space (CIE L*a*b*) data was recorded with a spectrophotometer, an electronic shade matching system, VITA Easyshade® (Panadent), preoperatively at the first intervention visit, following irrigation of the dressing material from the root canal at the second intervention visit, and at 12-month follow-up. Calibration of the device was carried out prior to each individual recording. The tip of the spectrophotometer device was then positioned on the labial surface of the clinical crown, at one third of the clinical crown height above the gingival margin. Three recordings were made per tooth, per visit, and the mean per visit was calculated for analysis. Objective colour difference (ΔE) was calculated.

9.6.2.5 Sensibility Testing

Sensibility testing of all teeth that received a regenerative endodontic procedure was carried out by the operator, with Roeko Endo-Frost Spray (Coltene), preoperatively and at 12-month follow-up. Testing was carried out on the contralateral central incisor, and the upper permanent lateral incisors if they were fully erupted, to aid comparison of the treated tooth with the presumably healthy dentition.

9.6.2.6 Feasibility and Acceptability

➤ Study Protocol

This exploratory study aimed to assess the feasibility and acceptability of the study, in relation to the recruitment, randomisation, retention and assessment protocols. Therefore, the analyses are largely descriptive, to estimate success rates, to establish levels of recruitment and participant flow, and to describe the appropriateness of the outcome measures. The number of visits and time taken to complete treatment using each intervention was recorded in order that any differences could be described. The acceptability of the interventions for patients, caregivers and clinicians, was noted throughout the study.

➤ Delivery of the Interventions

If practical or clinical complexities were encountered during provision of the interventions they were noted. Clinical complexity in placement of mineral trioxide aggregate at the divergent apices of immature teeth, and at the coronal aspect of immature root canals, was predicted (chapter 5). Assessment of the quality of the apical, or coronal, seal of mineral trioxide aggregate, as appropriate per intervention, was independently assessed by two investigators on postoperative radiographs in order to establish the feasibility of delivering the interventions.

Two investigators followed an agreed protocol for recording subjective, dichotomous outcomes (optimal, suboptimal) (Table 58). Both investigators had experience of performing the measure previously.

Table 58 Quality of seal

| | Optimal Seal | Suboptimal Seal |
|------------|--|--|
| MTA | <p>Optimal apical and coronal seal.</p> <p>MTA apical plug in-situ and appropriately situated and condensed at the immature apex.</p> <p>Well condensed gutta percha obturating the remainder of the root canal without deficiency.</p> | <p>Suboptimal apical and coronal seal.</p> <p>Deficiencies in the condensation of, or inappropriate siting of, the MTA coronal plug e.g. plug poorly condensed.</p> <p>Deficiencies in the gutta percha obturation e.g. voids or spacing between gutta percha and MTA apical plug.</p> |
| REP | <p>Optimal coronal seal.</p> <p>MTA coronal plug in-situ and appropriately situated and condensed at the coronal portion of the root canal.</p> <p>No separation of the MTA plug into the middle or apical thirds of the root canal.</p> | <p>Suboptimal coronal seal.</p> <p>Deficiencies in the condensation of, or inappropriate siting of, the MTA apical plug e.g. plug placed >1mm short of radiographic apex.</p> <p>Separation of the MTA plug into the middle or apical thirds of the root canal.</p> |

9.6.3 Data Storage

The procedures for handling, processing, storing and destruction of data were compliant with the Data Protection Act 1998. Data were collected using a coded and anonymous data collection form. Data collection forms were used for the purposes of this study only. The researchers had access to view identifiable data for monitoring of the quality of the research. No other persons had access to view data. Data were stored on a specified and password protected NHS computer.

Data will be kept securely for a period of 10 years following the date of completion of the final participant's final follow-up visit. Analysis of coded data was conducted at the Liverpool University Dental Hospital.

9.6.4 Blinding

Neither operator nor participant was blinded to the intervention in order that treatment could be delivered, and that participant's families could liaise with their primary dental care practitioner in case of emergency. Investigators were blinded to the interventions where possible as described for data extraction. Investigators were blinded to the intervention for data analysis.

9.7 Results

9.7.1 Demographics of Participants

The mean age of the 27 participants who completed 12-month follow-up was 9.85 years (SD 2.23, range 7-19 years). Some 70.4% (n=19) were male. There was equal presentation of Class 1 and Class 2 Division I incisor relationships. A single participant presented with a Class 2 Division II incisor relationship. No participants presented with a Class 3 incisor relationship. No participants had previously undergone any form of orthodontic treatment (Table 59). No participants experienced repeat dental trauma during the outcome observation period.

Table 59 Demographics of analysed participants

| | | Intervention | | Total Counts |
|------------------|-----------------|--------------|-----|--------------|
| | | MTA | REP | |
| | 7 to 10 | 11 | 10 | 21 |
| | 11 to 16 | 2 | 3 | 5 |
| | 16 to 21 | 0 | 1 | 1 |
| | Total | 13 | 14 | 27 |
| | F | 6 | 2 | 8 |
| | M | 7 | 12 | 19 |
| | Total | 13 | 14 | 27 |
| | 1 | 5 | 8 | 13 |
| | 2I | 7 | 6 | 13 |
| | 2II | 1 | 0 | 1 |
| | Total | 13 | 14 | 27 |
| | Yes | 0 | 0 | 0 |
| | No | 13 | 14 | 27 |
| | Total | 13 | 14 | 27 |
| Injury Sustained | Crown Fracture | 12 | 12 | 24 |
| | Luxation Injury | 1 | 2 | 3 |
| | Total | 13 | 14 | 27 |

9.7.2 Demographics of Participant Drop Outs

Three recruited participants did not complete the trial. Two participants (one per intervention group) discontinued the trial at the time of the second intervention visit due to a failure to cooperate with the trial protocol. Both participants completed treatment at a later date without local anaesthetic. The third completed both intervention visits (REP group) but failed to attend for review. When contacted, this participant reported a failure to comprehend the benefit of follow-up due to resolution of clinical symptoms.

The three participant drop outs shared characteristics with the analysed study population (Table 60). The mean age was 8.33 years (SD 0.58), and 66.7% (n=2) experienced clinical signs or symptoms of periapical inflammation at presentation. Of these participants, 100% (n=3), presented with a Class 2 Division I incisor relationship. None had previously undergone any form of orthodontic treatment. Data for the three participants who did not complete trial has been excluded from analysis.

Table 60 Demographics of drop out participants

| | MTA Refused | REP Refused | REP Failed to Attend Follow-Up |
|-------------------------|--------------|-------------|--------------------------------|
| Age | 9 years | 8 years | 8 years |
| Gender | M | F | M |
| At intervention visit 1 | Asymptomatic | Symptomatic | Symptomatic |
| At intervention visit 2 | N/A | N/A | Asymptomatic |

9.7.3 Aetiology of Traumatic Dental Injuries

Participants sustained traumatic dental injuries in a variety of ways, with little involvement in contact sport. The majority were experienced whilst playing outdoors at school, indoors at home, and on a bicycle (Figure 24).

9.7.4 Clinical Presentation

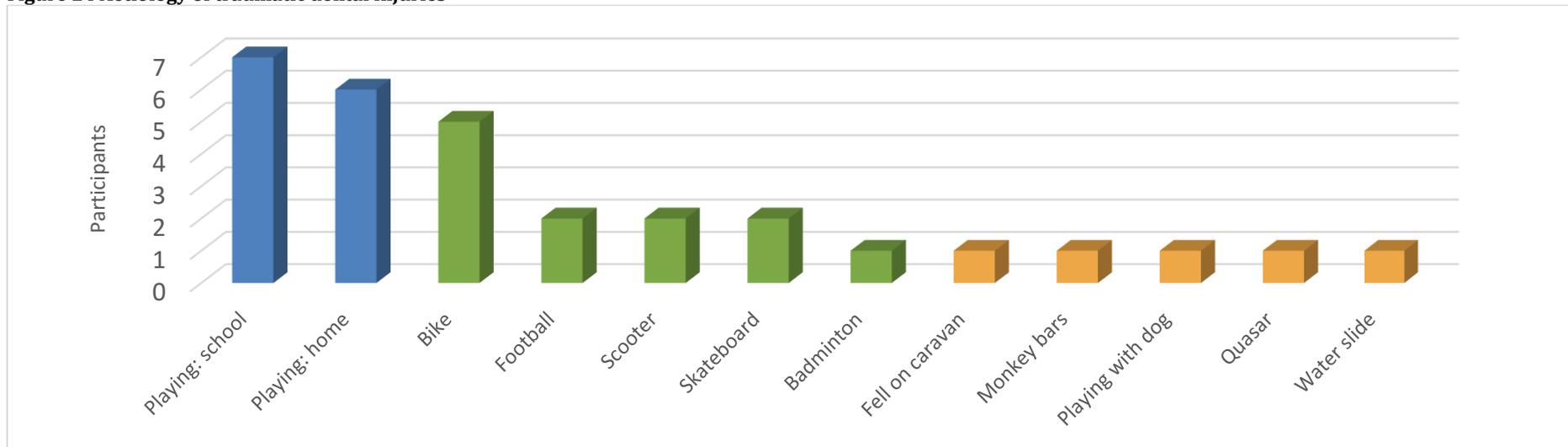
Some 96% (n=26) of participants experienced clinical signs or symptoms of periapical inflammation at presentation (Table 61). Pain and tenderness to percussion were the most commonly experienced symptoms.

There was no significant difference between the groups in relation to clinical signs or symptoms at presentation (pain <0.209, soft tissue pathology 0.252, mobility <0.165, tenderness to percussion <0.440)

Table 61 Clinical presentation of participants

| | | | Intervention | | Total |
|--------------------------|-----|-----------------------|--------------|-------|-------|
| | | | MTA | REP | |
| | | Count | 8 | 12 | 20 |
| | | % within Intervention | 61.5% | 85.7% | 74.1% |
| | | Count | 5 | 2 | 7 |
| | | % within Intervention | 38.5% | 14.3% | 25.9% |
| Soft Tissue Pathology | Yes | Count | 9 | 6 | 15 |
| | | % within Intervention | 69.2% | 42.9% | 55.6% |
| | | Count | 4 | 8 | 12 |
| | | % within Intervention | 30.8% | 57.1% | 44.4% |
| Mobility | Yes | Count | 4 | 1 | 5 |
| | | % within Intervention | 30.8% | 7.1% | 18.5% |
| | | Count | 9 | 13 | 22 |
| | | % within Intervention | 69.2% | 92.9% | 81.5% |
| Tenderness to Percussion | Yes | Count | 7 | 10 | 17 |
| | | % within Intervention | 53.8% | 71.4% | 63.0% |
| | | Count | 6 | 4 | 10 |
| | | % within Intervention | 46.2% | 28.6% | 37.0% |

Figure 24 Aetiology of traumatic dental injuries



9.7.5 The Primary Outcome Measure

The primary outcome measure was that of endodontic success for an immature tooth, incorporating both clinical and radiographic signs of healing plus radiographic signs of tooth development.

9.7.5.1 Clinical Signs of Healing

Data for 27 participants was available for analysis of clinical signs of healing at 12-month follow-up. Following intervention, there was a 100% success rate in relation to clinical signs of healing for both groups (Table 62). No statistical tests were computed as clinical resolution was a constant. Of note, 100% (n=28) participants exhibited clinical signs of healing at the second intervention visit, therefore, no difference in success rate was found between the root canal dressing materials.

Table 62 Clinical signs of healing

| Clinical Signs of Healing | Percentage (number) of participants |
|---|-------------------------------------|
| Retained, satisfactorily restored tooth | 100% (n=27) |
| Absence of pain | 100% (n=27) |
| Absence of soft tissue pathology | 100% (n=27) |
| Absence of tooth mobility | 100% (n=27) |
| Absence of tenderness to percussion | 100% (n=27) |

9.7.5.2 Radiographic Signs of Healing

Data for 27 participants was available for analysis of radiographic signs of healing at 12-month follow-up (Table 63). Some 96% (n=26) of participants experienced favourable healing, defined as radiological evidence of a normal periodontal ligament space around the root, decrease in size of the periapical lesion compared with preoperative radiographs, and absence of root resorption (

Figure 25). Some 4% (n=1) participant in the REP group was recorded as having an uncertain outcome at 12-month follow-up as there was no change in size of the periapical lesion compared to the preoperative radiograph (Figure 26). No participants experienced an unfavourable radiographic outcome. There was no

significant effect of intervention in relation to radiographic signs of healing, ($p < 0.326$). There was an observed inter- and intra-rater agreement of 100% (Kappa = 1).

Table 63 Radiographic signs of healing

| | | Radiographic Signs of Healing | | | Total |
|-------|-----|-------------------------------|-----------|--------------|-------|
| | | Favourable | Uncertain | Unfavourable | |
| | MTA | 13 | 0 | 0 | 13 |
| | REP | 13 | 1 | 0 | 14 |
| Total | | 26 | 1 | 0 | 27 |

Figure 25 Favourable radiographic signs of healing (MTA)

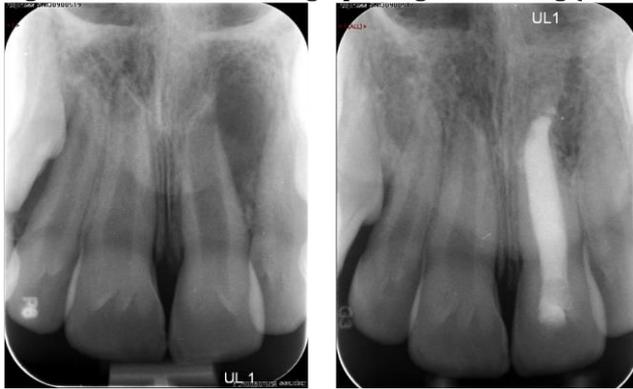


Figure 26 Uncertain radiographic signs of healing (REP)



9.7.5.3 Radiographic Signs of Tooth Development

Data for 24 (11 MTA, 13 REP) participants were available for analysis of radiographic signs of tooth development in relation to dimensional changes in root length and radiographic root area. Data for three participants was excluded from analysis with the investigators having 100% agreement that either the pre- or postoperative radiograph were unsuitable for measurement as the entire structure of the root canal was not visible on the radiograph, e.g. due to overlap of the lateral aspects of the roots of the central and lateral incisor.

➤ Root Length

Root length was measured in millimetres as previously described. Mean increases in root length were observed for both intervention groups. There was a mean increase in root length of 0.5mm for REP (SD 0.44, range 0.10 to 1.50mm). There was a mean increase in root length of 0.25mm for MTA (SD 0.36, range -0.10 to 1mm) (Table 64, Figure 27).

27.3% (n=3) participants from the MTA group experienced a decrease, or no change, in root length. No participants from the REP group experienced a decrease, or no change, in root length.

54.5% (n=6) participants from the MTA group, and 69.2% (n=9) participants from the REP group, experienced an increase in root length of up to 0.50mm. Some 18.2% (n=2) participants from the MTA group, and 30.8% (n=4) participants from the REP group, experienced an increase in root length of more than 0.50mm. The greatest increase in root length was 1.50mm experienced by a participant in the REP group (Table 65).

There was no significant effect of intervention in relation to root length, ($p < 0.093$) (Table 66). Inter-rater agreement was ICC 0.83 (SD 0.02). There was an observed intra-rater agreement of ICC 0.94 (SD 0.12) for investigator 1 and ICC 0.91 (SD 0.01) for investigator 2.

Table 64 Mean change in root length

| | Group | Number | Mean | Std. Deviation | Std. Error Mean |
|--|-------|--------|-------|----------------|-----------------|
| | MTA | 11 | .2545 | .35599 | .10733 |
| | REP | 13 | .5462 | .44275 | .12280 |

Table 65 Change in root length (mm) values

| | | Intervention Group | | Total |
|-------|------|--------------------|-----|-------|
| | | MTA | REP | |
| | -.10 | 1 | 0 | 1 |
| | .00 | 2 | 0 | 2 |
| | .10 | 4 | 2 | 6 |
| | .20 | 1 | 1 | 2 |
| | .30 | 0 | 4 | 4 |
| | .50 | 1 | 2 | 3 |
| | .80 | 1 | 0 | 1 |
| | .90 | 0 | 2 | 2 |
| | 1.00 | 1 | 0 | 1 |
| | 1.20 | 0 | 1 | 1 |
| | 1.50 | 0 | 1 | 1 |
| Total | | 11 | 13 | 24 |

Figure 27 Change in root length (transparent area represents combined interventions; purple area represents each individual intervention)

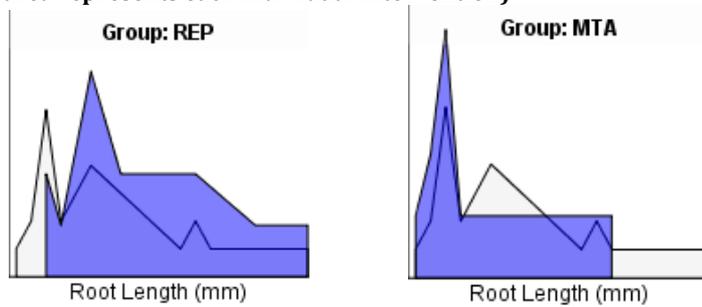


Table 66 Independent samples t test for root length (mm)

| | | Levene's Test for Equality of Variances | | t-test for Equality of Means | | | | | | | | |
|-----------|-------------------------|---|------|------------------------------|----|------|--------|-------|--------|-------|---|-------|
| | | | | | | | | | | | 95% Confidence Interval of the Difference | |
| | | | | | | | | | | | Lower | Upper |
| Length mm | Equal variances assumed | .697 | .413 | -1.755 | 22 | .093 | -.2916 | .1662 | -.6362 | .0530 | | |

➤ *Radiographic Root Area*

Radiographic root area (RRA) was measured in millimetres as previously described, and converted to percentage change to assist evaluation of the clinical significance of any dimensional change. There was a mean increase in RRA of 9.03% (SD 5.55, range 2.2 to 21.6) for REP. There was a mean increase in RRA of 0.85% (SD 2.92%, range -4.6 to 6.8) for MTA (Table 67, Figure 28).

36.4% (n=4) participants in the MTA group experienced a decrease, or no change, in RRA. No participants from the REP group experienced a decrease, or no change, in RRA.

54.5% (n=6) participants from the MTA group, and 23.1% (n=3) participants from the REP group, experienced an increase in RRA of up to 5%. A single (9.09%, n=1) participant from the MTA group, and a majority of participants (76.9%, n=10) from the REP group, experienced an increase in RRA of more than 5%. Some 38.5% (n=5) participants, all in the REP group, experienced an increase in RRA of more than 10%. The greatest increase in RRA was 21.6% experienced by a participant in the REP group (Table 68).

There was a significant effect of intervention in relation to radiographic root area, $p < 0.0001$ (Table 69). Inter-rater agreement was ICC 0.77 (SD 0.03). There was an observed intra-rater agreement of ICC 0.99 (SD 0.01) for investigator 1 and ICC 0.83 (SD 0.03) for investigator 2.

Table 67 Mean percentage change RRA

| | Group | Number | Mean | Std. Deviation | Std. Error Mean |
|--|-------|--------|--------|----------------|-----------------|
| | MTA | 11 | .00855 | .029225 | .008812 |
| | REP | 13 | .09031 | .054579 | .015138 |

Figure 28 Percentage change in RRA (transparent area represents combined interventions; purple area represents each individual intervention)

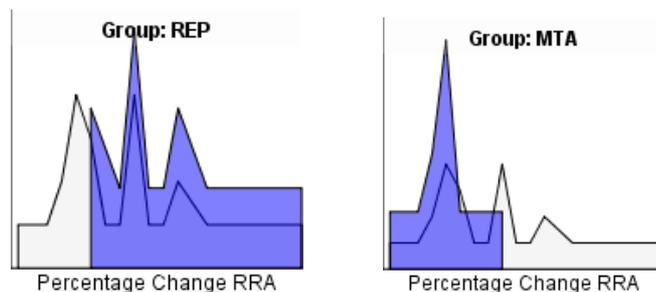


Table 68 Percentage change in RRA values

| | | Group | | Total |
|-------|------|-------|-----|-------|
| | | MTA | REP | |
| | -4.6 | 1 | 0 | 1 |
| | -1.6 | 1 | 0 | 1 |
| | -0.6 | 1 | 0 | 1 |
| | 0.0 | 1 | 0 | 1 |
| | 0.7 | 2 | 0 | 2 |
| | 0.8 | 1 | 0 | 1 |
| | 0.9 | 1 | 0 | 1 |
| | 2.2 | 0 | 1 | 1 |
| | 2.5 | 1 | 0 | 1 |
| | 2.8 | 0 | 1 | 1 |
| | 3.8 | 1 | 0 | 1 |
| | 5.0 | 0 | 1 | 1 |
| | 5.9 | 0 | 1 | 1 |
| | 6.2 | 0 | 1 | 1 |
| | 6.4 | 0 | 1 | 1 |
| | 6.8 | 1 | 0 | 1 |
| | 7.8 | 0 | 1 | 1 |
| | 8.7 | 0 | 1 | 1 |
| | 10.7 | 0 | 1 | 1 |
| | 11.1 | 0 | 1 | 1 |
| | 13.0 | 0 | 1 | 1 |
| | 16.0 | 0 | 1 | 1 |
| | 21.6 | 0 | 1 | 1 |
| Total | | 11 | 13 | 24 |

Table 69 Independent samples t test for RRA

| | | Levene's Test for Equality of Variances | | t-test for Equality of Means | | | | | | |
|-----------------------------|-------------------------------|---|------|------------------------------|----|------|--------|-------|--|--------|
| | | | | | | | | | 95% Confidence Interval of the Difference | |
| | | | | | | | | | Lower | Upper |
| Percentage change RRA | Equal variances assumed | 3.880 | .062 | -4.448 | 22 | .000 | -.0818 | .0184 | -.1199 | -.0436 |

9.7.6 Secondary Outcome Measures

9.7.6.1 Clinical Safety

There were no unexpected adverse effects or clinical safety concerns for either intervention group.

9.7.6.2 Effect Size

Effect size was determined in respect of a newly defined primary outcome of endodontic success for an immature tooth. As there was no statistically significant effect of intervention in relation to clinical or radiographic signs of healing, standard deviation of the outcome variable with significant effect of intervention (percentage change RRA) was 6% (observed SD was 5.5% in REP group and 3.1% in MTA group). Hence, an effect size of 6% was chosen as a conservative estimate.

The observed difference in means for RRA was 8.2% (0.9% MTA, 9.1% REP). The required sample size to detect a specified clinically significant difference between the groups with 90% power, at $\alpha=0.05$, has been calculated (Table 70).

Table 70 Effect: sample size

| Difference between groups to detect | Required Sample size |
|-------------------------------------|----------------------|
| 10% | 18 (9 per group) |
| 8% | 26 (13 per group) |
| 7% | 34 (17 per group) |
| 6% | 46 (23 per group) |
| 5% | 64 (32 per group) |
| 4% | 98 (49 per group) |
| 3% | 172 (86 per group) |
| 2% | 382 (191 per group) |
| 1% | 1516 (758 per group) |

9.7.6.3 Apical Closure

A total of 27 radiographs were analysed for apical closure as previously described at 12-month follow-up. Apical closure was recorded for all teeth in the MTA group. Apical closure was recorded for 64.3% (n=9) teeth in the REP group at 12-months (Table 71). There was a significant effect of intervention in relation to root end closure (

Table 72). Participants in the MTA group were significantly more likely to experience apical closure within 12-months than those in the REP group $p < 0.025$. There was an observed intra- and inter-rater agreement of 100% (Kappa = 1).

Table 71 Apical closure

| | | Apical Closure | | Total |
|-------|-----|----------------|--------|-------|
| | | Not closed | Closed | |
| | MTA | 0 | 13 | 13 |
| | REP | 5 | 9 | 14 |
| Total | | 5 | 22 | 27 |

Table 72 Chi-square test for independence in relation to the effect of group on apical closure

| | Value | df | Asymp. Sig. (2-sided) | Exact Sig. (2-sided) | Exact Sig. (1-sided) |
|---------------------|--------------------|----|-----------------------|----------------------|----------------------|
| Pearson Chi-Square | 5.698 ^a | 1 | .017 | | |
| Fisher's Exact Test | | | | .041 | .025 |

9.7.6.4 Colour Difference (Change in Tooth Colour)

➤ Subjective Clinical Assessment

Clinical photographs taken for 27 participants were subjectively assessed for change in tooth colour (pre- and postoperative colour difference) as previously described.

Colour difference was recorded for 45.5% (n=5) teeth in the MTA group. Colour difference was recorded for 92.9% (n=13) teeth in the REP group. Only one participant in the REP group did not experience pre- and postoperative colour difference. (Table 73). There was a statistically significant effect of intervention in relation to subjective dichotomous perceptible colour difference (

Table 74). Teeth in the REP group were more likely to experience colour difference than teeth in the MTA group ($p \leq 0.004$). There was an observed intra- and inter-rater agreement of 100% (Kappa = 1).

Table 73 Colour difference

| | | Pre-op/Post-op Colour Difference | | Total |
|-------|-----|----------------------------------|-----|-------|
| | | No | Yes | |
| | MTA | 8 | 5 | 13 |
| | REP | 1 | 13 | 14 |
| Total | | 9 | 18 | 27 |

Table 74 Chi-square test for independence in relation to the effect of group on colour difference

| | Value | df | Asymp. Sig. (2-sided) | Exact Sig. (2-sided) | Exact Sig. (1-sided) |
|---------------------|--------------------|----|-----------------------|----------------------|----------------------|
| Pearson Chi-Square | 8.975 ^a | 1 | .003 | | |
| Fisher's Exact Test | | | | .004 | .004 |

➤ *Objective Electronic Assessment*

Commission Internationale de l'Eclairage (CIE) L*a*b* values were recorded preoperatively, at the first intervention visit (_1), following irrigation of the dressing material from the root canal at the second intervention visit (_2), and at 12-month follow-up (_12). Data for 9 participants (MTA group n=5, REP group n=4) were available for statistical analysis.

Mean data values are presented (Table 75), which demonstrate that teeth in the REP group became darker (decreased lightness) than teeth in the MTA group following intervention, and that they experienced greater shifts within the colour space, commencing immediately following dressing of the root canal with triple antibiotic paste. Data collected for the remaining participants was excluded from analysis as it was collected with an aged device which was later found to be unreliable.

For the MTA group, mean a* values were positive at the commencement of treatment, became more positive (increased redness) between intervention visits 1 and 2, and then experienced a negative shift (increased greenness) over a period of 12-months. Mean b* values were positive at the commencement of treatment, remained fairly constant between intervention visits 1 and 2, and experienced a negative shift (increased blueness) over a period of 12-months. Despite an increase in lightness during the dressing period, teeth in the MTA group were marginally darker at 12-month follow-up than at baseline.

For the REP group, mean a* values were positive at the commencement of treatment, remained fairly constant between intervention visits 1 and 2, and then experienced a positive shift (increased redness) over a period of 12-months. Mean b* values were positive at the commencement of treatment, experienced a positive shift between intervention visits (increased yellowness), and then a negative shift, albeit a value that remained positive, (decreased yellowness) over a period of 12-months. Teeth in the REP group became progressively darker (decreased lightness) following commencement of treatment.

Table 75 Mean Commission Internationale de l'Eclairage (CIE) L*a*b* values

| Group | | L_1 | L_2 | L_12 | a*_1 | a*_2 | a*_12 | b*_1 | b*_2 | b*_12 |
|-------|----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Mean | 77.790 | 79.840 | 75.440 | 1.300 | 1.950 | -.620 | 28.073 | 29.320 | 20.313 |
| | Number | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| | Std. Deviation | 6.2083 | 5.7763 | 6.1702 | 2.1363 | 1.6993 | 1.0603 | 3.8415 | 5.9956 | 2.4625 |
| | Mean | 77.213 | 74.800 | 68.008 | .896 | .808 | 1.925 | 24.475 | 31.133 | 25.225 |
| | Number | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| | Std. Deviation | 5.3081 | 5.2686 | 5.5360 | .3086 | .3573 | 1.6141 | 9.8472 | 6.2638 | 3.6959 |

Delta E (ΔE) in both groups was detected at intervention visit 2 following root canal dressing, prior to placement of mineral trioxide aggregate, indicating colour difference that arises from the processes of pulp extirpation, irrigation, and dressing of the root canal; MTA 8.8 units (SD 5.5), REP 9.7 units (SD 4.7).

ΔE between the second intervention visit and 12-month follow-up was 12.2 units (SD 6.1) for MTA, and 9.5 (SD 6.6) for REP. From preoperatively at the first intervention visit to 12-month follow-up, mean ΔE for MTA was 8.8 units (SD 7.0), and for REP was 13.4 units (SD 9.1), indicating a greater mean colour difference from baseline to follow-up for participants in the REP group (CI 95%) (Table 76).

For MTA, the shift in ΔE is mainly explained by a large change in b^* and a small change in L, whereas for REP, the ΔE shift is mainly explained by a large change in L and an increased a^* value.

Table 76 Mean Delta E (ΔE) (colour difference intervention visits 1, 2 and 12-month follow-up)

| Group | | ΔE visit 1-visit 2 | ΔE visit 1-12months | ΔE visit 2-12months |
|-------|----------------|----------------------------|-----------------------------|-----------------------------|
| | Mean | 8.8431 | 8.8363 | 12.2046 |
| | Number | 5 | 5 | 5 |
| | Std. Deviation | 5.51523 | 7.04816 | 6.07070 |
| | Mean | 9.7511 | 13.4055 | 9.5197 |
| | Number | 4 | 4 | 4 |
| | Std. Deviation | 4.66017 | 9.13583 | 6.62043 |

Table 77 Delta E (ΔE) values

| Participant | Group | ΔE visit 1–visit 2 | ΔE visit 1-12months | ΔE visit 2-12months |
|-------------|-------|----------------------------|-----------------------------|-----------------------------|
| 20 | MTA | 16.13 | 2.70 | 16.16 |
| 21 | MTA | 1.46 | 8.75 | 9.92 |
| 22 | REP | 9.31 | 24.88 | 17.39 |
| 24 | MTA | 8.52 | 20.84 | 16.39 |
| 26 | REP | 3.32 | 2.55 | 1.23 |
| 27 | REP | 13.34 | 13.66 | 9.12 |
| 28 | MTA | 11.69 | 5.60 | 16.06 |
| 29 | MTA | 6.41 | 6.30 | 2.50 |
| 30 | REP | 13.02 | 12.53 | 10.33 |

9.7.6.5 Sensibility Testing

Some 14.3% (n=2) teeth in the REP group responded positively to sensibility testing with Roeko Endo-Frost Spray (Coltene), at 12-month follow-up.

9.7.6.6 Feasibility and Acceptability

➤ Study Protocol

Recruitment

Recruitment took place over a period of 36 months between 2011 and 2014. Four individuals who met the inclusion criteria declined to participate in the trial. Participation was reportedly declined due to travelling distance between the dental hospital and home town, or due to the number of follow-up visits required. Participants and their caregivers provided positive verbal feedback regarding the patient information leaflet and consent forms. No alterations were suggested.

Randomisation

There were no deviations from protocol throughout trial. The randomisation protocol was effective and prevented prediction of the allocation sequence. Sequence implementation at the first intervention visit necessitated that triple antibiotic paste was prepared for all participants although it was required for only 50%. However, patients expressed an interest in their group allocation and this remained unknown until the intervention commenced, omitting the possibility of participants seeking the alternative intervention without withdrawing from trial.

Retention

Some 93% (n=28) of participants were able to accept delivery of the interventions and complete the trial. Two participants were unable to complete the trial due to heightened anxiety relating to the administration of local anaesthetic at the second intervention visit. Some 4% (n=1) of the 28 participants who completed the intervention visits did not attend the pre-specified recall schedule. Follow-up appointments were scheduled for this participant throughout the year in case he wished to attend, however, he and his caregiver continued to decline review and described the resolution of clinical signs of inflammation as the reason for non-attendance.

Assessment

Twenty seven analysed participants attended for two intervention visits, two weeks apart, of between 60 to 90 minutes duration. There were no notable differences between the intervention groups. It was noted that methodological procedures for trial accounted for approximately 30 minutes of each intervention visit. In particular, the recording of subjective and objective colour data involved care in standardising images and locating the reference point on the clinical crown for the tip of spectrophotometer.

➤ *Delivery of the Interventions*

Practical or clinical complexities encountered during provision of the interventions are described here as they were noted.

Young participants had some difficulty accepting the interventions. Treatment visits were lengthy, at up to 90 minutes. Only three participants had previously undergone dental treatment with local anaesthesia prior to experiencing a traumatic dental injury. Despite this, it was noted that acceptability of the interventions for individual participants was difficult to predict by either the investigator, participant or caregiver in attendance. Employment of non-pharmacological behavioural management techniques aided acceptability of the interventions (Campbell C et al., Revised 2011). Of the 28 participants who were able to complete the interventions, few were comfortable to readily accept treatment, complicating the dextrous placement of mineral trioxide aggregate, either at the apex or at the coronal third of the root. The clinical aid of the endodontic microscope contributed to both positive and negative participant behavioural change. Placement of MTA at the apex was frequently complicated by the reiteration of effective management of anxious participants that necessitated regular repositioning of the endodontic microscope

Fuji IX (GC) has been suitable for use as a temporary restorative material. Its properties include biocompatibility, fluoride release and radiopacity. It demonstrated intrinsic adhesion to enamel and dentine and was placed in a single step without the need for etch or bond. These properties provided this material with some distinct advantages in the management of paediatric participants.

The investigator experienced practical complexities in relation to MTA placement in the delivery of both interventions. Placement of mineral trioxide aggregate at the coronal third of the root was complicated by the omission in the intervention protocol to provide a barrier against which to place the material. This was exacerbated by noted difficulties with inducing apical bleeding to the level of the cemento-enamel junction during regenerative endodontic procedures.

The quality of the apical, or coronal, seal of mineral trioxide aggregate, as appropriate per intervention, was assessed as previously described (Table 78). Some 67.9% (n=19) of teeth had an optimal seal. There was no significant effect of intervention in relation to quality of seal (<0.041).

Some 64.3% (n=9) teeth in the REP group were assessed as having an optimal coronal seal (mineral trioxide aggregate coronal plug in-situ and appropriately situated and condensed at the coronal portion of the root canal, without separation of the plug into the middle or apical thirds of the root canal).

Some 71.4% (n=10) teeth in the MTA group were assessed as having an optimal apical and coronal seal (mineral trioxide aggregate apical plug in-situ, and appropriately situated and condensed at the immature apex, coupled with well condensed gutta percha obturating the remainder of the root canal without deficiency). There was an observed intra- and inter-rater agreement of 100% (Kappa = 1).

Table 78 Quality of seal

| | | Quality of seal | | Total |
|-------|-----|-----------------|------------|-------|
| | | Optimal | Suboptimal | |
| | MTA | 10 | 4 | 14 |
| | REP | 9 | 5 | 14 |
| Total | | 19 | 9 | 28 |

9.8 Discussion

This randomised controlled trial was designed to address the research question: *Are regenerative endodontic procedures superior to mineral trioxide aggregate apexification in the management of necrotic, immature, permanent incisors?*

The objectives of the study will be discussed to determine the extent to which they have been met, and to consider the feasibility, and necessity, of conducting a future, larger randomised controlled trial.

9.8.1 The Primary Outcome Measure

The primary objective was newly defined to assess endodontic success for an immature tooth, subsequent to mineral trioxide aggregate apexification and regenerative endodontic procedures. The outcome measure incorporated both clinical and radiographic signs of healing, plus radiographic signs of tooth development, as is appropriate for reliable and standardised evaluation of dimensional changes in a growing child and developing tooth (Table 55 Primary outcome measure for endodontic success of an immature tooth). This objective was addressed in full as follows:

9.8.1.1 *Clinical signs of healing*

Measurement of descriptive criteria that fulfil widely accepted definitions of clinical signs of healing were appropriate and straightforward (chapter 5.6.1: Clinical Assessment of Periapical Health and Disease). These criteria aimed to encompass patient-based outcomes including tooth survival and the absence of symptoms associated with pulpal or periapical inflammation that may affect oral health related quality of life for patients and their families.

It is noted that the measurement of clinical signs of healing relies, to some extent, on patient-reported symptoms, including the absence of pain. Assessment of clinical signs of healing was, therefore, a shared process between clinician, participant, and caregiver where appropriate. It is considered unlikely, albeit possible, that either the participant or the caregiver would intentionally decline to inform the investigators of the presence of pain. A single investigator was responsible for assessment of clinical signs of healing. As this investigator was also the operator and therefore not blinded to the intervention, a future trial might aim to reduce the possibility of bias by requiring a second investigator to carry out data extraction. It is noted that this requirement may not be feasible in terms of investigator availability, and that it would require participants to undergo multiple, or lengthier, clinical examinations. If a multicentre trial were conducted, clinical calibration of investigators might be advisable.

100% (n=27) of participants fulfilled the descriptive criteria to satisfy a positive recording of endodontic success in relation to clinical signs of healing, including tooth survival. A comparative study of mineral trioxide aggregate versus calcium hydroxide apexification reported a clinically important 26% rate of tooth loss for calcium hydroxide apexification within 12 months as a result of cervical fracture, and no tooth loss for mineral trioxide aggregate (Bonte et al., 2015). This study provides evidence to support that mineral trioxide aggregate apexification is not associated with a high rate of rapid tooth loss. There were no differences between the interventions in relation to clinical signs of healing at any time during the period of observation. A constant and equal rate of clinical healing indicates success in relation to root canal dressing with calcium hydroxide and with triple antibiotic paste. It is also assumed that root canal preparation and irrigation protocols for each of the interventions were appropriate and effective.

9.8.1.2 *Radiographic signs of healing*

Measurement of descriptive criteria that fulfil widely accepted, post-endodontic radiographic outcomes that predict periapical healing were appropriate and straightforward (Strindberg, 1956). These criteria aimed to encompass primarily clinician-based outcomes of radiographic healing, which are associated with patient-based outcomes of tooth survival, and the resolution of clinical signs of inflammation.

Intraoral, bidimensional, conventional, plain film periapical radiographs, taken routinely following post-endodontic intervention were standardised in so far as was practically possible. Consistency of film size, exposure, and paralleling technique and the use of a film holder aided standardisation. All radiographs were taken on a single radiography system as described in a clinical setting similar to routine practice and a suitable environment in which to review the outcome data.

Construction of a customised jig for individual participants may further have aided reproducibility of radiographic exposure and reduced the extent of correction required prior to digital realignment with ImageJ (Beslot-Neveu et al., 2011, Dabbagh et al., 2012). If it was considered necessary to customise a jig for reproducible positioning of radiographic films within an individual participant over the course of follow-up in a future study, the use of a putty matrix to encase the incisal and lingual aspects of adjacent teeth has been described for the purposes of radiography (Durack et al., 2011). It is noted however, that this approach may be unsuitable in a growing child in the mixed dentition and is perhaps best reserved for ex-vivo studies, or studies of radiographic signs of healing in which no participant growth or development is predicted.

Efforts to standardise radiographs to this extent were unnecessary for the purposes of assessing the outcome criteria as defined in this study. Previous comparative studies of interventions for root end closure have described paralleling, bisecting angle techniques and alignment systems for aiding comparison of radiographs without the use of a customised jig (Bal et al., 1993, Damle et al., 2012, Nagy et al., 2014), although it is noted that few report inter-rater agreement.

Some 96% (n=26) of participants fulfilled the descriptive criteria to satisfy a positive recording of endodontic success in relation to radiographic signs of healing. There was no statistically significant difference between the interventions, although a single participant in the REP group had an uncertain outcome at 12-month follow-up, possibly as a result of suboptimal seal of the root canal with mineral trioxide aggregate, or the prolonged presence of an unrestored crown fracture prior to presentation.

Following completion of the trial observation period, this participant was invited to attend the paediatric dentistry clinic to ensure healing occurred. Subsequent radiographic examination at 36 months post-intervention confirmed radiographic signs of healing that fulfilled the outcome's descriptive criteria. A limitation of this study is, therefore, the short outcome assessment observation period for appropriate analysis of regenerative endodontic procedures, particularly in cases in which a fractured incisor has remained unrestored for a prolonged period of time. If a future study was undertaken, it may be wise to observe radiographic signs of healing for a longer period (chapter 5.6.5: Outcome Assessment Observation Period).

Inter- and intra-rater agreement of 100% indicates that assessment of plain film, intraoral radiographs for healing according to the trichotomous radiographic assessment criteria of the Strindberg Index is a reliable and reproducible measure that is suitable for determining endodontic success.

There were no unfavourable radiographic outcomes demonstrated, therefore, no participants required repeat endodontic intervention. This high success rate, coupled with a lack of a statistical difference between the groups, supports the appropriateness and effectiveness of the intervention protocols in relation to preparation and disinfection of the root canal dressing.

A majority of endodontists and paediatric dentists have reported that the likelihood of resolution of infection following endodontic intervention has a significant influence on their management of non-vital, immature teeth (chapter 7.5.16: Likelihood of Resolution of Infection). Therefore, it can be assumed from analysis of this data that there is no statistical or clinical difference between the interventions in relation to clinical or radiographic signs of healing.

9.8.1.3 *Radiographic Signs of Tooth Development*

Data for 89% (n=24, 11 MTA, 13 REP) of participants who completed the study were available for analysis of radiographic signs of tooth development in relation to dimensional changes in root length and radiographic root area. Data for the remaining three participants was excluded from analysis due to the impossibility of measuring the entire structure of the root canal on either the pre- or postoperative radiographs.

If this study were to be repeated, consideration could be given to assessing preoperative radiographs to meet eligibility criteria that include visibility of the entire structure of the root canal. However, it is noted that this may not negate the necessity to exclude participants from analysis for whom development of the dentition (such as eruption of the lateral incisor) unpredictably obstructs visibility at follow-up.

The use of ImageJ software, with the plug-in application TurboReg, for digital alignment of non-standardised radiographs, prior to measurement of root length, and radiographic root area (RRA) as described has provided a reliable, unbiased method of quantifying dimensional changes retrospectively in a growing patient with developing teeth (chapter 5.6.3: Imaging and Image Analysis).

Intra-rater agreement was almost perfect for both investigators in relation to measurement of root length and radiographic root area, indicating that RRA is reproducible. Inter-rater agreement was almost perfect in relation to measurement of root length and substantial for radiographic root area. Concordance was not as high in this study as described in the original testing of the validated tool for measuring RRA, in which intraclass correlation values were 0.99 for both inter- and intra-rater agreement following written instructions similar to those described in this study (Flake et al., 2014). If high concordance could be predicted, this method of measuring RRA would be valuable in the design of a larger, multicentre randomised controlled trial.

This study did not seek to compare RRA values with a descriptive analysis of dimensional changes evident following direct visual assessment of a plain film radiograph taken at 12-month follow-up.

If this study were to be repeated in the future, consideration could be given to incorporating this additional assessment step in order to determine the extent to which direct visual assessment of plain film radiographs might underestimate tooth development following REP.

If dimensional change is underestimated during routine assessment in a clinical environment, it appears possible that any dimensional changes offered as a result of a regenerative endodontic procedure may be undetected, and that clinically significant differences between regenerative endodontic procedures and apexification procedures may remain unaccounted for.

The construct validity of the RRA measurement method in demonstrating clinically meaningful dimensional changes evident on plain film radiographs has been reported (Flake et al., 2014), and if repeated in this study might support rejection of the null hypothesis. Conversely, apical closure may occur following regenerative endodontic procedures without any notable increase in root length or root thickness. A majority of endodontists and paediatric dentists have reported that the likelihood of apical closure following endodontic intervention had a significant influence on their management of non-vital, immature teeth (chapter 7.5.17: Likelihood of Root End Closure). If clinicians in routine practice are able to carry out direct visual assessment of plain film radiographs that reveal apical closure then recording of RRA may be without value in these cases.

Flake et al. (2014) proposed that their method of quantifying dimensional changes with RRA as described is easily taught to novice calibrators. The investigators in this study note that orientation with the software, and calibration of a series of cases prior to outcome assessment, was invaluable and required practice. It is considered unlikely that clinicians in routine practice would introduce measurement of RRA to their daily practice. However, for the purposes of comparing the interventions in this randomised controlled trial, the technique has been effective at demonstrating a statistically significant difference between the interventions.

If it is agreed that this difference is clinically significant, the null hypothesis can be rejected, as the success rate of regenerative endodontic procedures in achieving endodontic success for an immature tooth would be superior to that of mineral trioxide aggregate apexification.

9.8.2 Secondary Outcome Measures

9.8.2.1 Clinical Safety

There were no concerns in relation to clinical safety, hence this study supports the role of mineral trioxide aggregate and regenerative endodontic procedures in respect of their role as safe interventions for the management of necrotic, immature teeth, in line with the literature (chapters 5 and 8).

9.8.2.2 Effect Size

As clinical healing was constant, and there were no statistical differences between the groups in relation to radiographic healing or changes in root length, RRA was the determining criterion in the primary outcome measure of determining endodontic success for an immature tooth. The minimal difference in RRA between the groups that might indicate that regenerative endodontic procedures are superior to mineral trioxide aggregate apexification, is therefore appropriate for determining effect size.

Measurement of RRA in this study has indicated that teeth undergoing regenerative endodontic procedures may experience dimensional changes in relation to root thickness, and an increase in root surface area of approximately 10% in a 12-month period. In appraising the clinical significance of this dimensional change, the importance of root thickness in relation to tooth survival has been considered.

It is important to consider that dimensional changes may continue to occur over a longer period than that observed in this study (Chapter 5.6.5 Outcome Assessment Observation Period).

For teeth in the MTA group the mean increase in RRA of 0.85% (SD 2.92%, range -4.6 to 6.8) is unlikely to be of clinical significance. This value <1% might be attributable in part to the mean increase in root length of 0.25mm, or may be an error of measurement. Increase in root length of 0.25mm represents approximately 1/100th of the length of a mature permanent central incisor and is not considered to be clinically significant. No dimensional changes are expected following a mineral trioxide aggregate apexification procedure which acts as a control group (Flake et al., 2014).

This minimal increase does however, indicate that there has not been a net loss of root surface area within the group, which might result from root resorption and remodelling. It is, however, noted that three participants within the MTA group experienced a decrease in RRA (-4.6, -1.6 and -0.6%). It is unlikely that this decrease is clinically significant unless it is progressive, supporting the suggestion that a future trial should carry out outcome assessment over a longer period (chapter 5.6.5: Outcome Assessment Observation Period).

For teeth in the REP group the mean increase in RRA of 9.03% (SD 5.55, range 2.2 to 21.6) was statistically significantly different to MTA, and may also be clinically significant. This value is probably not attributable to the mean increase in root length of 0.5mm. Increase in root length of 0.5mm represents approximately 1/50th of the length of a mature permanent central incisor and is not considered to be clinically significant.

If 90% power is selected, the required sample size to detect a minimally clinically significant difference in RRA of 10% is 18 (9 per intervention group). However, it is probably not true to assume that difference in RRA of less than 10% is unimportant. In this study, 38.5% (n=5) participants in the REP group experienced an increase in RRA greater than 10%. However, the mean increase in RRA of 9.03%, and the observed difference between the intervention groups, may be important.

If the clinically significant difference between the interventions was 9% percentage change in RRA within 12-months, this study has demonstrated a clinically and statistically significant difference between the groups with 90% power. It is therefore arguable that this study need not be repeated on a larger scale, necessitating participation of children in further unwarranted research and allocation to an inferior control group, if effect size is agreed to be appropriate at 9%. However, the minimally significant difference in RRA is one that might reduce the risk of root fracture, thus, increasing the prognosis for long-term tooth survival, and this is somewhat difficult to establish. There may also be variation of risk for root fracture within the population.

If a future study was proposed to test regenerative endodontic procedures following recent developments of the intervention protocol (Kontakiotis et al., 2015a), including variations of disinfection and root canal dressing materials (Latham et al., 2016), then pragmatic planning would determine that the sample size should be operationally possible in relation to available resources, and in terms of being able to recruit sufficient participants. Furthermore, effect size should be achievable within a reasonable observation period for outcome assessment.

It is not known what mean increase in RRA might be achieved if the observation period was extended to 36 months. However, this timeframe might be achievable if the recall interval were extended and sufficient participants were recruited to counteract the likely increase in the dropout rate, which could result from greater demand on participants and their families. Only two participants in the REP group experienced an increase in RRA less than 5% (2.2 and 2.8%).

Repeating this study with an effect size of 5%, with 90% power, and an observation period of 36 months, would require a sample size of 64, therefore requiring recruitment of 70 participants if this study's dropout rate of 10% were expected. However, a 5% increase in RRA over a 36-month period is not as clinically important as a near 10% increase in RRA over a 12-month period. Hence, it is concluded that if this randomised controlled trial were to be repeated in order to analyse the superiority of new protocols for regenerative endodontic procedures to mineral trioxide aggregate apexification, an effect size of 10% increase in RRA, over an outcome assessment observation period of 36 months would be appropriate, achievable and operationally possible.

As previously discussed, a previous comparative study of interventions for root end closure have anticipated a success rate for calcium hydroxide apexification of 5%, and for mineral trioxide aggregate apexification of 50%, at 12-month follow-up, thus calculating that recruitment of 30 participants (or 30 teeth) provides 80% power (Bonte et al., 2015).

Other relevant studies that do not report statistical power have recruited similar numbers of participants, ranging from 18 (Dabbagh et al., 2012), through 20 (Pradhan et al., 2006, Narang et al., 2015), 30 (Bal et al., 1993, El-Meligy and Avery, 2006, Damle et al., 2012) and 36 (Nagy et al., 2014).

Inclusion of suspension criteria in the design of a future trial may aid power by reducing the dropout rate. If, for example, poor compliance is evident at the first intervention visit, and suspension criteria were applied prior to sequence implementation for that individual participant, there would be no missing data due to poor compliance. Alternatively, the intervention protocol could be adjusted so that sequence implementation (opening of opaque, sequentially numbered envelopes) could take place following access and preparation of the root canal, prior to placement of the root canal dressing.

It continues to be recommended that assessment of clinical and radiographic signs of healing, and changes in root length, are made and that the primary outcome measure is appropriate. Clinical signs of healing are of importance to young patients and their families. Radiographic signs of healing are of importance to clinicians. Changes in root length may be significant over a longer period of observation, and a favourable crown: root ratio may be important in relation to tooth survival.

9.8.2.3 Apical Closure

Paediatric dentists and endodontists who responded to a survey described earlier in this thesis (chapter 7), reported that the likelihood of successful root end closure following endodontic intervention had a significant influence on their management of non-vital, immature teeth.

In this randomised controlled trial, apical closure was recorded for all teeth in the MTA group, and for two thirds of teeth in the REP group, at 12-month follow-up. There was a statistically significant effect of intervention in relation to root end closure that may be clinically significant to paediatric dentists and endodontists.

Perfect intra- and inter-rater agreement was recorded, indicating that assessment of apical closure on plain film intraoral radiographs is a reliable outcome measure for future studies. Previous comparative studies of interventions for root end closure have focused on apical closure as a primary outcome measure, frequently also reporting the time taken for apical closure to be achieved.

Success rates for MTA apical closure at 12-month follow-up have been reported as 100% (n=14) (Damle et al., 2012), 70% (n=7) (Pradhan et al., 2006). Mean time taken for apical closure with MTA has been reported as 4.5 months (SD 1.56) (Damle et al., 2012), 3 months (SD 2.9) (Pradhan et al., 2006), 6.6 weeks (SD 1.9) (Lee et al., 2015).

Apical closure outcomes for REP have been previously discussed (Nagy et al., 2014, Narang et al., 2015). Success rates for MTA apical closure at 12-month follow-up in this study have been 100%, supporting the role of mineral trioxide aggregate apexification.

This study provided the first outcome data from a randomised controlled trial for regenerative endodontic procedures. Analysis of the data indicates that regenerative endodontic procedures can successfully induce apical closure in selected cases.

9.8.2.4 Colour Difference (Change in Tooth Colour) Discussion of Case Based Examples

Earlier review of the literature established a reference frame for the clinical significance of objective colour difference data (colour difference perceptible at > 4 ΔE units, and unacceptable at > 8 ΔE units) (chapter 5.6.6: Tooth Colour). As previously discussed, change in tooth colour following regenerative endodontic procedures has been attributed to both the presence of minocycline in triple antibiotic paste, and to mineral trioxide aggregate placed intracoronally, near the cemento-enamel junction (American Association of Endodontists, 2016, Galler, 2016).

Review of the raw data (Table 77) has revealed that participants with objective data available for statistical analysis experienced perceptible 77.8% (n=7) and unacceptable 66.7% (n=6) colour difference during the two-week root canal dressing period between the first and second intervention visits. Some 77.8% (n=7) and 55.6% (n=5) of teeth developed unacceptable colour difference that occurred between preoperative presentation and 12-month follow-up. Some 60% (n=3) of those teeth with unacceptable colour difference at 12-month follow-up were in the REP group. The increase in lightness recorded during the calcium hydroxide dressing period supports previously reported data (Day et al., 2011).

Subjectively measured perceptible colour difference was recorded for 45.5% (n=5) of teeth in the MTA group and 92.9% (n=13) of teeth in the REP group. This implies that there is some disagreement in subjective and objective outcome data in relation to perceptible and acceptable colour difference within this study. Explanations for this might include a variation in the clinical and oral environment, inaccurate measurement with the spectrophotometer, failure of the device to calibrate, or failure of the observers to accurately assess colour change from clinical photographs. Failure of the observers might be considered unlikely in view of intra- and inter-rater 100% agreement. In this study, two devices were employed over the study period as a result of failure of the first device requiring the investigators to purchase a newer, updated model.

Whilst colour difference outcomes were recorded in order to compare the interventions, it is noted that previous pulpal haemorrhage, thickening of dentinal root walls, root canal sclerosis, and the compromised aesthetics of restorations with a poor marginal seal, may also contribute to colour difference. A previously discussed study reported that neither commercially available cements containing bismuth oxide, nor endodontic irrigants induce colour difference (Dettwiler et al. 2016), however it is not known whether the intracoronary mineral trioxide aggregate or the triple antibiotic paste was primarily responsible for colour difference in this study. In order to compare objective and subjective data, and to draw conclusions in relation to the feasibility and clinical significance of collecting both data sets, colour difference outcome data for nine participants with objective data available for analysis, is discussed with associated clinical photographs and plain film radiographs (prior to digital standardisation in ImageJ software)^{1 2}. Participants are presented first for the MTA group, followed by the REP group, in order of decreasing postoperative colour difference (Table 77). Also discussed are two participants excluded from colour analysis due to incomplete objective data collection because of failure to attend for follow-up (participant ID 25, MTA), or failure of the spectrophotometer to function appropriately (participant ID 23, REP).

¹ There was an observed intra- and inter-rater agreement of 100% for subjective assessment of colour difference outcomes for all participants, at each measurement interval.

² Colour difference ΔE was assessed rather than colour – for example, if ‘discoloured’ at presentation but no further colour change occurred then ΔE would be zero / subjective change would not be recorded.

Participant ID 24

Subjective colour change

Colour difference was not perceptible in clinical photographs taken at intervention visits 1 and 2. Colour difference was perceptible in clinical photographs taken at intervention visit 1 and at 12-month follow-up (Figure 29).

Objective colour change

Participant ID 24 experienced the largest colour difference of participants in the MTA group (ΔE 20.84) between commencement and completion of trial. Colour difference was ΔE 8.52 between intervention visits 1 and 2, and ΔE 16.39 between intervention visit 2 and 12-month follow-up.

Case Based Discussion

Radiographs (Figure 30) reveal this tooth had thin dentinal root walls and a suboptimal coronal restoration in-situ at presentation (replaced following obturation at intervention visit 2). Apical seal was suboptimal. Gutta percha extended coronal to the cemento-enamel junction. It was noted that this young participant experienced difficulty accepting delivery of the interventions. Suboptimal seal may impact on perceptible colour difference. Notably, clinical and radiographic healing was successful despite the presence of a suboptimal seal, perhaps supporting the irrigation and dressing protocol, and the importance of the coronal seal. Colour difference recorded objectively between intervention visits 1 and 2 could perhaps be attributed to change in lightness values as a result of the presence of a temporary endodontic access restoration. This colour change was not subjectively perceptible on clinical photography despite having a $\Delta E > 4$. It is possible that the ΔE measurement taken at intervention visit 2 is inaccurate, or that the appearance of the fractured incisor reduces the effect of colour on appearance.

The tooth discolouration noted subjectively at 12-month follow-up is consistent with coronal extension of gutta percha and discolouration frequently associated with mineral trioxide aggregate. It is of interest that apical closure appears complete at 12-month follow-up, despite the nature of the intervention.

Figure 29 Participant ID 24: Clinical photographs taken at intervention visits 1, 2 and 12-months follow-up



Figure 30 Participant ID 24: Periapical radiographs taken at intervention visit 1 and 12-month follow-up



Participant ID 21:

Subjective colour change

Colour difference was not perceptible between intervention visits 1 and 2, or at 12-month follow-up (Figure 31).

Objective colour change

There was no experience perceptible colour difference between intervention visits 1 and 2 (ΔE 1.46). Unacceptable colour difference was recorded between intervention visit 1 and 12-month follow-up (ΔE 8.75).

Case Based Discussion

In this case, debilitating preoperative signs and symptoms of inflammation were present. Radiographs (Figure 32) reveal that apical seal was suboptimal and that gutta percha extended coronal to the cemento-enamel junction. This young participant experienced difficulty accepting delivery of the interventions. Despite this, subjective colour change was not judged to be clinically significant. This subjective opinion is at odds with objective data.

Figure 31 Participant ID 21: Clinical photographs taken at intervention visits 1, 2 and 12-months follow-up



Figure 32 Participant ID 21: Periapical radiographs taken at intervention visit 1 and 12-month follow-up



Participant ID 29:

Subjective colour change

Colour difference was not perceptible in clinical photographs between intervention visits 1 and 2, or at 12-month follow-up (Figure 33).

Objective colour change

Participant ID 29 experienced perceptible colour difference between intervention visits 1 and 2 (ΔE 6.41). The final recorded colour difference marginally improved between intervention visit 1 and 12-month follow-up (ΔE 6.30) and was slowly progressive between intervention visit 2 and 12-month follow-up (ΔE 2.50).

Case Based Discussion

Participant cooperation with delivery of the interventions was good. Radiographs (Figure 34) reveal that this tooth has thin dentinal root walls, a wide open apex, and a suboptimal coronal restoration in-situ at presentation (replaced following obturation at intervention visit 2). Despite this, subjective colour difference was not judged to be clinically significant. This subjective opinion is at odds with objective data which indicates a perceptible colour change. The marginal reduction in ΔE between intervention visit 2 and 12-month follow-up reported in the objective data is, however, reflected in the slight improvement in clinical appearance visible at 12-month follow-up. Decalcification of enamel adjacent to the inflamed gingival margin at presentation, which subsequently remineralised and resolved following the delivery of preventive care by the primary care practitioner, may have masked colour difference recorded objectively between intervention visits 1 and 2.

Figure 33 Participant ID 29: Clinical photographs taken at intervention visits 1, 2 and 12-months follow-up



Figure 34 Participant ID 29: Periapical radiographs taken at intervention visit 1 and 12-month follow-up



Participant ID 28:

Subjective colour change

Colour difference was not perceptible in clinical photographs between intervention visits 1 and 2, or at 12-month follow-up (Figure 35).

Objective colour change

Participant ID 28 experienced unacceptable colour difference between intervention visits 1 and 2 (ΔE 11.69). Colour difference between intervention visit 2 and 12-month follow-up was ΔE 16.06. However, colour difference between intervention visit 1 and 12-month follow-up was ΔE 5.60.

Case Based Discussion

In this case, debilitating preoperative signs and symptoms of inflammation were present. Participant cooperation with delivery of the interventions was good. Radiographs (Figure 36) reveal that this tooth had a suboptimal coronal restoration in-situ at presentation (replaced following obturation at intervention visit 2), and gutta percha that extends coronal to the cemento-enamel junction. Despite this, subjective colour change was not judged to be clinically significant. This subjective opinion is at odds with objective data, which indicates a perceptible objective colour difference, particularly whilst the tooth was temporarily dressed between intervention visits. This could perhaps be attributed to change in lightness values as a result of the presence of a temporary endodontic access restoration, or may indicate an error of measurement as a result of defective calibration of the spectrophotometer. The relatively low ΔE value for colour difference between intervention 1 and at 12-month follow-up is more in agreement with subjective clinical findings.

Figure 35 Participant ID 28: Clinical photographs taken at intervention visits 1, 2 and 12-months follow-up



Figure 36 Participant ID 28: Periapical radiographs taken at intervention visit 1 and 12-month follow-up



Participant ID 20:

Subjective colour change

Colour difference was not perceptible in clinical photographs between intervention visits 1 and 2, or at 12-month follow-up (Figure 37).

Objective colour change

Participant ID 20 experienced the lowest recorded colour difference value (ΔE 2.70) for participants in the MTA group between intervention visit 1 and 12-month follow-up. There was, however, considerable unacceptable colour difference recorded (ΔE 16.13) whilst the tooth was temporarily dressed between intervention visits.

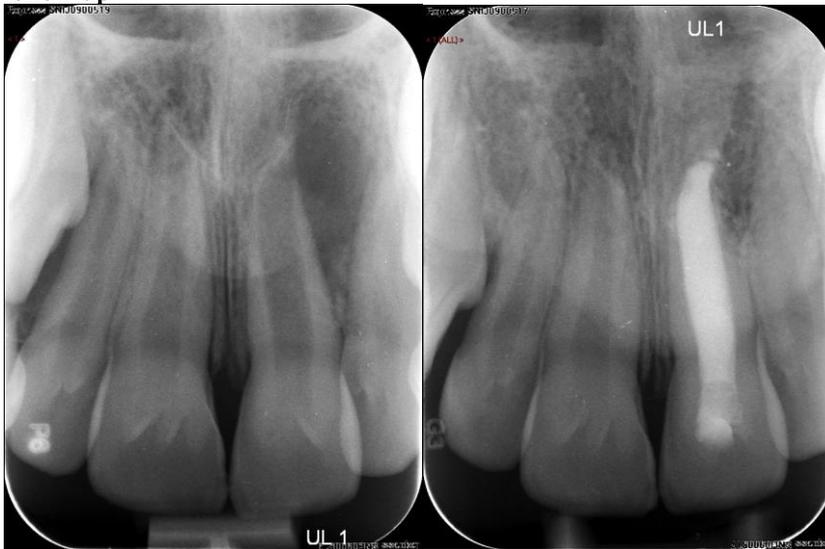
Case Based Discussion

In this case, debilitating preoperative signs and symptoms of inflammation were present. Participant cooperation with delivery of the interventions was good. Radiographs (Figure 38) reveal that gutta percha extended coronal to the cemento-enamel junction. The tooth was intact at presentation, and had not suffered a crown fracture, unlike those discussed previously and which experienced greater colour difference following intervention. It is possible that discolouration of in-situ incisal restorations affects subjective and objective assessment of colour difference, depending on the extent, and position, of the restoration. Subjective colour change at 12-month follow-up was not judged to be clinically significant, in agreement with objective data (ΔE approximately 2 units), which may not be perceptible to the inexperienced observer (chapter 5.6.6: Tooth Colour). There was however, a perceptible objective colour difference whilst the tooth was temporarily dressed between intervention visits that was not subjectively perceptible. This could, again, perhaps be attributed to change in lightness values as a result of the presence of a temporary endodontic access restoration, or to an error of measurement.

Figure 37 Participant ID 20: Clinical photographs taken at intervention visits 1, 2 and 12-months follow-up



Figure 38 Participant ID 20: Periapical radiographs taken at intervention visit 1 and 12-months follow-up



Participant ID 25:

Incomplete data is available for participant ID 25 due to failure to attend for follow-up. This participant was excluded from colour analysis as described. However, data available from intervention visits 1 and 2 is briefly discussed, due to the reported satisfaction of the participant and his caregiver following clinical signs of inflammation³.

Subjective colour change

Colour difference was not perceptible in clinical photographs between intervention visits 1 and 2 (Figure 39).

Objective colour change

Participant ID 25 experienced unacceptable colour difference (ΔE 8.43) between intervention visits 1 and 2.

Case Based Discussion

This case presented with poor dental aesthetics as a result of crown fractures, and preoperative discolouration, of the upper left and right permanent central incisors. The treated tooth was unrestored at presentation. Debilitating preoperative signs and symptoms of inflammation were present. Radiographs (Figure 40) reveal that the treated tooth had thin dentinal root walls, a wide open apex and gutta percha that extends coronal to the cementoenamel junction.

If the previous colour trend for such cases is assumed to continue it can be expected that this tooth may have experienced further deterioration in tooth colour following intervention visit 2. Subjective clinical findings were at odds with objective data.

³ It was confirmed that this participant attended for follow-up with his primary care practitioner despite his refusal to attend follow-up at the dental hospital. He later returned to the dental hospital, following referral for endodontic management of the contralateral tooth that became non-vital following repeat trauma and loss of the incisal restoration that was in-situ at initial presentation.

Figure 39 Participant ID 25: Clinical photographs taken at intervention visits 1 and 2



Figure 40 Participant ID 25: Periapical radiographs taken at intervention visits 1 and 2



Participant ID 22:

Subjective colour change

Colour difference was perceptible in clinical photographs between intervention visits 1 and 2, and at 12-month follow-up (Figure 41).

Objective colour change

Participant ID 22 experienced the largest colour difference (ΔE 24.88) for participants in the REP group at 12-month follow-up. There was unacceptable colour difference (ΔE 9.31) whilst the root canal was dressed. However, most colour difference occurred subsequent to intervention visit 2 (ΔE 17.39).

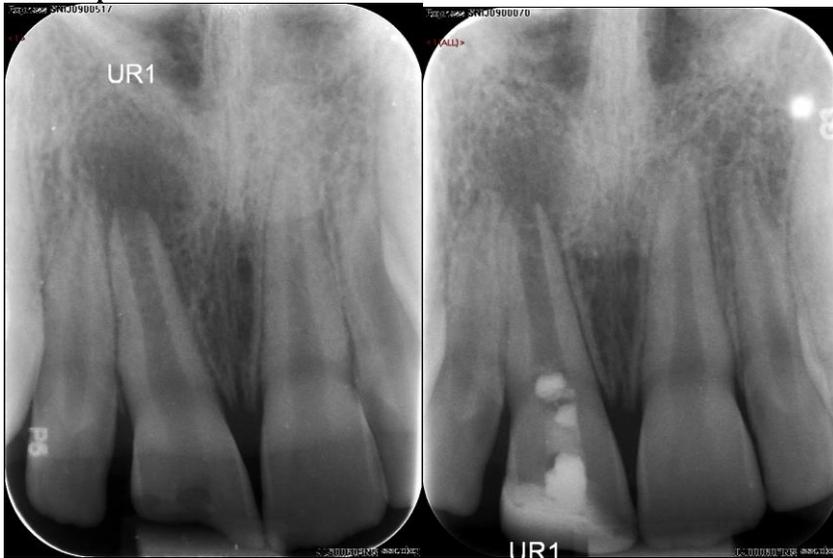
Case Based Discussion

In this case, debilitating preoperative signs and symptoms of inflammation were present. The tooth had suffered a crown fracture and was unrestored at presentation. Subjective colour change was judged to be clinically significant at intervention visit 2 and at 12-months follow-up, in agreement with objective data. A composite bandage was placed following endodontic treatment at intervention visit 1, however, a complete restoration was placed at intervention visit 2 in line with the study protocol. The participant remained unconcerned in relation to tooth colour. The participant's caregiver expressed concern in relation to tooth colour throughout the study. Removal of the triple antibiotic paste does not appear to have reduced colour difference, which progressed over the follow-up period. Radiographs (Figure 42) reveal that the tooth had a small coronal plug of mineral trioxide aggregate in-situ, and a large restoration of the access cavity. Mineral trioxide aggregate was placed below the level of the cemento-enamel junction. Participant 22 is identified as the single case who experienced clinical signs of healing, but who did not experience a decrease in the size of the periapical radiolucency.

Figure 41 Participant ID 22: Clinical photographs taken at intervention visits 1, 2 and 12-months follow-up



Figure 42 Participant ID 22: Periapical radiographs taken at intervention visit 1 and 12-month follow-up



Participant ID 27:

Subjective colour change

Colour difference was perceptible in clinical photographs between intervention visits 1 and 2, and at 12-month follow-up (Figure 43).

Objective colour change

Participant ID 27 experienced unacceptable colour difference between intervention visit 1 and 12-month follow-up (ΔE 13.66). There was considerable colour difference noted (ΔE 13.34) whilst the tooth was temporarily dressed between intervention visits. There was further progression in colour difference between intervention visit 2 and 12-month follow-up (ΔE 9.12).

Case Based Discussion

Participant 27 presented at 19 years of age following referral from an orthodontist who noted the presence of an untreated non-vital, immature incisor as an incidental finding during assessment for alignment of the traumatised tooth. The treated tooth had suffered a crown fracture and was in a protrusive position at presentation. Oral health was poor. Subjective colour change was judged to be clinically significant immediately at intervention visit 2 and at 12-months follow-up. This is in agreement with objective data. The participant expressed concern in relation to tooth colour throughout the follow-up period. Radiographs (Figure 44) reveal that the treated tooth had an appropriate coronal plug of mineral trioxide aggregate in-situ but that there had been a degree of separation of the plug within the root canal. Mineral trioxide aggregate extended to the cemento-enamel junction. It is noted, however, that the clinically significant discolouration noted in this case particularly reflects the colour of triple antibiotic paste.

Irrigation of the triple antibiotic paste from the root canal may have led to some improvement in objective colour change values subsequent to intervention visit 2.

Figure 43 Participant ID 27: Clinical photographs taken at intervention visits 1, 2 and 12-months follow-up



Figure 44 Participant ID 27: Periapical radiographs taken at intervention visit 1 and 12-months follow-up



Participant ID 30:

Subjective colour change

Colour difference was perceptible in clinical photographs at 12-month follow-up but not between intervention visits 1 and 2 (Figure 45).

Objective colour change

Participant ID 30 experienced unacceptable difference change between intervention visit 1 and 12-month follow-up (ΔE 12.53). There was unacceptable colour difference noted (ΔE 13.02) whilst the tooth was temporarily dressed between intervention visits. There was further progression in colour difference between intervention visit 2 and 12-month follow-up (ΔE 10.33).

Case Based Discussion

In this case, debilitating preoperative signs and symptoms of inflammation were present. Radiographs (Figure 46) reveal that the tooth had a suboptimal restoration and a coronal plug of mineral trioxide aggregate which extended coronal to the cemento-enamel junction. The participant was unconcerned in relation to tooth colour. The participant's carer expressed concern in relation to tooth colour throughout the follow-up period. Irrigation of the triple antibiotic paste from the root canal may have led to some improvement in objective colour change values subsequent to intervention visit 2. Subjective colour change was not judged to be clinically significant at intervention visit 2 but was noted at 12-months follow-up. These findings are not in agreement with objective data.

Figure 45 Participant ID 30: Clinical photographs taken at intervention visits 1, 2 and 12-months follow-up



Figure 46 Participant ID 30: Periapical radiographs taken at intervention visit 1 and 12-month follow-up



Participant ID 26:

Subjective colour change

Colour difference was not perceptible in clinical photographs between intervention visits 1 and 2, or at 12-month follow-up (Figure 47).

Objective colour change

Participant ID 26 experienced the smallest colour difference (ΔE 2.55) for participants in the REP group between intervention visit 1 and 12-month follow-up. Colour difference was greater (ΔE 3.32) whilst the tooth was temporarily dressed between intervention visits. There was later a degree of improvement subsequent to intervention visit 2 (ΔE 1.23).

Case Based Discussion

In this case, debilitating preoperative signs and symptoms of inflammation were present. Aesthetics at presentation were unusual in relation to the opacity of the labial enamel of the affected tooth. Remineralisation of the enamel before intervention visit 2 may have led to improvement in appearance that masked any colour change assessed subjectively. However, subjective assessment of colour change of the labial enamel did not reveal a clinical deterioration in tooth colour. Periapical radiographs taken at intervention visit 1 and following obturation at 12-months follow-up reveal that the treated tooth had a suboptimal restoration and a coronal plug of mineral trioxide aggregate which extended coronal to the cemento-enamel junction. Subjective colour change was not judged to be clinically significant. The participant and carer were unconcerned in relation to tooth colour. Irrigation of the triple antibiotic paste may have led to some improvement in objective colour change values subsequent to intervention visit 2. The objective and subjective findings are in agreement.

Figure 47 Participant ID 26: Clinical photographs taken at intervention visits 1, 2 and 12-months follow-up



Figure 48 Participant ID 26: Periapical radiographs taken at intervention visit 1 and 12-month follow-up



Participant ID 23:

Incomplete objective data is available for participant ID 23 due to failure of the spectrophotometer to function appropriately at intervention visit 1. Data available from intervention visit 2 and 12-month follow-up are discussed.

Subjective colour change

Colour difference was not perceptible in clinical photographs between intervention visits 1 and 2. There was, however, a clinically significant colour difference noted at 12-month follow-up (Figure 49).

Objective colour change

Participant ID 23 experienced unacceptable colour difference (ΔE 8.07) between intervention visit 2 and 12-month follow-up.

Case Based Discussion

Radiographs (Figure 50) reveal that the treated tooth had a coronal plug of mineral trioxide aggregate which extended coronal to the level of the cemento-enamel junction. The clinically significant discolouration noted in this case particularly reflects the colour of mineral trioxide aggregate rather than triple antibiotic paste. Between intervention visits 1 and 2, this participant suffered loss of the coronal restoration that was in-situ at presentation. Subjective assessment of colour difference was made in relation to the visible labial enamel as per the study protocol, therefore this should not, but may have, affected the results of subjective assessment.

Figure 49 Participant ID 23: Clinical photographs taken at intervention visits 1, 2 and 12-months follow-up



Figure 50 Participant ID 23: Periapical radiographs taken at intervention visit 1 and 12-month follow-up



As discussed in chapter 5, regenerative endodontic procedures were first described just 10 years ago. Therefore, it is possible that evidence will continue to emerge of root development, with or without incidence of tooth failure, associated with the placement of mineral trioxide aggregate at the cervical third of the immature root canal. It is noted that specialist opinion, voiced at a recent national meeting of the British Society of Paediatric Dentistry (2016), revealed that clinicians who regularly practice regenerative endodontic procedures, have taken to placing mineral trioxide aggregate within the crown, rather than the coronal third of the root canal when completing regenerative endodontic procedures.

This approach to achieving a seal may reduce the risk of cervical fracture, and allows the entire root canal to fill with scaffold, which stem cells of the apical papilla may then populate, encouraging tooth development across the full length of the root canal. It is this author's experience that this approach to placement of the intracoronal seal might also be more feasible in relation to preventing collapse of the mineral trioxide aggregate plug into the root canal. The disadvantage of this approach might be worsening of the postoperative tooth discolouration associated with the intervention.

The problem of change in tooth colour as a result of placement of either a coronal or apical intracanal seal might be avoided by substitution of mineral trioxide aggregate with an alternative material. A number of materials that might be suitable have emerged on to the commercial market since this randomised controlled trial was completed, demonstrating the rapid advance of material science in dentistry.

The most commonly available materials are TotalFill BC RRM Fast-Set Putty (Schottlander) and Endosequence BC RRM-Fast Set Putty (BC RRM-FS, Brasseler USA). The materials are marketed as biocompatible, calcium silicate bioceramics, which have osteogenic properties, and a faster setting time than mineral trioxide aggregate (Ma et al., 2011).

A recent ex-vivo study confirmed the suitability of bioceramic materials for root end closure (Tran et al., 2016). Bismuth oxide, added to mineral trioxide aggregate to provide radiopacity, has been replaced with zirconium oxide in these materials, thus they are non-staining of tooth tissues.

The materials are prepared for dispense from syringes or applicators, thus there is no requirement for mixing or waste of material, as is the case for mineral trioxide aggregate, which is supplied as a single-use sachet of powder that is mixed with sterile water. A number of these materials are also marketed as sealers for use in endodontic obturation, and have been shown to exhibit varying degrees of radiopacity, a basic pH, and a 'bioactive' ability to release calcium and phosphate ions (Candeiro et al., 2012).

BioDentine (Septodont, Saint Maur des Fosses. France) is a calcium silicate bioceramic material that is marketed as a substitute for dentine. BioDentine may accelerate the proliferation of dental pulp stem cells when compared to mineral trioxide aggregate (Agrafioti et al., 2016), perhaps enhancing its suitability for regenerative endodontic procedures. The material is presented as a tricalcium silicate powder, which is mixed with an aqueous calcium chloride solution. BioDentine has a similar radiopacity to dentine, hampering the ability of clinicians to distinguish between the material and the dentinal walls of an immature root canal. The lack of radiopacifier may limit the use of BioDentine in future comparative studies including mineral trioxide aggregate apexification as it may be difficult to reliably assess tooth development and apical barrier formation in the presence of an apical plug that is indistinguishable from the surrounding tooth tissue. Data presented in an ex-vivo study has confirmed that there is no statistically significant difference between BioDentine and white mineral trioxide aggregate in relation to resistance to root fracture, however, both materials exhibited less resistance to fracture than untreated positive controls (Elnaghy and Elsaka, 2016).

Bioceramic materials may, therefore, offer a viable alternative to the use of mineral trioxide aggregate in both apexification and regenerative endodontic procedures that may improve outcomes for young patients as a result of their biocompatibility, tissue-conductive properties, and colour stability. Their use has not yet been widely reported in the literature in relation to regenerative endodontic procedures (Kontakiotis et al., 2015a). Development of evidence in relation to the technique for placement and the material employed to achieve seal of the root canal is proposed as a suitable way forward.

9.8.2.5 *Sensibility Testing*

The pulpal response of teeth that have undergone regenerative endodontic procedures is rarely discussed in the literature, and has not been analysed in previous studies of interventions for root end closure. A case series of six immature teeth, managed with a regenerative endodontic procedure (irrigation with 5.25% sodium hypochlorite and 0.12% chlorhexidine, followed by root canal dressing with triple antibiotic paste), also reported positive response to vitality testing for two teeth (Petrino et al., 2010). Response to vitality testing has been classified as a tertiary outcome to healing and root development (Diogenes and Ruparel, 2017).

9.8.2.6 *Feasibility and Acceptability*

This exploratory study aimed to assess the feasibility and acceptability of the interventions, and the study protocols. Therefore, the analyses have been largely descriptive, to estimate success rates, to establish levels of recruitment and dropout, and the appropriateness of the outcome measures. The feasibility and acceptability of the interventions and of conducting a randomised controlled trial to investigate the clinical problem in question in a young population was assessed as follows:

➤ *Study Protocol*

Recruitment

Recruitment to trial was slower than expected. Although few patients declined to participate, strict application of the inclusion and exclusion criteria limited the eligible cohort. Exclusion criteria were applied to limit confounding factors that might arise, and which might disadvantage participants. For example, those children with roots less than half formed might be unsuitable for allocation to the MTA group.

A multicentre trial might reduce the time taken to recruit sufficient participants to a future study, however, it is noted that there may be some difficulty in standardising the clinical technique of multiple operators, even if they are calibrated and an intervention protocol is agreed. Multicentre studies are not thought to have any beneficial impact on methodological quality (Cartes-Velásquez and Manterola, 2017).

The efforts that were made to standardise the delivery of interventions and the recording of outcomes in this study would not be possible in a multicentre trial. Advantages of this monocentric study have been the ability to employ a single operator and standardised radiography equipment, strict adherence to study protocol, facilitation of data management, single hospital authorisation of patient information leaflets, and the ability of the investigating team to offer alternative treatment if a novel intervention doesn't go to plan. Clinics dedicated to the management of traumatic dental injuries take place at the study centre on a regular basis, yet they are staffed by a large number of busy clinicians of varying involvement and awareness of departmental research. It is possible that opportunities to recruit participants were hampered by this arrangement.

Randomisation

The randomisation protocol was effective and unpredictable. The operator was prevented from recording the allocation sequence in order to prevent its predication for the final participant. Previous comparative studies of interventions for root end closure have employed various randomisation methods including a random draw of lots by a participant (Damle et al., 2012), and a random numbers table (Bonte et al., 2015), whilst others have not described a randomisation protocol (Bal et al., 1993, El-Meligy and Avery, 2006, Nagy et al., 2014, Lee et al., 2015). Allocation concealment was successful using opaque envelopes, stored in an inaccessible location to the operator and study participants.

Retention

One participant withdrew from trial due to being unwilling to adhere to the retention protocol following clinical healing, indicating that the requirement of repeat follow-up might be unacceptable for a minority of children and their families. The 3-monthly follow-up protocol observed in this study is consistent with that of previous comparative studies of interventions for root end closure (Damle et al., 2012, Nagy et al., 2014, Bonte et al., 2015). If the aforementioned outcome observation period was extended to 36 months, retention may not be as successful as it was in this study.

Whilst 3-monthly follow-up is appropriate for the first comparative study of a novel intervention with the current gold standard intervention, as participants in this trial did not experience any clinical safety concerns or tooth loss, it is suggested that a future trial might be designed to include 6-month follow-up intervals over a 36-month period. A multicentre trial may allow a shorter total study period, although it is noted that delivery of the interventions is somewhat complex and that operator calibration and training would be required.

Two participants were excluded from the study following the first intervention visit, due to their being unable to accept delivery of a local anaesthetic infiltration to the operative site on a second occasion. A computer assisted single tooth anaesthesia system, incorporating dynamic pressure sensing to enhance patient comfort and reduce dental anxiety, was available and utilised to administer local anaesthetic throughout the study if required (The Wand Single Tooth Anaesthesia (STA™) System). The collection of patient reported outcome measures, and qualitative data to support participant and caregiver concerns regarding delivery of the interventions, may have aided compliance. Anxiety assessment may be beneficial for all participants (Lin et al., 2016a).

Of note, guides for cognitive behavioural therapy for anxious, young dental patients have become widely and freely available since this study was completed (Porritt et al., 2017). If this study were to be repeated, it is suggested that all investigators calibrated to deliver the interventions should be proficient in enabling young and anxious children to accept dental care. This measure may be worthwhile despite likely heterogeneity, and limitations in being able to determine proficiency, of the investigators' behavioural management skills. Better understanding of dental anxiety may prevent avoidance of endodontic treatment (Khan et al., 2016).

It is noted that no participants experienced repeat dental trauma during the outcome observation period. The study cohort may be at heightened risk of traumatic dental injury, and consideration should be given to the likelihood of repeat injury, and/or, the commencement of orthodontic treatment to correct a protrusive incisor relationship during an extended outcome observation period.

It is suggested that suspension criteria for a future trial incorporate repeat dental injury, and that determination of sample size should account for possible withdrawal of participants who wish to commence orthodontic treatment, and reduce the number of

Participant withdrawals raise the problem of missing data, which may be managed by dropping out data or simple imputation methods. If missing data is managed with worst-case analysis and missing values considered as a failure, there is no difference between the groups due to dropout of one participant from each group between the first and second interventions visits. The participant who dropped out following mineral trioxide aggregate apexification exhibited clinical signs of healing following root canal dressing, and would not be expected to experience radiographic signs of tooth development. However, if it is assumed that he did not experience radiographic signs of healing, the success rate for radiographic signs of healing would be equal for REP and MTA (one per group). If clinical signs of healing were not present at 12-month follow-up, REP would be superior to MTA.

If missing data for this participant is managed with best-case analysis, and missing values considered as a success (clinical and radiographic healing at 12-month follow-up with no expectation of tooth development), there is no change in the reported outcome per group as clinical healing remains equal, and MTA has been superior to REP for radiographic signs of healing. Last observation carried forward is not suitable for missing data for this participant as radiographic signs of healing are not usually expected within the dressing period.

Assessment

A two-week dressing period appears to have been successful in eliminating all clinical signs of inflammation that were present preoperatively. There is great variation in the dressing period observed by different investigators when carrying out regenerative endodontic procedures, ranging from one to ten weeks (Kontakiotis et al., 2015b). It is currently accepted that a dressing period of 1-4 weeks is appropriate for regenerative endodontic procedures (Geisler, 2012, Galler, 2016). It is advised that a prolonged dressing period with calcium hydroxide is avoided (Andreason et al., 2002). The dressing period observed in this study, therefore, appears to be appropriate and is supported by the outcome data.

The manufacturer's instructions for mineral trioxide aggregate (ProRoot MTA Dentsply, USA) advise that the material sets to a hard consistency within four hours. Investigators routinely postpone root canal obturation until a time at which this hardness might have been achieved, particularly when a lateral condensation technique for gutta percha is employed, but also following placement of a coronal plug of mineral trioxide aggregate during regenerative endodontic procedures, (El-Meligy and Avery, 2006, Pradhan et al., 2006, Beslot-Neveu et al., 2011, Damle et al., 2012, Dabbagh et al., 2012, Nagy et al., 2014).

The investigators' clinical experience indicated that postponement of obturation of the root canal and restoration of the access cavity may not be necessary, hence the intervention protocol was designed to include obturation and restoration of all teeth at the second intervention visit. Clinical and radiographic outcome data support this intervention protocol, and indicate that it is unnecessary to require children and their families to attend a third intervention visit, reducing the burden on patients' time and clinical resources.

The cooperative ability of some participants was challenged by the necessity to complete approximately 30 minutes of assessment procedures. It is, therefore, recommended that if a future trial is conducted, the requirement for the detailed collection of outcome data be included in advanced participant information.

As previously discussed, there was disagreement in subjective and objective outcome data in relation to perceivable and acceptable colour difference. It is suggested that in the design of a future trial, consideration is given to including patient, and perhaps parent-reported, outcomes in relation to colour difference.

Patient-reported outcomes might be more suitably compared to subjective clinician-reported outcomes as described in this study, and comparable with previous studies of colour difference (Alghazali et al., 2012). The recording of objective colour data in this study may have been unreliable, has prolonged visit duration for participants, and was carried out in order to obtain outcome data that is arguably of researcher-based interest only. It is estimated that intervention visit duration might be reduced by up to 15 minutes if objective measurement of deterioration of tooth colour were to be omitted from future study protocols.

If a future trial was designed to include collection of objective colour difference data as in this study, it is suggested that construction of a customised jig might aid reproducible location of a reference point on the clinical crown for the tip of spectrophotometer. Use of a customised jig may help to improve reliability of appropriate outcome data for colour assessment. It is also noted that objective outcome data for statistical analysis were available for only nine participants, because data for the remaining participants was excluded from analysis as it was collected with an aged device which was found to be unreliable. The investigators were unaware that the data extracted were unreliable until interim analyses took place as planned. It is, therefore, recommended that interim analyses take place on a regular and repeat basis if outcome data is collected with an electronic device.

Protocol development for regenerative endodontic procedures has led to the omission of minocycline from triple antibiotic paste, as it has been suggested that double antibiotic paste may be equally effective, and may reduce the risk of iatrogenic colour change (Chapter 5.3.3: Regenerative Endodontic Procedures). If colour change occurs as a result of minocycline present in triple antibiotic paste, the requirement for objective assessment of colour change is diminished.

Finally, it is noted that the spectrophotometer device may have become unreliable as a result of its regular use on an undergraduate clinic. It is, therefore, recommended that future investigators restrict the use of electronic devices for the purposes of similar studies.

➤ *Delivery of the Interventions*

Substantial developments in REP protocols have taken place since this study was undertaken (Kontakiotis et al., 2015a). Notably, widely acknowledged acceptance of tooth discolouration in association with the minocycline component of triple antibiotic paste has led largely to its abandonment, resulting in employment of a double antibiotic paste incorporating only metronidazole and ciprofloxacin. As previously discussed, concern has arisen within the *in-vitro* literature that commonly used endodontic irritants induce cell death and are perhaps unsuitable for future development of regenerative endodontic procedures (Kontakiotis et al., 2015a). A future comparative study could be justified as a result of this development of intervention protocol for regenerative endodontic procedures.

It was predictable that a number of young participants would have difficulty accepting complex endodontic interventions over visits of up to 90 minutes duration that required prolonged cooperation and multiple clinical and radiographic investigations. Dental clinicians frequently employ a variety of non-pharmacological techniques to help manage anxious child patients (Campbell et al., 2011). However, it has been reported that knowledge of behavioural principles amongst paediatric dentists is poor (Coxon et al., 2017).

Delivery of the interventions in a future multicentre trial may be aided if investigators are trained and calibrated in non-pharmacological behavioural management techniques, as previously discussed. It is noted that these skills may be useful for the management of all anxious patients, and that the 19 year old participant in this study exhibited dental anxiety that complicated her acceptance of the interventions.

Use of an endodontic microscope facilitated the placement of apical plugs of mineral trioxide aggregate, and it is suggested that its use is appropriate for comparative studies of interventions for root end closure, despite the difficulty that a small number participants initially faced with its acceptance. Participant cooperation may have affected quality of seal; however, it is noted that it does not appear to have affected healing.

Use of thermoplastic gutta-percha aided delivery of the interventions and may reduce the incidence of fracture following restoration of immature teeth with thin dentinal root walls that may be more likely to occur if a lateral condensation technique is employed (Chai and Tamse, 2012). Use of thermoplastic gutta-percha negates the use of apical forces and therefore may also aid the immediate obturation and restoration of a tooth following placement of a mineral trioxide aggregate apical plug.

It is recognised that regenerative endodontic procedures present a multitude of practical complexities, as might be expected with a novel intervention. In this study, difficulties were reported with inducing apical bleeding to the level of the cemento-enamel junction, and with collapse of the coronal plug of mineral trioxide aggregate into the root canal. Similar difficulties have been reported by previous investigators as previously discussed.

Local anaesthetic without vasoconstrictor was utilised to reduce difficulties obtaining apical haemorrhage. The role of a collagen sponge has not yet been fully investigated in the literature, hence it is suggested that inclusion of a collagen sponge, against which a coronal plug of mineral trioxide aggregate can be plugged, should be considered when designing a future study (American Association of Endodontists, 2016, Galler et al., 2016).

In preparation for this study, training of the principal investigator to deliver the interventions enhanced operator experience of successfully inducing apical bleeding by curving the tip of a narrow endodontic file to enable contact of a greater surface area of apical tissue. It has been reported that signs of tooth development, and periapical healing, are superior for regenerative endodontic procedures that include platelet-rich fibrin in comparison to apical bleeding that is manually induced.

Collapse of mineral trioxide aggregate into the root canal was evaded where possible by avoiding unnecessary instrumentation of the immature root canal that might make it wider, and by using a plugger typically employed for placement of amalgam following cavity preparation, rather than an endodontic plugger with a narrower bore. As a consequence of these attempts to avoid loss of the plug, post-operative radiographic assessment often revealed that mineral trioxide aggregate had been placed coronal to the cemento-enamel junction, possibly increasing the risk of iatrogenic colour change as reported for teeth in the REP group in this study.

In a study designed to compare various regenerative endodontic procedure protocols (Narang, Mittal, and Mishra 2015), 'good' or 'excellent', but unspecified and subjectively assessed, dentinal wall thickening at 18-month follow-up was reported for 100% of 5 participants who received platelet-rich fibrin, compared to 50% of 5 participants who underwent a regenerative endodontic procedure in the manner described in the study.

In the absence of objectively recorded data from randomised trials to support the use of platelet-rich fibrin, and in the presence of objectively recorded data to support tooth development in this study, it is suggested that the method of inducing apical bleeding in this study warrants further investigation in future studies in order to enhance protocol development that is likely to be accepted for routine chairside application in primary care.

It is not known whether displacement of mineral trioxide aggregate into the root canal might disturb the regenerative process, or whether the clinician's view of an unsatisfactory post-operative radiographic appearance has led to protocol development in this respect. As previously discussed, clinicians may strive to achieve optimal outcomes in terms of post-operative radiographic appearance (chapter 7.5.10: Influences on the Decision-Making Practices of Responders).

In this study, two thirds of teeth in the REP group were assessed radiographically as having an optimal coronal seal, compared to three quarters of teeth in the MTA group. There was no statistically significant difference between the groups in relation to quality of seal, indicating a lack of effect of the quality of seal on clinical and radiographic healing. However, this difference might be clinically significant in the long-term, despite an apparent lack of effect on healing at 12-month follow-up.

Nevertheless, it can be assumed that collapse of the coronal plug of mineral trioxide aggregate might compromise the coronal seal, and therefore, tooth prognosis. Suboptimal seal was present despite the completion of training and calibration of the operator in delivering the interventions, highlighting the practical complexities that frequently occur during these procedures when managing anxious children.

The clinical and radiographic healing of regenerative endodontic procedures in this study challenges evidence discussed previously that both a coronal and apical seal are important for successful, predictable endodontics (Williams and Williams, 2010). Protocol developments that aid the transition of this novel intervention into mainstream care by facilitating the practical aspects of delivery are welcomed.

9.8.3 Sources of Error and Bias in this Study

The importance of involving children in shared healthcare decisions was acknowledged and incorporated in to the study design (The NHS Confederation et al., 2011, Department of Health, 2012). The ability of participants to provide valid, informed consent for the study was therefore necessary in determining their eligibility. Children and young people want healthcare information to be provided in child-friendly formats, by professionals who have the appropriate skills to work with children, in appropriate environments (Lewis and Leneha, 2013).

Information leaflets and consent forms were, therefore, designed, piloted, and provided for young participants. These leaflets and consent forms were distinct to those provided for their caregivers, and were well received. It may have been beneficial for patient-based outcomes to be recorded in this study. Children should be given an opportunity to describe their healthcare experiences and to report on the outcomes that have made an impact on their lives (Department of Health Children Families and Maternity, 2010).

Investigators were blinded to the intervention group for the purposes of data analysis, and for the purposes of colour difference outcome assessment. However, it was not feasible to blind the investigators to the intervention group for the purposes of radiographic outcome assessment, due to the distinct postoperative radiographic appearances of the interventions. It was also not possible to blind the operator, or the participant, to the intervention as previously discussed, in order that treatment could be delivered, and that participant's families could liaise with their primary dental care practitioner in case of emergency. In a future study, it might be possible to blind the operator, and the participant, at the first intervention visit if double antibiotic paste, rather than triple antibiotic paste, is used.

Double antibiotic paste, omitting minocycline, may be constituted from a branded metronidazole that encases the drug within a white coloured shell, similar to ciprofloxacin. Double antibiotic paste prepared in this manner has a white colour, and a consistency, that matches that of calcium hydroxide.

If a second investigator was available to provide the root canal dressing material administered at the first intervention visit, blinding would be enabled subsequent to sequence allocation, for the root canal dressing period, until the second intervention visit at which time intervention group could be revealed to the operator.

Double-blinding at this stage might help to ensure that any preconceived views of the operator and participants is unable to systematically bias outcome assessment (Sibbald and Roland, 1998). Double-blinding ensures that the preconceived views of subjects and clinicians cannot systematically bias the assessment of outcomes.

Bias associated with lack of blinding might be greater in trials with subjectively assessed outcomes (Wood et al., 2008). As this randomised controlled trial assessed all possible outcomes with objective measurements, coupled with subjective measurements where necessary or where the comparison with objective assessments was of interest, it is concluded that bias has been minimised as much as possible.

9.8.4 Impact

Following review of the literature, and in light of a lack of randomised controlled trials to compare the interventions, a research question arose with regards the optimal management for the common, and complex, clinical problem of non-vital, immature, permanent incisors. The adequacy, acceptability and implementation of a novel intervention has been explored, and effect size for a newly defined primary outcome has been determined.

This randomised controlled trial is the first of its kind. It was designed to compare a gold standard intervention for root end closure versus a more novel intervention which aims to engineer tooth development, and for which there is little *in-vivo* evidence base and abundant discord amongst clinicians in relation to its realistic evolution and factors that contribute to success.

This study has successfully generated the first evidence arising from a randomised controlled trial that investigates whether regenerative endodontic procedures are superior to mineral trioxide aggregate apexification.

It is concluded that regenerative endodontic procedures may offer a viable alternative to the gold standard intervention, presenting the possibility of enhanced outcomes, and improved tooth survival, for children who have suffered traumatic dental injuries.

A novel primary outcome of endodontic success for immature teeth has been defined and tested; a primary outcome that incorporates patient and clinician-based measures of resolution of periapical inflammation, coupled with tooth development that is appropriate for traumatised, non-vital teeth that may be undergoing continued development.

The design of this research protocol has been enhanced by determining the optimum study design and outcome measures required to compare the success rate of REP versus MTA in the management of non-vital, immature maxillary central incisors in a young population. This study has thus provided the first comparative assessment of the interventions in relation to the feasibility of the reported protocols for use in a future randomised-controlled trial, to be conducted if appropriate.

This study has addressed a call for action for evidence that seeks to compare the interventions and to guide clinical practice (Murray et al., 2007). Furthermore, this study raises questions about the future role of apexification and regenerative endodontic procedures, and highlights the importance of dental research in regenerative medicine.

The null hypothesis was that there would be no difference in the success rate of regenerative endodontic procedures versus mineral trioxide aggregate apexification in achieving endodontic success for an immature tooth.

The null hypothesis is rejected. Whilst both interventions achieved equal success in relation to clinical resolution of inflammation, teeth that underwent REPs experienced a statistically significant increase in measures of tooth development. The clinical significance of tooth development in terms of dentinal wall thickening is likely to be important in relation to tooth survival and predisposition to fracture as a result of underdeveloped root walls.

The results of this study indicate that radiographic root area can be estimated to increase by approximately 10% within a period of 12-months following intervention. It is possible that tooth development could continue beyond the follow-up periods observed in this study and therefore that further dentinal wall thickening might be expected. There was no statistically significant difference in relation to radiographic resolution of inflammation, with only a single tooth managed with a REP affected. There may, however, be clinical implications, including endodontic retreatment, for teeth that do not exhibit radiographic signs of healing for the cautious clinician.

9.9 Future Work

Regenerative endodontic procedures represent a rapidly evolving field of clinical dentistry and significant opportunities for evidence-based research. Intervention protocols continue to develop at pace. It is hoped that the results of this study will inform that development further.

A future comparative study is proposed in respect of mineral trioxide aggregate apexification versus regenerative endodontic procedures, that incorporates recent protocol developments, estimate of effect size, and a primary outcome measure as defined in this trial. Use of this primary outcome measure in future studies would aid the standardisation of reported outcome measures used in clinical trials of treatment interventions following traumatic dental injuries (Sharif et al., 2015). An extended observation period would enable corroboration of the endodontic success established for regenerative endodontic procedures, and would determine whether, and for how long, tooth development continues.

Without this recent protocol development in regenerative endodontic procedures that warrant further investigation, a repeat study would be difficult to justify. If the body of professional opinion were to agree that a mean increase in dentine root area of 9% within 12 months is clinically significant in terms of tooth survival then this study is suitably powered to determine that traumatised, immature teeth that are managed with regenerative endodontic procedures, as described in this protocol, experience continuing tooth development that is not achieved with mineral trioxide aggregate apexification. If clinical opinion suggested that the important difference might be less than 9%, a larger study would not be necessary, or justifiable, in the absence of development of the novel intervention.

A new study would be justified if the data analysed in this trial might have overestimated the true difference, although the investigator has confidence in the accuracy of the results.

Case selection may be imperative to success for regenerative endodontic procedures. In this study, a regenerative endodontic procedure was successful in respect of clinical and radiographic healing, tooth development, and apical closure for selected participants aged 7 to 19 years of age. Factors other than age that might be related to these successes merit investigation, including stage of tooth development, cooperative ability of the participants, and clinical skill of the operator. A future study should identify determinants of the rate and success of tooth development.

A future trial might strive to incorporate patient reported outcome measures (PROMs) (Department of Health, 2009). PROMs might be included to assess the oral health of participants' at prespecified points in time, such as prior to intervention and at 12-month follow-up, and could be collected through short, self-completed questionnaires. It is noted that a broad range of PROMS tools are available, and that not all tools may be suitable for use across the range of ages that were eligible to participate in this study (Janssens et al., 2015).

Assessment of tooth development using cone beam computerised tomography (CBCT) would offer investigators a model for measurement of dimensional changes in relation to tooth development, and would enable comparison with the validated protocol for assessment of radiographic root area used in this study. It is perhaps unlikely that ethical approval would be granted for post-endodontic repeat assessment with CBCT for children in the UK in the near future. It has, however, been suggested that CBCT will be considered best practice in the near future due to the diagnostic accuracy of the imagery (Hargreaves et al., 2011). It is noted that ethical approval has recently been granted to a study in Thailand for review of endodontic outcomes with CBCT (Linsuwanont et al., 2016). The authors carried out retrospective examination of 15 patients who had completed a regenerative endodontic procedure according to the protocol reported in this study (Banchs and Trope, 2004). Patients underwent both conventional and CBCT examination, at a range of 12-96 months post-regenerative endodontic procedure.

CBCT was used to determine the contents and shape of the root canals, rather than tooth development, which was measured with the validated method as reported in this thesis (Bose et al., 2009, Flake et al., 2014). Those teeth that had been managed more than 60 months previously showed the best root formation and had cone shaped apices. The authors reported conventional radiographs were misrepresentative of the root canal calcification observed on CBCT images. The authors also noted that radiographic examination using both conventional radiographs and CBCT is not suitable for the routine assessment of regenerative endodontic procedures, due to unnecessary exposure of patients to radiation. The randomised controlled trial reported in this thesis has provided further evidence that tooth development in terms of radiographic root area can be reliably assessed with freely available imaging software.

If it has been established that necrotic pulp is removed during regenerative endodontic procedures, and subsequently replaced with vital tissue, the nature of that tissue is yet to be agreed. Several recently published case reports have reported that the root canals of teeth extracted following the failure of regenerative endodontic procedures were filled with debris and bacterial biofilms (Lin et al., 2014, Žižka et al., 2016). In this author's experience, no teeth that have undergone a regenerative endodontic procedure have failed. However, a future study of the intervention might seek to incorporate ethical approval, and patient consent, for histological examination of any teeth that might fail. In doing so, data might start to be generated from experimental studies in relation to the possible adverse effects of the intervention, and to determine whether differing protocols are associated with higher rates of failure in the longer-term. However, the question may remain of how those teeth that fail differ histologically to those that have been successful.

Within those teeth that respond successfully, it is not yet known whether regenerative endodontic apexogenesis proceeds at the same rate as maturogenesis, and whether iatrogenically-induced apexogenesis proceeds until completion of tooth development. It has yet to be established whether it is the disinfection protocol, the root canal dressing material, the optimal intracoronary seal, the presence of a scaffold, the regenerative potential of stem cells, or an as yet undescribed entity, that brings about healing and tooth development in regenerative endodontic procedures.

Although our knowledge of the processes underlying pulp regeneration have considerably improved, questions also remain regarding signalling pathways, timing, and the influence of various stress conditions, in translating regenerative science into predictable chairside interventions for dentistry (Rombouts et al., 2016).

On balance, it is concluded that it is not justifiable to repeat this study on a larger scale with the methodology, and intervention protocol, as it has been described. However, an application for ethical approval for a retrospective study of the trial participants, to collect long-term outcome assessment data, would be of interest.

9.10 Conclusion

The null hypothesis was that there would be no difference in the success rate of regenerative endodontic procedures versus mineral trioxide aggregate apexification in achieving endodontic success for an immature tooth. The null hypothesis has been rejected in respect of the primary outcome.

Primary Objective

- Endodontic success was apparent for both intervention groups at 12-month follow-up.
- There was no statistically, or clinically, significant difference between the interventions for clinical and radiographic signs of healing. Clinical and radiographic signs of healing following delivery of the interventions as described is predictable within a 12-month follow-up period.
- Teeth that underwent a biologically based procedure in this randomised controlled trial experienced notable maturogenesis of ~9% in just 12 months. Differences between the interventions in terms of tooth development were found in relation to root dentine thickness, rather than root length. This may be important, and optimal, for tooth survival.

Secondary Objectives

- There were no unexpected adverse effects for the novel intervention. Furthermore, no tooth loss, root resorption, root fracture nor failure of restoration was experienced by participants in either intervention group.
- Effect size in respect of a newly defined primary outcome of endodontic success for an immature tooth has been estimated to aid the planning of sample size for future comparative studies of the interventions.

- The observed difference in means was 8.2% and this was statistically significant. It is proposed that mean increases in root dentine thickness of 5% within 12 months may be clinically significant if it can be agreed that tooth development continues for longer than a 12-month observation period.
- The success rate of apical closure for mineral trioxide aggregate apexification was 100% at 12-month follow-up, and was not affected by quality of seal. Regenerative endodontic procedures can successfully induce apical closure within 12 months in selected cases, and may be affected by quality of seal.
- Both mineral trioxide aggregate apexification, and regenerative endodontic procedures, may induce postoperative colour difference. Regenerative endodontic procedures are more likely to induce colour difference and it is not known to what extent this colour difference can be attributed to root canal irrigants, dressing material or material used to achieve seal of the coronal third of the root canal. It is suspected that either the minocycline component of the triple antibiotic paste, or the placement of mineral trioxide aggregate at the cemento-enamel junction, is primarily responsible.
- Teeth that undergo regenerative endodontic procedures may respond positively to sensibility testing. Further research is required to determine the nature of the tissue that encourages maturogenesis.
- The feasibility of conducting a randomised controlled trial to investigate the clinical problem in question in a young population has been described. Acceptability of the study protocols, and the adequacy, acceptability and implementation of a novel intervention, has been reported. The research protocol has been enhanced to optimise the study design of a future study to compare the interventions following development of the intervention protocol for regenerative endodontic procedures, particularly in respect of root canal irrigants and dressing materials.

This randomised controlled trial has appropriately addressed the research question. The conclusion of this study is that regenerative endodontic procedures may be superior to mineral trioxide aggregate apexification in the management of non-vital immature permanent incisors, and that further research is promptly required to investigate the ability of clinicians to harness the therapeutic potential of stem cells of the apical papilla, to achieve optimal outcomes for children who experience traumatic dental injuries.

There is great merit in pursuing development of the clinical protocol, in order that predictable patient, and clinician-based, outcomes of interest can be achieved. If continued tooth development can be equated with improved tooth survival in the longer term, renewal of guidance for the management of non-vital, immature teeth is justified. Likewise, the introduction of regenerative endodontic procedures to the undergraduate dental curriculum would be befitting of the evidence-base generated. With the passage of time, the novel intervention might be expected to become more widely recognised outside of specialist practice environments, and a greater proportion of children might benefit from optimal outcomes.

10 Conclusions and Clinical Impact

This research was embarked upon in order to address the question of the optimal management for necrotic, immature, permanent teeth. This thesis has described the innovative efforts made to answer this research question.

It has been established that the dental profession has an unquestionable mounting interest in the concept of regenerative endodontic procedures, and the optimal management of non-vital, immature teeth. The literature is vast in relation to novel therapies and the therapeutic potential they appear to hold.

Survey of the specialist professionals who frequently face the clinical problem in question has exposed the extent of diversity of the technical approach, and has united the specialties in their call for the generation of evidence to guide the profession. This survey was the first of its kind, and the results are likely to be of significant interest to those who plan the delivery of healthcare services and the establishment of managed clinical networks, developed to enhance patient experience, and for the effective utilisation of skill mix.

The majority of surveyed specialists reported that they frequently manage non-vital, immature teeth in their routine practice, however, many primary care clinicians may not have the same experience of managing traumatic dental injuries. Therefore, it is sensible to assume that children's access to good quality management of immature apices may improve if a feasible, practicable, and conservative, intervention was available, at relatively low material cost. Resource allocation for healthcare interventions is limited in the current climate of the National Health Service (Robertson et al., 2017). This situation may have established, or exacerbated, the consequences of limited budgets for clinicians working in practice environments with restricted access to endodontic interventions associated with high financial costs.

The clinical decision-making practices of specialists when considering root end closure procedures is affected by various factors that are important for the planning of collaborative and coordinated care in the current climate of redesign of healthcare services.

Systematic review of the literature has provided a thorough, and explicit descriptive analysis of variations in study and intervention protocols, an estimate of the effects of the individual interventions, and has described areas where knowledge is lacking. This systematic review was the first to compare the three interventions and to search the literature for an evaluation of the weaknesses of the available studies to guide future research, and inform the design of a future randomised controlled trial.

The first randomised controlled trial of its kind has been designed to answer the call for high quality comparative evidence of the effectiveness of the interventions. This comparative trial has generated reliable evidence to support the clinical and radiographic effectiveness of the interventions, and the occurrence of clinically significant tooth development in regenerative endodontic procedures at a rate of up to 10% within a 12-month outcome observation period.

The feasibility and acceptability of the interventions has been examined for incorporation in future comparative trials and pragmatic studies, and hence thereafter, for use in routine care. If regenerative endodontic procedures can offer a viable alternative to apexification procedures, there is great merit in pursuing development of the clinical protocol, in order that predictable patient, and clinician-based, outcomes of interest can be achieved. If continued tooth development can be equated with improved tooth survival in the longer term, renewal of guidance for the management of non-vital, immature teeth is justified. Likewise, the introduction of regenerative endodontic procedures to the undergraduate dental curriculum would be befitting of the evidence-base generated. With the passage of time, the novel intervention might be expected to become more widely recognised outside of specialist practice environments, and a greater proportion of children might benefit from optimal outcomes.

The distinctions between patient, clinician and researcher-based outcomes have been considered separately, and as a shared, consolidated outcome, throughout this thesis. A novel outcome for defining endodontic success for an immature tooth has thus been investigated following consideration of the literature, and in line with efforts to standardise outcome reporting for children who suffer traumatic dental injuries, thus optimising the value of future research.

The prevalence, complexity and ambiguity of the clinical problem of non-vital, immature teeth has been communicated throughout this research. Some children fail to receive the highest standards of healthcare attainable, a right of all children as set out in Article 24 of the United Nations Convention on the Rights of the Child (Office of the High Commissioner for Human Rights, 1989). Regenerative endodontic procedures may offer a minimally interventive, cost-effective approach to improving endodontic outcomes, and reducing the inequality of access to interventions that are deliverable in primary dental care.

An unresolved question remains in relation to the mechanisms that are at play in regenerative endodontic procedures. It is important that researchers continue to ask the right questions as our knowledge advances, and that the voice of the child is heard. Children and young people are key stakeholders of the National Health Service and their interests must be at the centre of health and local government services (The NHS Confederation et al., 2011). The participation of children in healthcare decisions has been encouraged by policies such as “No decisions about me without me”, and It is recognised that the voice of the child should be incorporated in to the design and evaluation of healthcare services in order that they are truly child-centred (Department of Health Children Families and Maternity, 2010).

In the wake of public interest about child oral health, herein lies an opportunity to discover the unknown, to embrace new philosophies, and to raise the profile of children who have suffered traumatic dental injuries, and for those who will continue to do so in the future.

11 Appendices

1. Survey Ethical Approval: University of Liverpool, ILT Ethics Review Group
2. Survey Cover Letter: First Contact
3. Survey: Questionnaire
4. Randomised Controlled Trial: North West National Research Ethics Service Approval (10/H1014/50)
5. Randomised Controlled Trial: University of Liverpool Co-Sponsor Approval (UoL000590)
6. Randomised Controlled Trial: Royal Liverpool and Broadgreen University Hospitals Trust Co-Sponsor Approval (RD&I 3968)
7. Randomised Controlled Trial: Participant Information Sheet
8. Randomised Controlled Trial: Participant Consent Form
9. Randomised Controlled Trial: Caregiver Information Sheet
10. Randomised Controlled Trial: Caregiver Consent Form
11. Randomised Controlled Trial: GDP Information Letter

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30th June 2015

Dear Dr Albadri

I am pleased to inform you that the ILT Ethics Review Group (staff) has approved your application for ethical approval. Details of the approval can be found below:

Ref: 201506200

Title of the Research: How do specialists in Paediatric Dentistry and Endodontics manage non-vital, immature teeth?

(How do specialists treat teeth that have failed to complete natural development?)

PI: Dr Sondos Albadri

Title: Senior Clinical Lecturer

Student Investigator: Laura Gartshore

School: Dentistry

First Reviewer: David Taylor

Second Reviewer: Ben Shaw

Date of Initial Review: 10/06/15

Date of Approval: 25/06/15

This approval applies for the duration of the research. If it is proposed to extend the duration of the study as specified in the application form, the ILT Ethics Review Group (staff) should be notified. If it is proposed to make an amendment to the research, you should notify the ILT Ethics Review Group (staff) by the Notice of Amendment procedure. If the PI/Supervisor leaves the employment of the University during the course of this approval, the approval will lapse. Therefore please contact the RGO at ethics@liverpool.ac.uk in order to notify them of a change in PI/Supervisor.

Best wishes and good luck with the study.

Jennie Jebb

Jennie Jebb
ILT Ethics Review Group (Staff) Secretary

E: jjebb@liv.ac.uk
T: 0151 794 8753

1st February 2016

Dear Specialist

As part of my PhD at the University of Liverpool, School of Dentistry, I am carrying out a survey of all UK specialists in Paediatric Dentistry and Endodontics to discover if there is a common approach to the clinical problem of non-vital, immature permanent teeth.

As you know, there are a variety of traditional, as well as more novel, approaches to root end closure. These include apexification with calcium hydroxide, placement of an apical plug, and regenerative endodontics. There are recognised complications with each and an 'ideal' solution is yet to be found.

I am interested to find out whether or not there are variations in practice between and within specialties, to identify factors that may affect your treatment planning decisions and to gather your thoughts about managing open apices, whether or not you manage them on a regular basis.

In order to be able to produce reliable information, I need to receive responses from as many specialists as possible. All Paediatric Dentists and Endodontists on the General Dental Council Specialist lists have been invited to participate. Your reply is, therefore, very important to this research.

No judgements will be made about whether any approach is 'right' or 'wrong'. No patient data will be collected. Responses will be anonymised, summarised and disseminated in a peer reviewed dental journal. Identification numbers are provided in order that we may follow up non-responders whilst maintaining anonymity. All information identify coding will be destroyed once data has been collected so that you cannot be identified as a participant. The study has received Research Ethics approval on this basis.

As a measure of my appreciation for your time, all respondents are invited to enter a draw for the opportunity to win the cost of membership, for the forthcoming year, for either the British Society of Paediatric Dentistry or the British Endodontic Society. If you wish to enter, please provide your name and email address in the allocated space on the survey. There will be one winner who will be notified directly.

Please return the questionnaire by 1st March 2016 in the Freepost envelope provided (no stamp required).

If you would like to discuss the questionnaire with the research team, please telephone 0151 706 5030 or e-mail l.gartshore@liverpool.ac.uk.

I believe that the clinical problem of managing non-vital, immature teeth is a topical and relevant one, for both of our specialties and for our patients. I look forward to informing the profession of the results of this survey.

Many thanks for your time.

Yours sincerely,

Ms Laura Gartshore
Clinical Lecturer / Specialist, Paediatric Dentistry
University of Liverpool

PhD Supervisors

Dr Sondos Albadri, Senior Clinical Lecturer / Honorary Consultant, Paediatric Dentistry
Dr Kathryn Fox, Senior Clinical Lecturer, Restorative Dentistry
Dr Fadi Jarad, Senior Clinical Lecturer / Honorary Consultant, Restorative Dentistry

How do Specialists and Consultants Manage Open Apices?

About Yourself

1. To which of the following specialties are you associated?
 - Paediatric Dentistry
 - Endodontics
2. How would you best describe your primary role?
 - Specialist
 - Consultant
 - Academic Specialist or Consultant
3. Where is the majority of your work based?
 - Hospital Dental Service
 - Community Dental Service
 - NHS Practice
 - Private Practice
 - Mixed Practice
4. Please indicate the region most applicable to your current place of work
 - Northern England
 - Southern England
 - Midlands (West Midlands, Nottinghamshire, Leicestershire, Derbyshire, Staffordshire, Shropshire, Warwickshire, Worcestershire)
 - Wales
 - Scotland
 - Northern Ireland

About Open Apices

5. To what extent do you agree with this statement?: In my experience, young people have difficulty accessing good quality management of non-vital, immature apices in general dental practice
 - Strongly agree
 - Agree
 - Neutral
 - Disagree
 - Strongly disagree
6. How many non-vital, immature apices do you personally manage in an average month?
 - None
 - Between 1 and 5
 - More than 5
7. Do you routinely carry out root end closure procedures with the aid of a microscope?
 - Yes
 - No
 - On occasion but not routinely
8. Do you have personal experience of carrying out root end closure with placement of an apical plug? (Tick all that apply)
 - No
 - Yes, with MTA
 - Yes, with Biodentine
 - Yes, with another material, please specify:

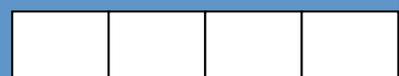
9. Do you have personal experience of carrying out root end closure with a regenerative endodontic procedure?
- Yes
 No
10. If you were to manage a non-vital, immature tooth with a **regenerative endodontic** procedure, which of the following methods of disinfection or dressing of the root canal system would you employ between visits if more than one visit was required?
- Triple antibiotic paste
 Dual antibiotic paste
 Calcium hydroxide root canal dressing
 Copious irrigation without the routine use of a dressing material
 Not sure: I have not previously completed or planned a pulp regeneration procedure
11. If a compliant, medically well, 9 year old patient presented to your clinic tomorrow, requiring root end closure of a non-vital, single rooted tooth, which of the following would you be most likely to plan as a definitive management technique?
- Apexification with calcium hydroxide
 Root end closure with mineral trioxide aggregate (or a similar equivalent)
 Regenerative endodontics
 Referral to a Paediatric Dentist
 Referral to an Endodontist or Restorative Dentist
 Other, please specify:

12. To what extent do the following influence your management of a non-vital, immature apex?

| Factor | No influence | Some influence | Significant influence |
|---------------------------------------|--------------|----------------|-----------------------|
| Material cost | | | |
| Local departmental/practice choice | | | |
| Evidence-based literature | | | |
| Previous clinical experience | | | |
| Dimensions of the tooth root | | | |
| Likelihood of resolution of infection | | | |
| Likelihood of root end closure | | | |
| Likelihood of complications | | | |
| Patient age and/or cooperation | | | |

Are there any limitations or restrictions imposed on your management of open apices? Do you have any other thoughts you would like to share?

If you would like to enter the draw for a chance to win the cost of membership for either the British Society of Paediatric Dentistry or the British Endodontic Society, for the forthcoming year, please provide your name and email address:



National Research Ethics Service

North West 9 Research Ethics Committee – Greater Manchester West

Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7821

Facsimile:

31 August 2010

Miss Laura Gartshore
School of Dental Sciences
Pembroke Place
Liverpool
L3 5PS

Dear Miss Gartshore

Study Title: Revascularisation versus Mineral Trioxide Aggregate in the Management of Non-Vital Immature Permanent Incisors in a Young Population: A Randomised Controlled Trial (Pilot Study)

REC reference number: 10/H1014/50

Protocol number: 2.1

Thank you for your letter of 27 August 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to

This Research Ethics Committee is an advisory committee to North West Strategic Health Authority

the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

| <i>Document</i> | <i>Version</i> | <i>Date</i> |
|---|-----------------|----------------|
| Investigator CV | Callum Youngson | |
| Investigator CV | Sondos Albadri | |
| Investigator CV | Laura Gartshore | |
| Protocol | 2.1 | 15 March 2010 |
| Email from MHRA | | |
| REC application | 3.0 | 30 June 2010 |
| Covering Letter | | 25 March 2010 |
| Summary/Synopsis | 2 | 28 June 2010 |
| Letter from Sponsor | NHS | 24 March 2010 |
| Letter from Sponsor | University | 06 May 2010 |
| GP/Consultant Information Sheets | 1 | 30 June 2010 |
| Participant Information Sheet: Child | 1 | 25 April 2010 |
| Participant Information Sheet: Parent | 2 | 22 August 2010 |
| Response to Request for Further Information | | 27 August 2010 |
| Participant Consent Form: Child | 2 | 22 August 2010 |
| Participant Consent Form: Parent | 3 | 27 August 2010 |
| Device Instructions | | |

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H1014/50

Please quote this number on all correspondence

Yours sincerely



 **Dr Lorraine Lighton**
Chair

Email: Shehnaz.ishaq@northwest.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: Professor Callum Youngson
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Mrs Lindsay Carter - University of Liverpool

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Faculty of Health and Life Sciences Ref: UoL000590

Professor Callum Youngson (Laura Gartshore)
School of Dental Sciences

Thursday, 06 May 2010

Dear Professor Youngson

I am pleased to confirm that the University is prepared to act as Co-Sponsor with the Royal Liverpool & Broadgreen University Hospitals NHS Trust under the Department of Health's Research Governance Framework for Health and Social Care (2005) for your study entitled "Revascularisation versus Mineral Trioxide Aggregate in the Management of Non-Vital Immature Permanent Incisors in a Young Population: A Randomised Controlled Trial (Pilot Study)". This approval for co-sponsorship is subject to the following:

1. The University expects you, as Chief Investigator, to conduct the study in full compliance with the requirements of the Framework so that it is able to meet its obligations as Co-Sponsor.
2. In addition to sponsorship, your study will require NHS ethical approval through the National Research Ethics Service (NRES). If you have not already done so, in order to apply for this please use the Integrated Research Application System (IRAS) at <https://www.myresearchproject.org.uk/Home.aspx>. Please contact me on 0151 706 4523 or at sponsor@liverpool.ac.uk for further advice.
3. As the Chief Investigator, the University expects you to comply, where appropriate, with the University's policy on the use and / or storage of human tissues, details of which may be found at www.liverpool.ac.uk/humantissues.
4. An appropriate agreement should be completed with the Co-Sponsor which details the allocation of responsibilities between the Co-Sponsors. Please contact me for further advice.

In addition to the above agreement, if you wish to conduct any part of the study in a site outside the UK, or the study requires the participation of a site other than one belonging to the Co-Sponsor, or you wish to sub-contract any part of the study to a third party (not including the Co-Sponsor) please contact me to ensure that appropriate contractual arrangements are in place.

5. University professional indemnity and study's insurances will apply to the study as appropriate. This is on the assumption that no part of the study will take place outside of the UK. Such cover will extend to cover for non-negligent harm.
6. A copy of the equivalent confirmation of co-sponsorship from the Co-Sponsor should be sent to me within 60 days of the date of this letter.

I trust that this statement will enable you to proceed with your research but if you have any queries please contact me on 0151 706 4523 (email sponsor@liverpool.ac.uk).

Yours sincerely,

A handwritten signature in black ink, appearing to read 'L. Carter'.

Mrs Lindsay Carter
Research Coordinator, Faculty of Health and Life Sciences

The Royal Liverpool and Broadgreen University Hospitals



NHS Trust

TRUST SPONSORSHIP LETTER

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24th March 2010

Dear Prof Youngson

Re: - Revascularisation versus mineral trioxide aggregate in the management of non-vital immature permanent Incisors in a young population : A randomised controlled Trial (Pilot Study)
R&D No 3968

I am pleased to confirm that the Trust accepts the responsibilities of Co-Sponsorship for the above study with the University of Liverpool.

Please note this does **NOT** constitute final Trust approval to allow your project to proceed. Trust approval will be given when final research ethics, financial and other regulatory requirements have been met.

In accordance with the SOPTS002 Roles and Responsibilities of the Sponsor and in order to meet the requirements of the Research Governance Framework 2nd Ed 2005, the Trust requires you to agree to the following PI responsibilities: -

- Inform R&D within 24 hours of awareness of any SUSAR's within the Trust as per Trust policy and provide copies to R&D of annual and safety reports to Ethics and if appropriate the MHRA.
- Report SAE's as per protocol and Trust policy
- Comply with the Research Governance Framework 2nd Ed 2005 including but not limited to the Medicines for Human use (Clinical Trials) 2004 act plus it's appendices and the Data Protection Act 1998.
- Ensure biannual training in GCP of all essential research staff on the study
- Read, disseminate to research team and acknowledge to R&D, Trust research SOP announcements
- Inform R&D of any amendments to, or changes of status in, the study

- Complete and return the R&D annual report form in a timely manner
- Maintain the study site file (if not provided by the sponsor a template is available on the Trust intranet)
- Make available for review said site file and any patient CRF's and notes requested for monitoring.
- Provide the Trust with copies of Data Management Committee reports
- Provide the Trust with draft publications 30 days prior to submission to the publisher.

Investigators who do not comply with the above will be dealt with in accordance with the Trust disciplinary policy

I wish you every success with your research please contact the R&D Department if you require any advice on the above points

Yours sincerely



Julia West
Deputy Director R&D

cc. Head of Directorate
Sponsor

I.....agree to the terms and conditions of the Trust sponsorship approval for Revascularisation versus mineral trioxide aggregate in the management of non-vital immature permanent Incisors in a young population : A randomised controlled Trial (Pilot Study) R&D No 3968 and am aware of my responsibilities under the Research Governance framework and Trust Research SOP's.

Sign.....date.....

Please return this slip to the R&D Department, 4th Floor Linda McCartney Centre, RLBHHT

Thankyou

Child Information Leaflet

Thank you for reading this leaflet. We hope that it will help you to understand the dental treatment that we would like to do for your tooth. We also want to tell you about a project that we are doing and to ask you if you would like to help us with this project. Please read this leaflet carefully and take your time to decide if you are happy to help us.

1. What is happening to my front tooth?

Unfortunately, when you knocked your tooth, the damage caused the tooth to stop growing. We would like to do some dental treatment on the tooth to stop it from becoming sore and to help it to heal.

2. What dental treatment do you want to do?

There are 2 different types of dental treatment that might help your tooth to heal. You will have 1 of these treatments.

You will be asked to come to the Dental Hospital 2 or 3 times for treatment. During your visits, we will clean your tooth and put some tooth medicine inside it. We will also take x-rays of your tooth. When we are finished doing the treatment, we will ask you to come back 4 times in 1 year so that we can check that your tooth is healing and that you are happy.

You have nothing to worry about when you come to see us, but it is ok to feel nervous at first. We will make sure you feel relaxed and happy during your visits. You will be able to ask questions about your treatment at any time.

3. What is your project about?

Dentists do projects that help them to understand about teeth and about how

the different treatments that we do can help teeth to be strong and healthy.

This project is about teeth like yours that have been damaged and have stopped growing. We will be asking 30 children to help us with this project. When we finish our project we hope to be able to help lots of other children with teeth like yours.

4. Will joining in help me?

We will make sure that you have good dental treatment. We will make sure that you are happy and relaxed when you visit us. We hope that you will find the visits interesting and that you might learn a little bit about teeth and science.

5. Will anyone else know I'm doing this?

The only people that will know about the project will be your parent or carer, your dentist and the dentists and nurses that you meet in the Dental Hospital.

6. Do I have to take part?

No. It is up to you if you take part.

7. What happens if I don't want to do it anymore?

If you decide you do not want to have treatment you are allowed to say no. If you decide that you do not want to be part of the project that is ok. We will not be cross with you.

Thank you for reading this leaflet. I hope that it has helped to answer some of your questions. Please let me know if you have any more questions that you would like to ask.

Laura Gartshore (Dentist)

Consent Form For Children

Title: Revascularisation versus Mineral Trioxide Aggregate in the Management of Non-Vital Immature Permanent Incisors in a Young Population

Please tick in the box for your answer to each question below

Have you read (or had read to you) the information leaflet given to you?

Yes No

Do you understand what this project is about?

Yes No

Have you had a chance to ask questions about your treatment and the project?

Yes No

Have all of your questions been answered?

Yes No

Do you understand it's OK to stop taking part in this project at any time?

Yes No

Are you happy to have photographs of your teeth taken?

Yes No

By signing your name below you will **only** be asked to do the parts you have signed **YES** to.

If you **don't** want to take part at all, **don't** sign your name!

Your name _____

Your signature _____

Date _____

The dentist who explained this project to you needs to sign too:

Print name _____

Signature _____

Date _____

Thank you for your help.

Parent Information Sheet

Title: Revascularisation versus Mineral Trioxide Aggregate in the Management of Non-Vital Immature Permanent Incisors in a Young Population: A Randomised Controlled Trial (Pilot Study)

Your child has qualified for an invitation to participate in a research project, which is being carried out at the University of Liverpool Dental Hospital.

Children often damage their front teeth. In approximately 6% of cases, the nerve inside the affected tooth dies (becomes 'non-vital') and natural root development stops. In these cases, the tooth requires a root canal treatment in order to prevent problems such as pain and dental abscesses from arising. However, because the roots of these young teeth are not fully formed, they are weaker and prone to fracture. In addition, root canal treatment is difficult because a normal root canal filling cannot be placed in a tooth which is not yet fully formed, due to the fact that the immature root has an 'open' end.

The aim of this research is to discover whether there is a difference between one of two methods of treating immature non-vital teeth with open ends, such as the one that your child has.

Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please feel free to contact us if you would like more information or if there is anything that you do not understand. Please take time to decide whether or not you wish to take part.

1. What is the purpose of the research?

The aim of this study is to discover whether there is a difference between one of two methods of treating non-vital teeth with open ends.

Children with teeth that fall into this category and require root canal treatment will be given one of two treatments, both of which aim to treat infection, close the root end and to allow healing to take place.

Your child will receive one of the following methods of root treatment:

1. Revascularisation (recovery of the natural blood supply to the tooth) following placement of an antibiotic paste into the tooth root. The aim of this treatment is to allow 'natural' root growth to restart. Root growth will allow the tooth to form a barrier at the end of the root. No root canal filling will then be necessary.
2. Closure of the open root end by placement of an artificial barrier at the end of the root so that a root canal filling can then be placed. This will be done with a dental material called Mineral Trioxide Aggregate (MTA). Non-vital teeth with an open end are routinely treated in this way at Liverpool Dental Hospital.

Participants will be randomly allocated in to one of the above treatment groups. Neither the participants, nor the researchers, will be able to choose which group a participant will be allocated to.

In both techniques, in order to learn about the bacteria involved in non-vital teeth, we may take samples of the bacteria within the root canal.

The outcomes of the research will provide us with further information about root growth, the bacteria involved in infection of non-vital teeth and the success of the different treatment methods that are available. This information will enable us to increase our understanding of the treatment of non-vital teeth with an open end and help us to explain our treatments to future patients.

2. Why has my child been chosen to take part?

Your child has a non-vital tooth with an open end that requires root treatment.

3. Does my child have to take part?

No. It is up to you and your child to decide whether or not to take part. You and your child are free to withdraw at any time and without giving a reason. A decision to withdraw or a decision not to take part, will **not affect the dental care your child receives now or at any time in the future.**

4. What will happen if my child takes part?

If you agree for your child to take part in our study we will contact you in order to arrange an appointment for treatment. On the day of your appointment, you will be seen by the main researcher (Dr. Laura Gartshore), who is a Specialist Registrar in Paediatric Dentistry. You will have the chance to discuss any concerns you have and then sign a consent form. Your child will be given an assent form to sign if they wish.

A clinical examination of your child's teeth will be carried out and radiographs (x-rays) will be taken in accordance for normal practice when carrying out root treatment. You will be allocated into a treatment group and treatment will then commence. Your child will require between 2 to 3 separate treatment appointments.

Following treatment we require your child to attend Liverpool Dental Hospital for review once every 3 months for a 1 year period.

5. Are there any disadvantages or risks in taking part?

No. However, if the tooth does not respond to treatment, or if symptoms of infection arise, then alternative treatment methods may be initiated as necessary.

6. Are there any benefits in taking part?

By taking part in this study your child will benefit from the most up to date specialist care in Children's Dentistry and will contribute to our understanding of how natural root growth may allow us to provide root treatment for non-vital teeth.

7. What if I, or my child, is unhappy or if there is a problem?

If you are unhappy, or if there is a problem, please discuss this with us we will strive to resolve the problem for you. If you remain unhappy or have any concerns about any aspect of the way you have been approached or treated during the course of the study, the National Health Service complaints mechanism will be available to you.

The Royal Liverpool and Broadgreen University Hospitals NHS Trust Customer Relations Team is on hand to help with queries, problems or concerns you might have. You can contact them directly on 0151 706 4903.

8. Will my child's participation be kept confidential?

Yes. All the information gained from the study will be kept confidential. Any information that is used to inform colleagues working outside of the hospital about the results of the research will be made anonymous so that your child cannot be recognised from it.

9. What will happen to the results of the study?

Our aim is to publish the results of the research in a scientific journal; a link to this publication will be available on the University website.

10. What will happen if I want to stop my child from taking part?

You can withdraw at anytime, without explanation. Results up to the period of withdrawal may be used, if you are happy for this to be done. Otherwise you may request that they are destroyed and no further use is made of them.

11. Who can I contact if I have any further questions?

Dr Sondos Albadri, Paediatric Dentistry Department,
Liverpool University Dental Hospital,
Pembroke Place, Liverpool, L3 5PS
Tel: 0151 706 5030
Email: sondos.albadri@liverpool.ac.uk

Parent Consent Form

| | |
|--|---|
| <p>Title of Research Project: Revascularisation versus Mineral Trioxide Aggregate in the Management of Non-Vital Immature Permanent Incisors in a Young Population: A Randomised Controlled Trial (Pilot Study)</p> <p>Researcher(s): Dr Laura Gartshore, Dr Sondos Albadri, Dr Fadi Jarad, Dr Kathryn Fox</p> | <p>Please tick the boxes below</p> |
| <p>1. I confirm that I have read and have understood the information sheet dated 22nd August 2010 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered to my satisfaction.</p> | <p><input type="checkbox"/></p> |
| <p>2. I understand that my child's participation is voluntary and that they are free to withdraw at any time without giving any reason, without their dental or legal rights being affected.</p> | <p><input type="checkbox"/></p> |
| <p>3. I understand that, under the Data Protection Act, my child and I can at any time ask for access to the information we provide and we can also request the destruction of that information if we wish.</p> | <p><input type="checkbox"/></p> |
| <p>4. I consent for photographs of my child's teeth to be taken.</p> | <p><input type="checkbox"/></p> |
| <p>5. I am happy for you to contact my child's dentist with any relevant information.</p> | <p><input type="checkbox"/></p> |
| <p>6. <u>I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my child taking part in this research. I give permission for these individuals to have access to my child's medical records.</u></p> | <p><input type="checkbox"/></p> |
| <p>7. I agree for my child to take part in the study.</p> | <p><input type="checkbox"/></p> |

Parent / Guardian:

Print name _____

Signature _____

Date _____

Researcher:

Print name _____

Signature _____

Date _____

If you have any further questions, please contact:

Dr Sondos Albadri,
Paediatric Dentistry Department,
Liverpool University Dental Hospital,
Pembroke Place,
Liverpool,
L3 5PS
Tel: 0151 706 5030
Email: sondos.albadri@liverpool.ac.uk

Department of Paediatric Dentistry
Liverpool University Dental Hospital
Pembroke Place
Liverpool
L3 5PS
0151 706 5030

Date:

Patient Details (insert sticker):

For the attention of the General Dental Practitioner,

The above patient has been diagnosed with a non-vital, immature incisor. They have subsequently been enrolled in the following randomised controlled trial: Revascularisation versus Mineral Trioxide Aggregate (MTA) in the Management of Non-vital Immature Permanent Incisors.

This trial will take place in the Departments of Paediatric Dentistry and Restorative Dentistry at Liverpool University Dental Hospital.

The patient will receive one of the following treatments:

- Root end closure with MTA followed by endodontic obturation
- Revascularisation following placement of a triple antibiotic paste (no endodontic obturation required if healing and further root development occur)

Following completion of treatment, the patient will be reviewed on a three monthly basis for a period of one year. They will then be discharged back to your care.

During the course of the trial, the patient will be asked to maintain regular reviews and to undergo routine treatment as necessary within your practice. The patient will be advised to contact the Dental Hospital directly if they experience any symptoms which are associated with the tooth undergoing one of the above treatments. Please avoid intervention of the treated tooth at your practice during the study period except in the case of a dental emergency.

Please do not hesitate to contact me if you have any queries.

Kind regards

Laura Gartshore