Effectiveness of extraction of primary canines for interceptive management of palatally displaced permanent canines - a meta-analysis

By

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ABSTRACT

Effectiveness of extraction of the primary canines for the interceptive management of palatally displaced permanent canines - a meta-analysis

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AIM: Although extraction of primary canines in the mixed dentition has been suggested as a measure to prevent impaction of palatally displaced permanent canines (PDC), the relevant evidence has been inconclusive. The aim of this study was to investigate the effectiveness of this practice.

MATERIALS AND METHOD: Search without restrictions for published and unpublished literature and hand searching took place. Data on the prevalence of physiologic PDC eruption, patient reported outcomes, adverse effects and economic evaluation data from randomized controlled trials (RCTs) that compared extraction of primary canine to no treatment (including delayed treatment) were reviewed. The random effects method of combining treatment effects was used and the individual study risk of bias and the overall quality of the available evidence (confidence in the observed effect estimates) were assessed using the Cochrane Risk of Bias Tool and Grades of Recommendation, Assessment, Development and Evaluation approach, respectively.

RESULTS: We initially identified 1878 references and finally included data from 5 RCTs involving 329 patients with 479 PDC in total, following them for up to 48 months post-

intervention. One study also presented data for the 12-month evaluation. Two studies were at low and the rest at high risk of bias. At the 12-month evaluation, extraction of the primary canine does not result in a statistically significant benefit compared to no treatment [Risk Ratio (RR): 1.537; 95% Confidence Interval (CI): 0.656 – 3.601; 1 study, n = 67 participants]. Beyond 12 months, overall, there is only low quality evidence that extraction of primary canines provides a statistically significant benefit compared no treatment or delayed treatment [RR: 1.784; 95% CI: 1.376 – 2.314; 5 studies, n = 214 participants; I^2 = 0%]. Analysis of the studies at low risk of bias confirmed the abovementioned result [RR: 1.713; 95% CI: 1.226 – 2.394; 2 studies, n = 91 participants; I^2 = 0%]. Moreover, the intervention did not result in a statistically significant benefit compared to no treatment regarding root resorption of adjacent permanent teeth [RR: 0.602; 95% CI: 0.277 – 1.308; p = 0.200 n = 67 participants]

CONCLUSIONS: Extraction of primary canines in mixed dentition may increase the chance of subsequent successful eruption of PDC in the long term. However, better study standardization and reporting of long follow-ups are necessary.

DEDICATION

At the beginning most of all thanks to Allah (God) who without I would not have what I am thankful for now. I like also to dedicate my Master Thesis to my parents, husband and kids for their understanding, continuous prayers and support. Without them being around me and bearing the circumstances, I might not have been able to write it.

DECLARATION

I declare that all the content of the thesis is my own work. There is no conflict of interest with any other entity or organization.

Name: Ameirah Saeed Alyammahi

Signature:

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Table of Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. INTRODUCTION

Maxillary permanent canine impaction occurs quite commonly (Becker, 2012). Its prevalence ranges between 0.9%-5.2% in the Caucasian population (Ericson and Kurol, 1986; Moss, 1972; Thilander and Jakobson, 1968; Bass, 1967) and more frequently affects females than males (Sacerdoti and Baccetti, 2004; Grover and Lorton, 1985; Kramer and Williams, 1970). The majority of impacted maxillary permanent canines are displaced in the palatal direction (Becker, 2012; Mossey et al., 1994; Oliver et al., 1989; Becker et al., 1981) and are associated with adverse effects, such as an increased risk of root resorption to the neighboring teeth (Becker, 2012; Ericson and Kurol, 2000; Stivaros and Mandall, 2000; Ericson and Kurol, 1987; 1986) and on rare occasions cyst formation or infection (Becker, 2012; Shafer et al., 1963).

Impacted maxillary permanent canines usually require intervention in the form of surgical exposure and subsequent orthodontic traction (Becker, 2012). Such comprehensive management may necessitate significant commitment and costs from the patient and the healthcare provider (Parkin et al., 2012). Moreover, it may involve risks and complications, if the prognosis, treatment planning and biomechanics are not thoroughly considered (Becker, 2012).

Interceptive extraction of the deciduous canines in cases of palatally displaced permanent canines was first suggested in 1936 (Buchner, 1936). In such cases, provided that space conditions are normal, extraction of the primary canine is supposed to lead to a change in the path of the eruption of the permanent and ultimately guide it into the dental arch. This practice was later investigated in case series studies such as those by Ericson and Kurol (1988) and

Power and Short (1993) that followed a consecutive group of children. However, up to now the relevant evidence has been inconclusive (Naoumova et al., 2011; Parkin et al., 2009).

The aim of this thesis was to investigate the available data on the effectiveness of the extraction of primary canines in mixed dentition as a measure to prevent impaction of palatally displaced canines in the permanent dentition.

2. REVIEW OF THE LITERATURE

Maxillary permanent canines have the longest period of development among the teeth of the human permanent dentition, as they develop early in time but erupt late (Dewel, 1949). Their calcification starts at 4-5 months after birth, while they usually erupt at the mean age of 10.5 years in girls and 11.5 years in boys, although significant variation in the exact timing may be observed (Shapira and Kuftinec, 2001; Hägg and Taranger, 1986). Since the maxillary permanent canine erupts late, there is a greater potential for being exposed to unfavorable developmental and/or environmental conditions (Becker, 2012). In addition, it develops at a higher plane than all other teeth, being usually displaced upward as the premolars begin to calcify, reaching a final developmental position above the apex of the primary canine. Therefore, maxillary permanent canine displacement or impaction could be somehow related to the long distance the tooth has to travel before it erupts into the dental arch (Dewel, 1949).

Peck et al. (1996) defined palatal displacement of the canines as ‘‘a developmental dislocation of the maxillary canine to a palatal site often resulting in tooth impaction requiring surgical and orthodontic treatment’’. Those canines that are prevented from eruption into the normal functional position by bone, tooth or fibrous tissue are considered as impacted (Becker 2012).

2.1. Epidemiology of palatally displaced permanent maxillary canines

Palatally impacted canines have been observed in human skull fragments dating back to the 6th century BC (Baccetti et al., 1995). The prevalence of the condition in contemporary populations has been reported to range between 0.9% to 5.2% in Caucasians (Ericson and Kurol,

1986; Moss, 1972; Thilander and Jakobson, 1968; Bass, 1967). Moreover, palatally impacted canines affect females more frequently than males, with an approximate ratio of 2:1 (Sacerdoti and Baccetti, 2004; Leifert and Jonas, 2003; Mossey et al., 1996; Peck et al., 1996; Oliver et al., 1989; Grover and Lorton, 1985; Kramer and Williams, 1970), and are observed more often unilaterally than bilaterally (Mossey et al., 1996).

Impacted maxillary permanent canines are usually displaced in the palatal direction compared to those lying buccally or on the same line as the dental arch (Becker, 2012; Mossey et al., 1994; Oliver et al., 1989; Becker et al., 1981). The proportion of palatal displacement has been reported to be around 50-65% (Stivaros and Mandall, 2000; Ericson and Kurol, 1986; Fournier et al., 1982), although, with the use of cone-beam computed tomography, their prevalence has been observed to reach up to 93% (Walker et al., 2005).

2.2. Etiology of palatally displaced permanent maxillary canines

Up to now, no single confirmed, or even apparent factor has been recognized as responsible for the developmental palatal dislocation and subsequent impaction of the permanent maxillary canines (Becker, 2012; Bishara, 1992). However, a number of general and local factors and conditions have been implicated in its etiopathogenesis (Becker, 2012).

2.2.1. General factors

In the context of general factors, **late development of the dentition** has been reported to present a link with palatally displaced canines (Becker, 2012). This phenomenon may be

observed in various *endocrine disorders*, such as hyper- and hypo-thyroidism, hypo-parathyroidism and hypo-pituitarism (Thilander and Rönning, 1985). Moreover, long-term *Vitamin A or Vitamin B deficiencies*, as well as *amelogenesis imperfecta* may have a retarding effect on the eruption of teeth (Hu et al., 2007; Thilander and Rönning, 1985). Finally, febrile diseases and irradiation have been associated with palatally displaced canines, although no clear explanation of the causative link has been provided (Bishara, 1992).

In addition, a **direct genetic influence** has been suggested as an exclusive etiological factor of palatal canine displacement, dismissing other possible causes (Peck et al., 1994). The proponents of this explanation have attributed the disruption in the eruption process to a complex of genetically determined phenomena resulting from developmental disturbances in the dental lamina (Peck et al., 1994). Furthermore, they have provided further evidence on the hereditary causation by observing concurrence in twins and triplets, as well as, gender and racial differences in the prevalence of the phenomenon (Peck et al., 1996). Corroborating data have been shown by epidemiological studies in the general population associating palatally impacted permanent maxillary canines with other dental anomalies including abnormalities of tooth size, shape, structure and number, which are genetically linked (Baccetti et al., 1998), and especially in cases of small, pig-shaped, or missing lateral incisors (Brin et al., 1986). Other researchers have also reported a very high prevalence of palatally displaced canines and related lateral incisor anomalies (small, peg-shaped, missing lateral incisors, etc.) in the immediate families (parents and siblings) of affected children (Zilberman et al., 1990), offering additional support to the suggestions of genetic influence.

However, explaining the phenomenon of palatal canine displacement accompanied by lateral incisor anomalies as a genetically determined because of the common occurrence may constitute an oversimplification (Becker, 2012). Although, it is widely accepted that heredity plays an important role in the etiopathogenesis of the condition, the eruptive path of the

permanent maxillary canine may be affected by various local parameters that may finally determine the outcome between eruption and impaction (Becker, 2012). Therefore, 'there is currently too little robust statistical or genetic evidence to definitively ascribe malposition of the permanent canine as an isolated disorder of either genetics or environment (Becker et al., 1999; Chaushu et al., 2003). Other concepts support the idea that genetic factors, such as, abnormally shaped or missing lateral incisors, spaced dentitions, etc., play their role by altering the local surroundings that contribute to the loss of guidance to the expected canine eruption path (Becker et al., 1995).

2.2.2. Local factors

It is reasonable to assume that failure in the eruption process of a permanent maxillary canine, and the subsequent impaction, may be the result of **ankylosis** due to follicle or periodontal ligament disturbances (Bishara, 1992; Franklin, 1972). In such cases, persistently recurring perturbations may lead to tooth resorption and replacement of the resorbed tissues by osseous tissue or cementum, resulting in locking the tooth in its place (McDonald et al., 2004). However, classically, the fairly common phenomenon of permanent maxillary canine displacement has been associated with the long eruption path of the permanent maxillary canine and the consequent greater potential of being exposed to unfavorable developmental and/or environmental conditions (Becker, 2012). In this context, a variety of local factors interacting in the surrounding environment have been implicated in the observed displacement and possible impaction.

Earlier observations had already provided some insight on the role of **lateral incisor disturbances** in the pathogenesis of the canine displacement phenomenon. Miller (1963) and Bass (1967) reported that there appeared to be an unusually high prevalence of *congenitally*

missing lateral incisors associated with palatally impacted canine teeth. They proposed that under these conditions, the permanent canine looses the eruption guidance provided by the distal surface of the lateral incisor root. Similar findings have been observed in cases with cleft lip and/or palate, where missing lateral incisor is a common abnormality (Vichi and Franchi, 1995), and has been considered to constitute one of the possible risk factors that might affect the impaction of the permanent maxillary canine, in addition to the timing of the grafting surgical procedure of course (Russell and McLeod, 2008; Vichi and Franchi, 1996). As already mentioned in the context of genetic influence, various epidemiological studies have also shown an association between congenitally absent lateral incisors and displaced permanent maxillary canines (Baccetti et al., 1998; Zilberman et al., 1990; Brin et al., 1986).

Regarding *lateral incisors with abnormal shape* (i.e. peg-shaped teeth), Miller (1963) originally presumed that as they eventually develop a relatively normal root length, they may offer the needed guidance for the canine to erupt. However, other studies have shown an association between palatal canine displacement and an abnormally shaped lateral incisors (Baccetti et al., 1998; Brin et al., 1986; Zilberman et al., 1990), although in these cases it may be less pronounced than in the case of congenitally missing teeth (Becker, 2012).

Becker and co-workers (1995), with the *guidance theory*, attempted to provide an integrated framework concerning the role of normal root development of the lateral incisor as guidance for the canine in order for it to appear early with a palpable bulge in the buccal sulcus during the normal development of the dentition. They postulated that, at the initial stages of the canine eruption path, the lack of guidance due to a congenitally absent or developmentally delayed lateral incisor may lead to deviation of the maxillary canine to the palatal direction. In cases where the lateral incisor is absent, the vertical alveolar process growth that follows, may help the palatally displaced canine to move downward and then bucco-mesially, in order to locate itself in a more normal bucco-lingual alignment. However, in cases of minimal vertical

movement of the canine due to the alveolar process growth, a horizontal dislocation may be observed. In addition, if self-correction at the previous stage fails to occur due to an abnormally shaped or late-developing lateral incisor root, further palatal deflection of the canine could be seen. At this stage, spontaneous correction may be observed after interceptive interventions such as extraction of the over-retained deciduous canine or the abnormal lateral incisor, leading to eruption of the palatally displaced canine.

The numerous components in the eruption process of the permanent canine, as described by Becker and co-workers (1995) underline the fact that it may be strongly influenced by **other local factors** present in the surrounding tooth environment, which interact so as to determine either the eventual success of the eruption or the subsequent displacement and impaction of the tooth (Becker 2012).

Among these factors, *failure of the primary canine root to resorb* was among the parameters implicated early leading to eventual permanent maxillary canine impaction (Lappin, 1951) and formed the basis for the interceptive extraction of retained primary canines (Power and Short, 1993; Lindauer et al., 1992; Ericson and Kurol, 1988). Other possible causes relating to the primary canines include *inflammatory changes* resulting in persistent chronic irritation, residual infection, or granulation tissue around the tooth apex. An untreated decayed primary canine with time will transform into a necrotic tooth and a periapical lesion may develop, which may lead to eruption path deflection. In unusual cases, the periapical lesion may develop into a radicular cyst possibly affecting the normal eruptive movement of the permanent canine; in the same manner as the even more rare cystic changes of the dental follicle of the canine tooth itself (Becker, 2012; Ericson and Kurol, 1987; 1986; Shafer, 1963).

Dental arch crowding has been suggested as a contributory factor to canine displacement (Hitchin, 1956). However, according to the normal developmental pattern of the dentition, in

crowded early mixed dentition dental arches, it is more likely that the lateral incisors will be affected because, lacking a space to migrate between the roots of the newly erupted central incisors and the primary canines, and therefore may erupt palatally (Becker, 2012). Indeed, studies have shown that in most patients with palatal canine impaction sufficient space is usually available to accommodate these teeth (Brin et al., 1986; Becker et al., 1984; Jacoby, 1983).

Traumatic injuries to the lateral incisors have been reported as potentially affecting the eruption of the permanent maxillary canines (Brin et al., 1993). In these cases, the palatal displacement and impaction of the maxillary permanent canine may result from the direct displacement of the lateral incisor, the indirect displacement of the unerupted canine or even a consequence of the arrest in the development of the lateral incisor root and the subsequent disturbance in the eruption process of the permanent canine itself, according to the guidance theory (Becker, 2012). Furthermore, trauma might affect dental arch development by causing root dilaceration (Brin et al., 1993), i.e. a deviation or bend in the linear relationship of a crown of a tooth to its root (Shafer et al., 1983). Dilacerations can cause impaction of either the affected tooth itself or by obstructing the path of an erupting tooth by the dilacerated root (Becker, 2012; Bishara, 1992).

2.3. Consequale of palatally displaced permanent maxillary canines

Palatal displacement and the subsequent impaction of permanent maxillary canines may have significant effects on function and esthetics as they are considered to be the cornerstones of the dental arch. The situation may be complicated even further by the **early loss of the deciduous predecessor** due to root resorption and mobility (Becker, 2012). Furthermore, the deciduous tooth may have to be extracted because of caries, left untreated by the general dental practitioner on the grounds of its imminent replacement by its permanent successor. In both situations, function and esthetic rehabilitation problems may arise, as the space left is usually considered too small to be filled successfully by an implant or a conventional prosthesis (Becker, 2012).

Moreover, the carious process may also result in necrosis and asymptomatic periapical pathology. Subsequently, the periapical lesion might undergo **cystic alteration to a radicular cyst** and expand considerably leading to the displacement of the adjacent teeth (Becker, 2012). In addition, the direct contact of such lesions with the follicle of the impacted successor may cause **the follicular sac of the permanent canine to become enlarged** or **transformed into a dentigerous cyst** (Becker, 2012; Ericson and Kurol, 1987; 1986; Shafer, 1963). This latter phenomenon has been observed even in the absence of stimuli from a necrotic deciduous canine (Becker, 2012; Ericson and Kurol, 1987; 1986; Shafer, 1963) and in unusual circumstances, the follicle might expand considerably, moving the impacted canine even higher (Becker, 2012).

To make matters worse, the close proximity of the follicular sac of the unerupted permanent maxillary canine to neighboring structures may trigger, together with the anticipated resorption of its predecessor, the **resorption of roots of the adjacent permanent teeth** (Becker, 2012). The risk is significantly increased when a space deficiency is present and orthodontic treatment is postponed (Becker, 2012). Ericson and Kurol (1988) reported that 12% of cases with

impacted or ectopically erupted canines in the age range of 10-13 years exhibited resorption of the lateral incisor root. In a subsequent CT investigation such untoward effects were observed in as many as 38% of the lateral incisor teeth and 9% of the central incisors (Ericson and Kurol, 2000). Owing to the close proximity of the developing permanent maxillary canine to the root apices of the adjacent teeth during normal dental arch development, such sequelae may appear not only in unsuccessful, but also in successful eruptive movements (Becker, 2012). In such cases, the extent of the resorptive process merely depends on further eruptive advancement of the impacted canine (Ericson and Kurol, 2000; Rimes et al., 1997).

Another consequence impaction might be **enamel resorption** in the crown area of the permanent maxillary canine(Becker, 2012). The reduced enamel epithelium may degenerate and loose its integrity, allowing osteoclasts to resorb areas of the enamel that are later replaced by bone. Radiographs taken after a long period of follow-up may present low defined enamel margins with reduced opacity over time. Subsequent surgical exposure of that tooth might display a pitted crown surface, which is difficult to separate from the embracing structures (Becker, 2012). This condition is more usually seen in adult patients, where the tooth has been kept impacted for more than two decades (Azaz and Shteyer, 1978) and has been connected to clinical findings where attempts to treat impacted teeth in adults in their fourth or fifth decades are not predictable, as the tooth might not move (Becker and Chaushu, 2003).

2.4. Diagnosis and localization of palatally displaced permanent maxillary canines

Over-retained primary canines do not usually constitute a problem for the patients themselves, so it is common that prolonged retention and the possible concomitant permanent canine impaction are discovered during routine check-ups with the pediatric dentist or the general practitioner. Following initial diagnosis, the exact determination of the position of the displaced canine and its relation to the surrounding structures is crucial for accurate planning and subsequent successful treatment. In general, the diagnostic methodology in the cases of palatally impacted canines involves the steps of clinical inspection, palpation and radiographic examination.

2.4.1. Inspection

Although significant variation in the exact timing of permanent maxillary canine eruption can be observed, the expected time is around 11 years of age (Shapira and Kuftinec, 2001; Hägg and Taranger, 1986). Absence of the canine during this period should prompt some investigation, especially if the contralateral one is present.

Bearing in mind that the correlation between chronological and dental ages is poor and that the overall dental development must be considered when investigating the delayed eruption of a canine (Richardson and Russell 2000), the clinical signs that may indicate a displaced or impacted succedaneous canine, include the following:

a. Lack of a canine bulge in the buccal sulcus at the age of 10 years (Thilander and Jakobsson, 1968).

b. Persisting “ugly duckling” feature for more than the age of 11 years (Becker, 2012).

c. Primary canines that are retained beyond the age of 13 years and have no significant

mobility (Power and Short, 1993; Thilander and Jakobsson, 1968).

d. Delay in the eruption of the permanent successor (Shapira and Kuftinec 1998).

e. Asymmetry in the exfoliation and eruption of the right and left canines (Shapira and Kuftinec 1998).

Additional clinical features that have been proposed as requiring further investigation may be:

a. Loss of vitality and increased mobility of the permanent incisor (Kettle1957).

b. Presence of peg-shaped or small in size lateral incisors (Becker, 2012).

c. Late developing dentition and dentition with congenitally missing teeth, as these factors have been reported to be linked with palatally displaced canines (Becker, 2012).

The inclination of the erupted permanent lateral incisor could provide an indication on the position of the canine. Palatal crown tip, or even in some cases a crossbite, and a very prominent lateral incisor root labially, are suggestive of permanent maxillary canines displaced in the palatal direction (Becker, 2012).

2.4.2. Palpation

Frequently, impacted maxillary canines can be located by digital palpation. However, this may not always be possible and the clinician then has to rely on radiographs to confirm the diagnosis (Becker, 2012).

The clinician should also manipulate the primary canine to determine if it is mobile. If it is, this indicates that the root has undergone significant resorption (Jacobs, 1999). However, this mobility does not guarantee that the permanent canine is erupting normally (Preda et al., 1997; Ericson and Kurol, 1987). Radiographs are still essential to localize and assess the morphology

of an unerupted permanent maxillary canine (Becker, 2012).

2.4.3. Radiography

Different radiographic options are available to help determine the position of displaced permanent maxillary canine (Becker, 2012). A single periapical radiograph is beneficial for initial localization of the impacted canine in relation to surrounding structures. In addition, a second periapical radiograph using the parallax method may be helpful, but exact localization of the crown and the apex of the impacted tooth might still be difficult (Becker, 2012). As a part of orthodontic treatment planning, panoramic radiographs and lateral cephalometric radiographs are important and can be used as initial assessment in localizing the impacted canine in the three planes of space (Sajnani and King, 2012; Ericson and Kurol, 1987). However, the radiation dose is somewhat high compared to the amount of information provided (Becker, 2012).

Plain film radiography cannot provide reliable information in the bucco-lingual direction and, therefore, incisor root resorption may occur and remain undiagnosed until an advanced stage (Becker, 2012). In addition, the bucco-lingual distance that exists between the impacted tooth and its neighboring structures is very difficult to assess. Consequently, in some circumstances extra radiographic images might be required for detailed evaluation of the canine position in relation to surrounding structures. The most accurate one among the available options of different types of radiographs is Cone Beam CT (Naoumova et al., 2014; Becker, 2012).

2.5. Interventions for palatally displaced permanent maxillary canines

During normal dental arch development, palpation of the erupting permanent maxillary canine should be possible by the age of 9-10 years (Thilander and Jakobsson, 1968). If crowding is present at that time, and especially after the eruption of the first premolar, the bulge of the unerupted canine usually increases. In the opposite situation, where the palpation of the unerupted canine is not possible, an appropriate radiographic examination should take place to help in determining its presence and location and provide general information about its shape, size and stage of development, inclination, vertical and bucco-lingual position, as well any eventual associated pathology (Becker, 2012).

In cases were palatal displacement of the permanent maxillary canine goes unnoticed during this period, the eventual impaction may warrant surgical intervention as the only treatment option to reposition the tooth in the dental arch and avoid the possible development of adverse sequelae; this should include detailed treatment planning and a thorough consideration of the biomechanics involved (Becker, 2012). On the other hand, timely detection may enable an early intervention to intercept the developing displacement and its sequelae and simplify the overall management of the situation (Becker and Chaushu, 2003).

2.5.1. Surgical interventions

Surgical intervention, and the most appropriate procedure type to uncover an already impacted permanent maxillary canine, to achieve the desired esthetic and periodontal health results, has been a topic of an ongoing controversy (Becker et al., 1983). Although the exact type of surgical technique can be chosen by the surgeon (Kohavi et al., 1984), the overall procedure is complex and warrants close cooperation with the orthodontist (Becker, 2012). Overall, such

comprehensive management may necessitate significant commitment and costs from the patient and the healthcare provider (Parkin et al., 2012). Moreover, it may involve risks and complications, if prognosis, treatment planning and biomechanics are not thoroughly considered (Becker, 2012).

The two main surgical techniques available, the open and the closed, have been recommended for the management of palatally impacted permanent maxillary canines (Becker, 2012). The closed technique involves raising a flap, removal of any bone to uncover the tooth, placement of an orthodontic attachment and repositioning of the flap (Wisth and Norderval, 1976). Following initial healing light forces are exerted in order to erupt the tooth first to the level of the palatal mucosa and then in the appropriate position in the dental arch (Becker, 2012). On the other hand, the open technique involves excision of a portion of tissue corresponding to the impacted tooth, removal of the overlying bone and placement of periodontal dressing to cover the exposed area. Subsequently, after healing the dressing is removed and either a bracket is placed, to mechanically erupt the canine, or the tooth is allowed to erupt autonomously (Becker, 2012; Clark, 1971). In cases of deep impaction a soft tissue flap may also be raised.

Although the closed approach has been recommended in cases of high impacted canines in relation to the occlusal plane because it is believed to help minimize compromising the periodontal tissue (Felsenfeld and Aghaloo, 2002), there is insufficient evidence to support one procedure over the other in terms of oral health, esthetic evaluation, socio-economic evaluation and patient reported parameters (Parkin et al., 2008). Both surgical techniques involve the significant disadvantage of loss of supporting bone if the covering bone is removed up to the level of cement-enamel junction (Kohavi et al., 1984). Moreover, in the closed technique, moisture control during attachment bonding may be a common problem and if debonding occurs, re-exposure may be needed (Pearson et al., 1997).

2.5.2.Interceptive intervention

Interceptive management of palatally displaced permanent maxillary canines has been proposed as a means to shorten orthodontic treatment duration, simplify orthodontic biomechanics, reduce treatment costs and avoid possible adverse situations associated with the subsequent impaction (Becker and Chaushu, 2003).

Interceptive extraction of the deciduous canines in cases of palatally displaced permanents was first suggested in 1936 (Buchner, 1936). In these cases, provided that space conditions are normal, extraction of the primary canine is supposed to lead to a change in the path of eruption of the permanent tooth, and ultimately guide it into the dental arch. This practice was later investigated in the case series studies of Ericson and Kurol (1988) and Power and Short (1993), which followed a group of consecutively treated children without untreated controls. These studies concluded that, if extraction was performed at the correct time, a significant proportion of palatally displaced canines erupted spontaneously or their position was improved. However they observed that the prognosis for eruption became less favorable if the crown of the impacted tooth crossed medially the root of the lateral incisor (Power and Short, 1993; Ericson and Kurol, 1988) and as the angle between long axis of the impacted canine and mid-sagittal plane increased (Ericson and Kurol, 1988) or in the presence of crowding (Power and Short, 1993). Ericson and Kurol (1988) also noted that if positional improvement of the canine was not observable after 12 months from the preventive extraction, improvement would not occur.

Subsequent research teams have examined the added benefit of the supplementary removal of the first deciduous molars (Bonetti, 2011; 2010), the simultaneous space maintenance with a trans-palatal arch (Baccetti et al., 2011) or auxiliary orthodontic interventions to gain space such as headgear (Baccetti et al., 2008; Leonardi et al., 2004) and rapid palatal expansion

alone or followed by trans-palatal arch placement (Baccetti et al., 2011). However, up to now the respective evidence has been inconclusive (Naoumova et al., 2011; Parkin et al., 2009).

3. AIM OF THE SYSTEMATIC REVIEW

3.1. The aim of the systematic review

To compare the effectiveness of the extraction of primary canines in mixed dentition compared to no intervention in preventing the impaction of palatally displaced permanent canines (PDCs).

3.2. Objectives of the systematic review

To examine the percentage of PDCs erupting in the dental arch between patients after extraction of the primary canines in mixed dentition compared to no intervention.

To examine differences in patient reported outcomes, adverse effects and economic evaluation data between patients after extraction of the primary canines in mixed dentition compared to no intervention.

3.2. Null hypotheses

There is no difference in the percentage of PDCs erupting in the dental arch after extraction of the primary canines in mixed dentition compared to no intervention.

There is no difference in patient reported outcomes, adverse effects and economic evaluation data between patients after extraction of the primary canines in mixed dentition compared to no intervention.

4. MATERIALS AND METHODS

4.1. Protocol development

The present review was based on a specific protocol developed following the guidelines outlined in the PRISMA statement (Moher et al., 2001) and the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) (Higgins and Green, 2011).

The present protocol comprised part of a general protocol registered with PROSPERO - International prospective register of systematic reviews, which is produced by the Centre for Reviews and Dissemination (CRD) at the University of York, United Kingdom, and is funded by the National Institute for Health Research (NIHR), United Kingdom. This protocol is available free online on the PROSPERO registry website (see Appendix I, Ameirah Alyammahi, Eleftherios Kaklamanos, Athanasios Athanasiou. Effectiveness of interceptive orthodontic treatment for palatally displaced permanent canines: a systematic review and meta-analysis. PROSPERO 2015:CRD42015029130 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015029130

4.2. Selection criteria applied for the review

The selection criteria for the domains of study design, participant characteristics, intervention characteristics and principal outcome measures that were applied for the present review were as follows:

4.2.1. Types of study design

Studies included in the present thesis should be Randomized Clinical Trials (RCTs) with at least 12 months of observation period after the intervention

Animal studies, non-comparative studies (case reports and case series), systematic reviews and meta-analyses were excluded from the present review.

The type of study design was assessed using the algorithm available from SIGN (Scottish Intercollegiate Guidelines Network) available from http://www.sign.ac.uk (Appendix II).

4.2.2. Types of participants

The included studies should involve individuals with mixed dentition and unilateral or bilateral palatally displaced permanent canines.

Studies that included subjects with craniofacial anomalies or syndromes of the head and neck region were excluded from the present review.

4.2.3. Types of interventions

The included studies should compare the outcome of the extraction of a primary maxillary canine or canines compared to no treatment [or delayed treatment, as for example in cases where initially a patient was randomized to the non-extraction group but at a later observation because of lack of improvement, or even worsening of the canine position, the primary tooth is extracted for ethical reasons].

Studies or study groups involving interventions that combined extraction of the canines with other interventions, such as, but not limited to, extraction of additional primary teeth, headgear, trans-palatal arch, headgear, palatal expansion, etc., or compared extraction of primary maxillary canine or canines to alternative interceptive approaches were excluded from the present review.

4.2.4. Types of outcome measures

The studies included in the present review had to primarily provide data on the percentage of successful outcome in each arm of the study, i.e. the prevalence of eruption of permanent maxillary canines in the dental arch.

Secondarily, we aimed at including additional outcome measures, such as, patient reported outcomes (pain, patient satisfaction; etc.), safety assessments and adverse effects, as well as, economic evaluation data.

4.3. Search strategy for identification of studies

The principal investigator (ASA) developed detailed search strategies for each database searched. They were based on the strategy developed for MEDLINE but revised appropriately for each database to take account of the differences in controlled vocabulary and syntax rules. The following electronic databases were searched (Appendix III): MEDLINE via PubMed (http://www.ncbi.nlm.nih.gov/pubmed), the Cochrane Central Register of Controlled Trials (CENTRAL) (http://onlinelibrary.wiley.com/cochranelibrary), the Cochrane Database of Systematic Reviews (http://0-ovidsp.tx.ovid.com.amclb.iii.com), Scopus (www.scopus.com),

Web of Science Core Collection (http://apps.webofknowledge.com/), Latin-American and Caribbean System on Health Sciences Information (LILACS) (http://lilacs.bvsalud.org/en/), National Databases of Indian Medical Journals (IndMed) (http://indmed.nic.in/indmed.html), Scientific Electronic Library Online (Scielo) (http://www.scielo.org/php/index.php?lang=en), Arab World Research Source (http://0-web.a.ebscohost.com.amclb.iii.com) and Deutsche Zentralbibliotek fuer Medizin (https://www.livivo.de). Unpublished literature was accessed electronically using Google Scholar (https://scholar.google.com), ClinicalTrials.gov (http://clinicaltrials.gov), International Standard Randomised Controlled Trial Number (ISRCTN) registry (http://www.isrctn.com) and Open Grey (http://www.opengrey.eu). In addition, Pro-Quest Dissertation and Theses Global database (http://search.proquest.com) was searched.

No restriction was placed on the language, date or status of publication. In addition, efforts to obtain conference proceedings and abstracts were made where possible and the reference lists of all eligible studies for additional studies were searched.

4.4. Selection of studies and data extraction

The principal investigator (ASA) and the thesis co-supervisor (EGK) assessed the retrieved records for inclusion independently. They were not blinded to the identity of the authors, their institution, or the results of the research. Subsequently, they obtained and assessed, again independently, the full report of records considered by either reviewer to meet the inclusion criteria. Disagreements were resolved by discussion or consultation with the thesis supervisor (AEA). A record of all decisions on study identification was kept.

The same two investigators (ASA and EGK) performed data extraction independently and any disagreements were again resolved by discussion or consultation with the thesis supervisor (AEA). Data collection forms were used to record the desired information.

a. Bibliographic details of the study.

b. Details on study design, duration of the observation period and verification of study eligibility.

c. Participant characteristics (where available number, age, gender) at the beginning and at the point of data analysis (if patient attrition was observed the respective reasons were noted).

d. Intervention characteristics.

e. Prevalence of successful eruption of permanent maxillary canines in the dental arch. Where needed numerical data where transformed in the desired formats and tested statistically using MedCalc (©2016 MedCalc, Belgium) and QuickCalcs (©2016 GraphPad Software, Inc. USA).

f. Data on patient reported outcomes (pain, patient satisfaction etc.), safety assessments and adverse effects, as well as, economic evaluation data.

g. Additional information (where available): a priori sample size calculation, baseline comparability of the groups (regarding age, gender, maxillary canine position, space availability in the arch and malocclusion) and reliability of the method of assessment.

4.5. Estimates of intervention effect, data synthesis and assessment of publication bias

Data on the primary outcome of the successful eruption of the permanent maxillary canine in the dental arch are dichotomous, thus they were expressed as Risk Ratios (RR) together with the relevant 95% Confidence Intervals (CI).

The random effects method for meta-analysis was used to combine data (Borenstein et al., 2007; Der Simonian and Laird, 1986), since they were expected to differ across studies due to diversity, in terms of population groups, settings, procedures and follow-up.

To identify the presence and extent of between-study heterogeneity, the overlap of the 95% CI for the results of individual studies was inspected graphically, and Cochrane's test for homogeneity and the I^2 statistic were calculated (Higgins and Green, 2011). The results of the I^2 statistic were interpreted as follows (Higgins and Greene, 2011):

- I^2 from 0% to 40%: heterogeneity might not be important;
- I^2 from 30% to 60%: may represent moderate heterogeneity;
- I^2 from 50% to 90%: may represent substantial heterogeneity;
- I^2 from 75% to 100%: considerable heterogeneity.

If deemed possible, exploratory subgroup analyses were planned according to participant characteristics, such as gender, or the position of the displaced canine. In addition, if a sufficient number of trials were identified, analyses were planned for “small-study effects” and publication bias (Higgins and Green, 2011).

All analyses were done with Comprehensive Meta-analysis software 2.2.046 (©2007 Biostat Inc.). Significance (a) was set at 0.05, except for the 0.10 used for the heterogeneity tests (Ioannidis, 2008).

4.6. Risk of bias assessment and determination of the level of certainty in the evidence

The principal investigator (ASA) and the thesis co-supervisor (EGK) assessed the risk of bias in the included studies, independently and in duplicate during the data extraction process, using The Cochrane Collaboration's Risk of Bias assessment tool for RCTs (Higgins and Green, 2011). Any disagreements were resolved by discussion or consultation with the thesis supervisor (AEA). The Risk of Bias assessment tool includes the following domains.

a. Random sequence generation (selection bias).

b. Allocation concealment (selection bias).

c. Blinding of participants and personnel (performance bias).

d. Blinding of outcome assessors (detection bias).

e. Incomplete outcome data (attrition bias).

f. Selective outcome reporting (reporting bias).

g. Other sources of bias.

After entering in the data extraction form the information reported in each study, every domain would receive a judgment of low, high or unclear risk of bias (indicating either lack of sufficient information to make a judgment or uncertainty over the risk of bias) (Higgins and Green, 2011).

Subsequently, studies were to be judged as being of low, unclear or high risk of bias.

a. Low risk of bias (plausible bias unlikely to seriously alter the results)

b. Unclear risk of bias (bias that raises some doubt about the results)

c. High risk of bias (bias that seriously weakens confidence in the results)

The quality of evidence (confidence in the observed estimate) at longest follow up available was ultimately to be assessed based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2011). The GRADE profiler

(GRADEpro) software (available www.gradepro.org; © 2015, McMaster University and Evidence Prime Inc.) was to be used to facilitate the summary regarding the quality of evidence using the GRADE approach. The principal investigator (ASA) and the thesis co-supervisor (EGK) were to assess the quality of evidence independently and in duplicate. Any disagreements were to be resolved by discussion or consultation with the thesis supervisor (AEA).

During the GRADE assessment and for the purpose of summarizing risk of bias across studies, where possible, relevant information was to be judged as being of low, unclear or high risk of bias.

a. Low risk of bias: most information is from studies at low risk of bias.

b. Unclear risk of bias: most information is from studies at low or unclear risk of bias.

High risk of bias: information from studies at high risk of bias could have an effect on the interpretation of the results.

5. RESULTS

5.1. Results of the search

The flow of records through the reviewing process is shown in Figure 1. We initially identified 1878 references, and excluded 1007 as duplicates and 836 more on the basis of their title and abstract. From the 35 records that remained, we excluded 30 papers for various reasons. Finally, 5 full-text trial reports were included in the systematic review (Naoumova et al., 2015; Bazargani et al., 2014; Baccetti et al., 2011; 2008; Leonardi et al., 2004).

5.2. Study characteristics

The characteristics of the studies included in the present systematic review are presented in Tables 1 and 2. The papers were published between 2004 and 2015, and involved, ,in various groups, 329 patients with 479 PDCs in total. Regarding the comparison of interest (i.e. extraction of primary maxillary canine or canines compared to no treatment) the retrieved studies analyzed 214 patients with 294 PDCs.

Regarding the total observation period, patients were followed for periods of up to 48 months post-intervention (Naoumova et al., 2015; Bazargani et al., 2014; Baccetti et al., 2011; 2008; Leonardi et al., 2004). One study presented data also for the 12-month evaluation (Naoumova et al., 2015).

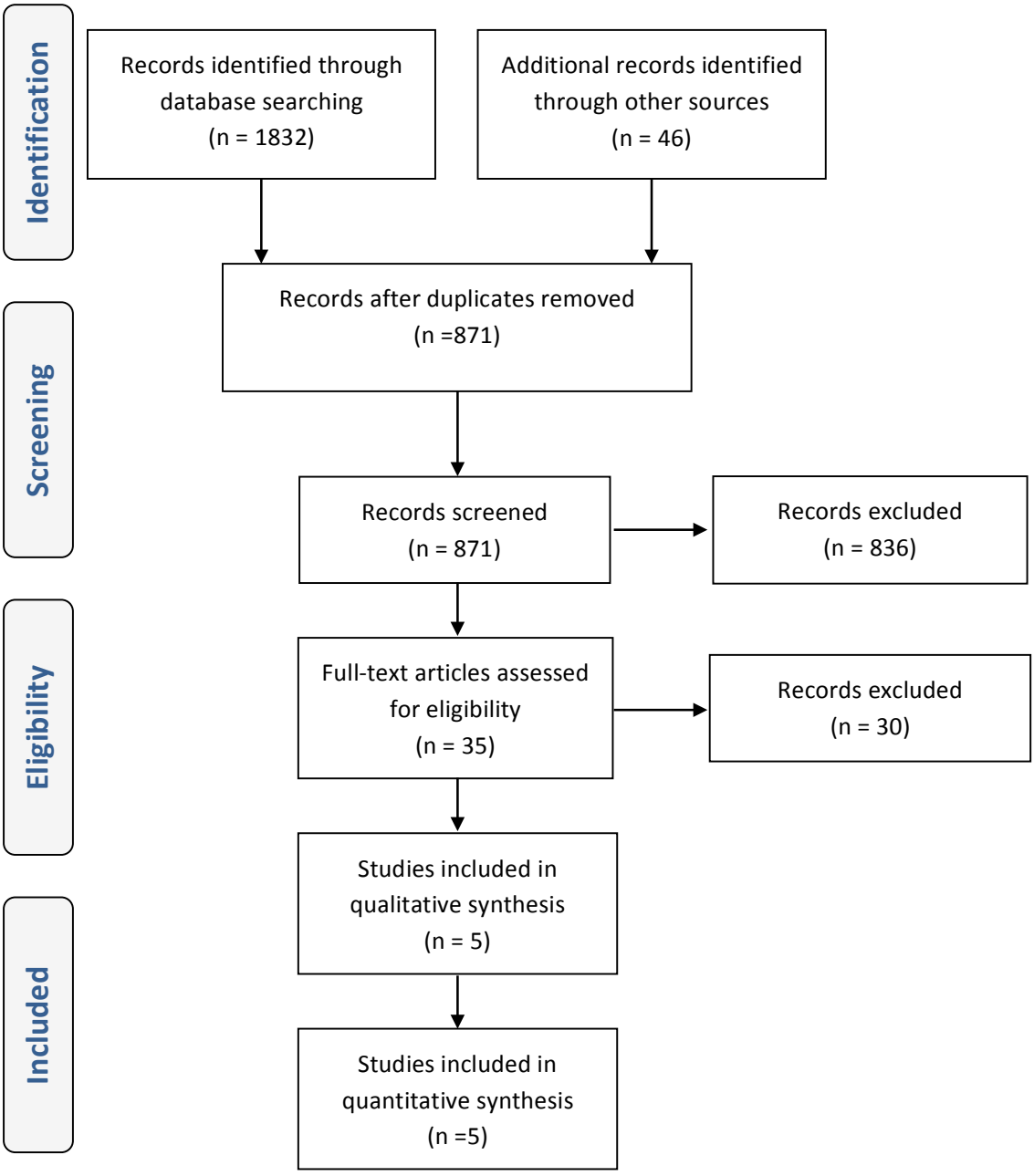

Figure 1. Flow of records through the reviewing process.

In addition, three studies reported *a priori* calculation of sample size (Naoumova et al., 2015; Bazargani et al., 2014; Baccetti et al., 2011; 2008; Leonardi et al., 2004), and one made reference to the power of the study but it was not specified if the power was calculated *a priori* or *post hoc*. In addition, all five included studies, considered examining the reliability of the

measurements carried out in some way and included reference to baseline comparability (Naoumova et al., 2015; Bazargani et al., 2014; Baccetti et al., 2011; 2008; Leonardi et al., 2004).

All five studies provided data on the prevalence of successful canine eruption after the extraction of the primary canine(s) (Naoumova et al., 2015; Bazargani et al., 2014; Baccetti et al., 2011; 2008; Leonardi et al., 2004). However, no study included additional outcome measures, such as, patient reported outcomes (pain, patient satisfaction etc.), safety assessments and adverse effects, as well as, economic evaluation data. Only one study (Naoumova et al., 2015), provided data on root resorption of the adjacent permanent teeth.

Table 1. General characteristics of the studies included in the systematic review.

Study	Total observation period and Outcomes	Additional information
Baccetti *et al.* (2008) RCT [Italy]	**Total observation period** 18 months for both groups **Definition of successful eruption and assessment** Full eruption of the tooth, permitting bracket positioning for final arch alignment when needed; unsuccessful outcome represented by the lack of eruption of the permanent canine at the completion of the clinical observation period [18 months after the initial observation]	***A priori* sample calculation:** Reference that […The power … was greater than 0.85. …] **Baseline group comparability:** Reference that […The severity of canine displacement was similar…] **Measurement reliability considered:** Yes
Baccetti *et al.* (2011) RCT [Italy]	**Total observation period** Until subjects had an early permanent dentition and a post-pubertal stage of cervical vertebral maturation (CS 5 or CS 6; Baccetti et al., 2005). Extraction Group ($\overline{x}$ ±SD): 26 ±10 months; Control Group ($\overline{x}$ ±SD): 37 ±14 months; Non-statistically significant **Definition of successful eruption and assessment** Full eruption of the tooth, permitting bracket positioning for final arch alignment when needed; unsuccessful outcome represented by the lack of eruption of the permanent canine at the completion of the clinical observation period [a time point when the subjects had an early permanent dentition and a post-pubertal stage of cervical vertebral maturation (CS 5 or CS 6) (Baccetti et al., 2005)]	***A priori* sample calculation:** Yes **Baseline group comparability:** Yes [age; gender ratio; d (mm), α (°), sector (Ericson and Kurol, 1987); CS (Baccetti et al., 2005), Unilateral PDC/Bilateral PDCs, Root development of PDC (Nolla, 1960)] **Measurement reliability considered:** Yes
Bazargani *et al.* (2014) RCT [Sweden]	**Total observation period** 18 months for both groups **Definition of successful eruption and assessment** Eruption above the gingival margin in an esthetically acceptable location in the dental arch after 18 months [assessment at baseline and at 18 months]	***A priori* sample calculation:** Yes **Baseline group comparability:** Yes [d (mm), α (°), sector (Ericson and Kurol, 1988); age and gender were controlled within the split mouth design] **Measurement reliability considered:** Yes

RCT: Randomized Controlled Trial, PDC: Palatally Displaced Canine, NR: Not Reported

Table 1. General characteristics of the studies included in the systematic review. [Continued]

Study	Total observation period and Outcomes	Additional information
Leonardi*et al.*(2004) RCT [Italy]	**Total observation period** 48 months for both groups **Definition of successful eruption and assessment** Full eruption of the tooth, permitting bracket positioning for final arch alignment when needed; unsuccessful outcome represented by the lack of eruption of the permanent canine at the completion of the clinical observation period [48 months after the initial observation]	***A priori* sample calculation:** NR **Baseline group comparability:** Yes [age, gender distribution] Reference that […Severity of canine displacement was similar…] **Measurement reliability considered:** Yes
Naoumova*et al.*(2015) RCT [Sweden]	**Total observation period** 24 months for both groups **Definition of successful eruption and assessment** Canine emerged through the gingiva[assessment at baseline, 12 and 24 months]	***A priori* sample calculation:** Yes **Baseline group comparability:** Yes [gender; mesioangular angle (^{o}), sagittal angle (^{o}), vertical position (mm), canine cusp tip-dental arch plane (mm), canine root apex-dental arch plane (mm), canine cusp tip-midline (mm); root resorption (Ericson and Kurol, 2000)] **Measurement reliability considered:** Yes

RCT: Randomized Controlled Trial, PDC: Palatally Displaced Canine, NR: Not Reported

Table 2. Participant characteristics of the studies included in the systematic review.

Study	Inclusion and exclusion criteria	Number of patients and PDCs included and analyzed
Baccetti *et al.* (2008)	**Inclusion criteria:** Caucasians; unilateral or bilateral PDCs; dental age at baseline 8 – 13 years according (Becker and Chaushu, 2000); skeletal age at baseline showing active phases of skeletal growth (before CS 3, Baccetti et al., 2005) **Exclusion criteria:** Previous orthodontic treatment; craniofacial syndromes, odontomas, cysts, cleft lip and/or palate, sequelae of traumatic injuries to the face, or multiple or advanced caries; crowding at the upper arch as evaluated by means of intraoral inspection; aplasia or severe hypoplasia of the crowns of the upper lateral incisors **Diagnostic criteria for PDCs:** Intraosseous palatal position of the maxillary permanent canines from panoramic radiographs and periapical radiographs (displacement of the upper canine to the palatal side was checked by means of double determination from periapical radiographs)	**Group 1 -Extraction of the deciduous canine** Analyzed: 23 subjects (8 M, 15 F); 25 PDCs Age ($\bar{x}$): 11.7 years **Group 2 - Non-extraction of the deciduous canine** Analyzed: 22 subjects (9 M, 26 F); 26 PDCs Age ($\bar{x}$): 11.6 years
Baccetti *et al.*(2011)	**Inclusion criteria:** Caucasians; unilateral or bilateral PDCs, age at baseline 9.5 – 13 years; late mixed dentition stage; skeletal age at baseline showing active phases of skeletal growth (before CS 4, Baccetti et al., 2005); presence of Class II or Class III tendency or mild tooth-size/arch-size discrepancy **Exclusion criteria:** Previous orthodontic treatment; craniofacial syndromes, supernumerary teeth, odontomas, cysts, sequelae of traumatic injuries **Diagnostic criteria for PDCs:** Intraosseous palatal position of the maxillary permanent canines from panoramic radiographs (PDCs showing α angle equal to or greater than 15^{o} according to Ericson and Kurol (1987)); palatal displacement of the canine(s) was confirmed by evaluating the position of the canine on the lateral cephalogram, and, when necessary, by means of Clark's tube shift rule using multiple intraoral radiographs of the canine region.	**Group 1 - Extraction of the deciduous canine** Included: 25 subjects (11 M, 14 F) Analyzed: 24 subjects (10 M, 14 F); 34 PDCs Age ($\bar{x}$ ±SD): 11.1 ±0.9 years **Group 2 - Non-extraction of the deciduous canine** Included: 30 subjects (12 M, 18 F), Analyzed: 29 subjects (11 M, 18 F); 42 PDCs Age ($\bar{x}$ ±SD): 10.4 ±0.8 years

PDC: Palatally Displaced Canine, M: males, F: females

Table 2. Participant characteristics of the studies included in the systematic review. [Continued]

Study	Inclusion and exclusion criteria	Number of patients and PDCs included and analyzed
Bazargani *et al.*(2014)	**Inclusion criteria:** Inability to locate the canines by digital palpation, bilateral PDCs identified on the panoramic and intraoral occlusal radiographs, age at diagnosis between 10 and 14 years, with dental stage in the late mixed dentition **Exclusion criteria:** Patients with previous or ongoing orthodontic treatment, aplasia of the upper lateral incisors, moderate to severe crowding in the upper arch (>3 mm), and/or craniofacial syndromes, odontomas, cysts, or cleft lip and/or palate **Diagnostic criteria for PDCs:** Non palpable canine bulge in the alveolar process, canine within sectors 2–5, in an intraosseous position within the palate, and exceeding the long axis of the upper lateral incisors on an intraoral occlusal radiograph (Ericson and Kurol, 1988)	Included: 24 subjects (8 M, 16 F); 48 PDCs Age ($\bar{x}$ ±SD): 11.6 ±1.2 years **Group 1 - Extraction of the deciduous canine** Included: 24 subjects; 24 PDCs Analyzed: 24 subjects; 24 PDCs **Group 2 - Non-extraction of the deciduous canine** Included: same 24 subjects; 24 contralateral side PDCs Analyzed: same 24 subjects; 24 contralateral side PDCs
Leonardi*et al.*(2004)	**Inclusion criteria:** Caucasians; unilateral of bilateral PDC; dental age at baseline 8 – 13 years according (Becker and Chaushu, 2000); skeletal age at baseline showing active phases of skeletal growth (before CVMS IV, Baccetti et al., 2002) **Exclusion criteria:** Previous orthodontic treatment; craniofacial syndromes, odontomas and/or cysts, cleft lip and/or palate, sequelae of traumatic injuries to the face, multiple or advanced caries (or both); crowding at the upper arch; aplasia or severe hypoplasia of the crown of upper lateral incisors **Diagnostic criteria for PDCs:** Intraosseous palatal position of the maxillary permanent canines from panoramic radiographs and periapical radiographs.	**Group 1 -Extraction of the deciduous canine** Analyzed: 11 subjects (5 M, 6 F); 14 PDCs Age ($\bar{x}$): 11.6 years **Group 2 - Non-extraction of the deciduous canine** Analyzed: 14 subjects (4 M, 10 F); 16 PDCs Age ($\bar{x}$): 11.6 years

PDC: Palatally Displaced Canine, M: males, F: females

Table 2. Participant characteristics of the studies included in the systematic review. [Continued]

Study	Inclusion and exclusion criteria	Number of patients and PDCs included and analyzed
Naoumova*et al.*(2015)	**Inclusion criteria:** Caucasians at age 10–13 years with either maxillary unilateral or bilateral PDC, persisting deciduous canine, no previous experience of orthodontic treatment **Exclusion criteria:** Crowding in the maxilla exceeding 2 mm, ongoing orthodontic treatment, resorption of the adjacent teeth, grades 3 and 4 according to Ericson and Kurol (2000), either at the start or during the trial caused by the displaced canine, craniofacial syndromes, odontomas and/or cysts, cleft lip and/or palate **Diagnostic criteria for PDCs:** Non palpable canine bulge in the alveolar process, canine crown diagnosed on intraoral radiographs as palatally positioned using Clark's rule (Clark, 1909)	67 subjects, Age ($\bar{x}$ ±SD): 11.4 ±1.0 years 27 M, Age ($\bar{x}$ ±SD): 11.4 ±0.9 years 16 F, Age ($\bar{x}$ ±SD): 11.3 ±1.1 years **Group 1 -Extraction of the deciduous canine** 45 PDCs (45 analyzed following Intention-to-treat analysis) **Group 2 - Non-extraction of the deciduous canine** 44 PDCs (44 analyzed following Intention-to-treat analysis)

PDC: Palatally Displaced Canine, M: males, F: females

5.3. Results of risk of bias assessment

Table 3 presents a summary of findings regarding the risk of bias assessment for the included studies and more details can be found in Appendix IV.

Table 3. Summary of the risk of bias assessment. [Domains examined: 1: Random sequence generation; 2: Allocation concealment; 3: Blinding of participants and personnel; 4: Blinding of outcome assessment; 5: Incomplete outcome data; 6: Selective outcome reporting; 7: Other potential threats to validity]

	Study				
Domain	**Baccetti *et al.* 2008**	**Baccetti*et al.* 2011**	**Bazargani *et al.* 2014**	**Leonardi et al. 2004**	**Naoumova*et al.* 2015**
1	Unclear	Unclear	Low	Unclear	Low
2	High	High	Low	High	Low
3	Low	Low	Low	Low	Low
4	Unclear	Unclear	Low	Unclear	Low
5	Unclear	Unclear	Low	Unclear	Low
6	High	High	Low	High	Low
7	Unclear	Unclear	Low	Unclear	Low
Summary	**High**	**High**	**Low**	**High**	**Low**

Two studies were classified as being at low risk of bias (Naoumova et al., 2015; Bazargani et al., 2014). The rest were considered to be at high risk of bias (Baccetti et al., 2011; 2008; Leonardi et al., 2004) mainly because of problems regarding the domains of random sequence generation and allocation concealment.

Regarding the rest of the considered domains, blinding of the participants and the personnel providing the instructions was not possible. However, in the context of the present research design, there was no reason to believe that bias could be introduced because of absence of blinding in these cases. On the contrary, blinding of the outcome assessment could possibly involve risk of bias because it is not possible to blind the extracted canine and only baseline assessments could be blinded. As the reporting, and maybe the conduct, of some of the included

studies presented general deficiencies, it is not clear how these could have affected the appraisal of the outcomes included in the present systematic review. Moreover, the risk from incomplete outcome data because of the existence of dropouts was unclear in the studies considered, whereas, regarding the domain selective outcome reporting, most studies were assessed as being of high risk of bias, because significant outcomes were not described adequately. Finally, most studies appeared to be at unclear risk of other sources of bias due to insufficient data.

5.4. Effect of primary canine extraction in the successful eruption of the permanent

The results of the studies included in the present review are presented below. Because it was not possible to retrieve a sufficient number of trials (Higgins and Green, 2011), we were not able to conduct analyses for "small-study effects" and publication bias.

At the 12-month evaluation, extraction of the primary canine did not result in a statistically significant benefit compared no treatment [Risk Ratio (RR): 1.537; 95% Confidence Interval (CI): 0.656 – 3.601; $p = 0.323$; n = 67 participants] (Naoumova et al., 2015).

Beyond 12 months, overall, extraction of the primary canine provides a statistically significant benefit compared to no treatment [RR: 1.784; 95% CI: 1.376 – 2.314; $p = 0.000$; 5 studies, n = 214 participants; $I^2 = 0\%$] (Naoumova et al., 2015; Bazargani et al., 2014; Baccetti et al., 2011; 2008; Leonardi et al., 2004) (Figure 2).

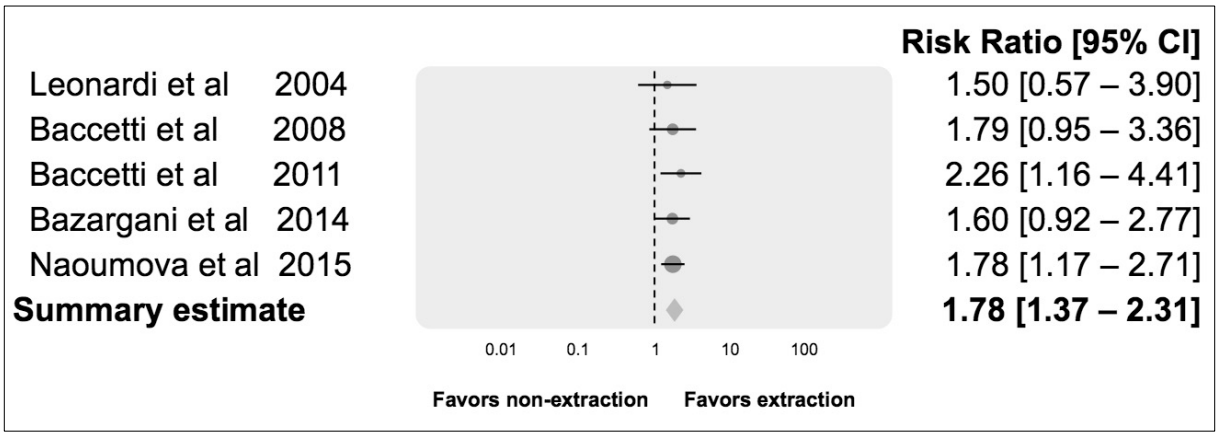

Figure 2. Successful eruption of palatally displaced permanent maxillary canine after extraction of the corresponding primary. [Observation beyond 12 months – all studies]

Further analysis of the retrieved data focusing on the studies at low risk of bias, according to relevant guidelines (Higgins and Green, 2011), confirmed the abovementioned result [RR: 1.713; 95% CI: 1.226 – 2.394; p = 0.02; 2 studies, n = 91 participants; I^2 = 0%] (Naoumova et al., 2015; Bazargani et al., 2014) (Figure 3).

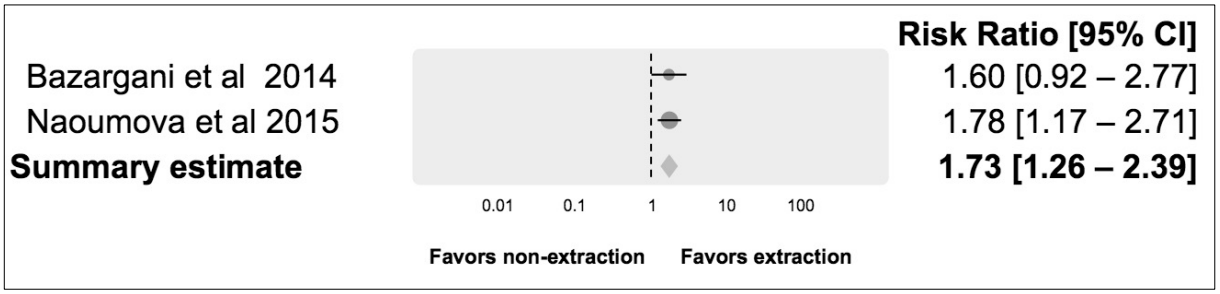

Figure 3. Successful eruption of palatally displaced permanent maxillary canine after extraction of the corresponding primary. [Observation beyond 12 months – low risk of bias studies]

Overall, the quality of evidence (confidence in the observed estimate), based on the data from the two low risk of bias studies (Naoumova et al., 2015; Bazargani et al., 2014) and assessed using the GRADE (Guyatt et al., 2011), was considered as low (Table 4.).

Table 4. Quality of available evidence on the effect of primary canine extraction in the successful eruption of the permanent.

Quality assessment						№ of Canines		Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Extraction**	**Control**	**Absolute (95% CI)**	
2	Not serious	Not serious	Serious[1]	Serious[2]	None	69	68	RR **1.713** (1.226 lower to 2.394 higher)***p*=0.002**	⊕⊕◯◯ **Low**

CI: Confidence interval; RR: Risk Ratio
[1]Results may not applicable in populations with different ethnical background.[2]The number of canines analyzed was limited.

5.5. Effect of primary canine extraction on root resoprtion of adjacent permanent teeth

Only one study (Naoumova et al., 2015) reported on the effect of primary canine extraction on root resorption of adjacent permanent teeth. The intervention did not result in a statistically significant benefit compared to no treatment [RR: 0.602; 95% CI: 0.277 – 1.308; p = 0.200 n = 67 participants]

The quality of evidence (confidence in the observed estimate) assessed using the GRADE (Guyatt et al., 2011), was considered as low (Table 5).

Table 5. Quality of available evidence on the effect of primary canine extraction on root resorption of adjacent permanent teeth.

Quality assessment						№ of Canines		Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Extraction**	**Control**	**Absolute (95% CI)**	
11	Not serious	Not serious	Serious[1]	Serious[2]	None	45	44	RR **0.602** (0.277 lower to 1.308 higher)***p*= 0.200**	⊕⊕◯◯ **Low**

CI: Confidence interval; RR: Risk Ratio
[1]Results may not applicable in populations with different ethnical background.[2] The number of canines analyzed was limited.

6. DISCUSSION

Palatal displacement of the maxillary permanent canine constitutes a fairly common condition with a prevalence exceeding that of buccal displacement (Rayne, 1969;Hitchin, 1956). This frequently results in impaction (Peck and Peck, 1994; Bishara, 1992 Ericson and Kurol, 1987), the management of which could be time and money consuming for both the patient and the health care provider and which might be accompanied by adverse effects on the neighboring dentition (Ericson and Kurol, 1988).

Interceptive management could contribute to shortening orthodontic treatment duration, simplification of orthodontic biomechanics, reducing treatment costs and avoidance of possible adverse effects associated with the subsequent impaction (Becker and Chaushu 2003). However, to date, the respective evidence had been inconclusive (Naoumova et al., 2011; Parkin et al., 2009).

6.1. Summary of available evidence

The records originally identified were reduced to five randomized clinical trials involving 329 patients with a total of 479 palatally displaced canines, followed for up to 48 months post-intervention (Naoumova et al., 2015; Bazargani et al., 2014; Baccetti et al., 2011; 2008; Leonardi et al., 2004). This small number of studies reflects on the scarcity of relevant research at the top of the widely accepted hierarchy of scientific evidence, although it is widely accepted that well-designed and properly executed RCTs provide the best evidence on the efficacy of health care interventions (Altman et al., 2001; Oxford Centre for Evidence-based Medicine, 2009).

The consequent lack of extensive data with high evidence based potential is rather surprising bearing in mind not only the prevalence of the problem (Ericson and Kurol, 1986; Moss, 1972; Thilander and Jakobson, 1968; Bass, 1967), but also the fact that the management of impacted permanent maxillary canines necessitates a comprehensive approach potentially requiring significant commitment and costs from the patient and healthcare provider (Parkin et al., 2012). This management may also involve risks and complications, if prognosis, treatment planning and the orthodontic biomechanics are not thoroughly considered (Becker, 2012). Thus, relevant, evidence-based information on possible interceptive management of the condition would be beneficial in supporting the care provided in these cases.

In general, based on the information provided from the two low-risk of bias studies eligible for inclusion in the present review, at the assessments conducted later than 12 months, the extraction of the primary maxillary canine resulted in more permanent canines successfully erupting compared to no treatment [RR: 1.713; 95% CI: 1.226 – 2.394] (Naoumova et al., 2015; Bazargani et al., 2014), thus repudiating the null hypothesis. Regarding root resoprtion of adjacent permanent teeth, no significant differences were noted (Naoumova et al., 2015), thus supporting the null hypothesis.

6.2. Quality of the available evidence

Overall, the quality of evidence assessed using the GRADE approach (Guyatt et al., 2011) was considered as low, indicating caution regarding the strength of the relevant recommendations.

The relevant data representing the top of the widely accepted hierarchy of scientific evidence was only available from two low risk of bias studies for the outcome of successful eruption and one low risk of bias study for the outcome of resorption of adjacent permanent teeth. These findings indicate the **scarcity of evidence-based information** on a frequently encountered problem with significant consequences for patients.

Nevertheless, exploratory quantitative data synthesis was attempted where applicable. The I^2 statistic obtained from the meta-analytic calculations suggested a relatively insignificant degree of heterogeneity, indicating that **inconsistency** during the GRADE assessment was not considered serious. In the context of the present review, heterogeneity can arise from diversity in terms of the characteristics of population groups, settings, procedures and follow-up and was incorporated into a justifiable random effects model.

The **risk of bias** was assessed by considering the various possible sources of bias for randomized controlled trials, and it was classified being at low risk of bias for the two studies included in the final analysis (Bazargani et al., 2014; Naoumova et al., 2015).

In the outcomes considered, the overall quality of evidence was downgraded because of problems related to **indirectness** of the evidence retrieved and problems related to **imprecision**. The results obtained were derived from populations with a particular ethnic background; hence even this limited set of data cannot be applied with certainty in clinical settings characterized by a different patient mix. Moreover, for varying reasons, the numbers of patients analyzed were limited, creating serious problems regarding the precision of the results obtained.

6.3. Strengths and limitations of the present review

The strengths of the present review include the methodology that followed well-established guidelines and the fact that it focused exclusively on randomized controlled trials, as it is widely accepted that well-designed and properly executed RCTs provide the best evidence with reduced risk of bias on the efficacy of health care interventions (Oxford Centre for Evidence-based Medicine, 2009; Altman et al., 2001). The available empirical evidence suggests that intervention effects in orthodontic research seem to differ in non-RCTs compared to RCTs (Papageorgiou et al., 2015). In addition, an attempt was made to summarize the quality of available evidence and thus provide an insight into the strength of the relevant recommendations based on the GRADE approach (Guyatt et al., 2011).

Moreover, the search strategy employed was exhaustive, covering electronic, manual, and gray literature material up to November 2015, and comprehensive, including every available randomized controlled trial comparing extraction of the primary canine to no treatment, irrespective of language, date and status of publication. Every effort to decrease bias in the methodology employed was made. Screening, verification of eligibility, abstraction of information, assessment of risk of bias and of the quality of evidence were performed in duplicate, and any disagreement was resolved by discussion or consultation with the thesis supervisor until a final consensus was achieved. Finally, the random effects model was employed during exploratory quantitative data synthesis to incorporate any observed heterogeneity (Lau et al., 1997).

There are also some limitations to the present review, mainly arising from the nature and characteristics of the data retrieved during the review process, which resulted in an assessment of the level of available evidence as, at best, low. The scarcity of relevant information from low risk of bias RCTs rendered quantitative syntheses exploratory until additional research becomes

available. However, current concepts support that data from as few as two studies can be combined, provided that these can be meaningfully pooled (Ryan, 2013), as all other summarizing techniques are less transparent and/or are less likely to be valid (Valentine et al., 2010). Furthermore, exploratory subgroup analyses and analyses for "small-study effects" and publication bias (Higgins and Green, 2011), could not be carried out even though they were incorporated as possibilities according to the review protocol.

Another limitation of the data retrieved in this study stems from the small number of patients finally analyzed resulting in subsequent problems regarding the precision of the effect estimates. It has to be acknowledged that the results of this review relate mostly to patients from the specific ethnic backgrounds of the patients under study. Bearing in mind the reported racial differences in the prevalence of the phenomenon of palatally displaced canines (Peck et al., 1996) the directness and generalizability of the available evidence may be diminished.

6.5.Recommendations for future research

Since canine impaction is a relatively common phenomenon, and its management potentially complex and challenging, the need for well-designed RCTs with better standardization and reporting over long follow-up period could be useful. It would also be beneficial to have future RCTs examining different groups from ethnic backgrounds other than Caucasian to find if any differences exist. Moreover, to more fully understanding the effect of these strategies, further investigation of the possible predictors of success; inclusion in the analyses of patient-reported outcomes like quality of life; analyses of costs and benefits in the socioeconomic context, as well as investigation of any possible adverse effects should be carried out. Finally, future scientific endeavors should take into consideration any possible additional

benefit from supplementary interventions, for which present knowledge of effectiveness remains inconclusive.

7. CONCLUSIONS

The present systematic review and meta-analysis highlight the fact that extraction of the primary canines in the mixed dentition may increase the probability of the subsequent successful eruption of palatally displaced canines in the long term. However, more low risk of bias studies, with sufficient sample sizes, are needed in order to enrich the available evidence, increase the precision of the observed effect estimates and unequivocally guide clinical decisions.

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Appendix I. Systematic review protocol used for registration with international prospective register of systematic reviews (PROSPERO).

Ameirah Alyammahi, Eleftherios Kaklamanos, Athanasios Athanasiou. Effectiveness of interceptive orthodontic treatment for palatally displaced permanent canines: a systematic review and meta-analysis. PROSPERO 2015:CRD42015029130 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015029130

Review question(s)

The aim of this study is to compare the effectiveness of the various approaches used in an interceptive orthodontic manner in mixed dentition for preventing impaction of patalally displaced permanent canines.

Searches

Comprehensive electronic database searches will be undertaken (up to November 2015) without language restriction in the following databases:

MEDLINE via PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, Scopus, Web of Science, LILACS, IndMed, Scielo, Arab World Research Source and Deutsche Zentralbibliotek fuer Medizin. Unpublished literature will be accessed electronically using Google Scholar (https://scholar.google.com), ClinicalTrials.gov (http://clinicaltrials.gov), International Standard Randomised Controlled Trial Number (ISRCTN) registry (http://www.isrctn.com) and OpenGrey (http://www.opengrey.eu).

In addition, ProQuest Dissertation and Theses Global database will be searched. Efforts will be made to obtain conference proceedings and abstracts where possible. Authors will be contacted

to identify unpublished or ongoing clinical trials and to clarify methodology and data as necessary. Reference lists of included studies will be screened for additional relevant research.

Types of study to be included

The trials to be included should be RCTs.

Condition or domain being studied

Interceptive orthodontic treatment of palatally displaced permanent canines.

Participants/ population

Patients in mixed dentition with unilateral or bilateral palatally displaced permanent canines.

Intervention(s), exposure(s)

Various interceptive orthodontic approaches (such as, but not limited to extraction of primary teeth, extraction of primary teeth plus headgear, extraction of primary teeth plus transpalatal arch, headgear, palatal expansion).

Comparator(s)/ control

No treatment or alternative interceptive approaches.

Outcome(s)

Primary outcomes

Percentage of successful outcomes.

Secondary outcomes

Side effects, economic evaluation data, patient reported outcomes (pain, patient satisfaction etc.).

Data extraction, (selection and coding)

All assessments including titles and/or abstract screening, full text evaluation, and extraction of data will be performed independently and in duplicate by two investigators (AA and EGK). The investigators will not be blinded to the authors or the results of the research. Disagreements will be resolved by discussion and consultation with a third author where necessary (AEA).

Risk of bias (quality) assessment

Assessment of risk of bias will be performed independently and in duplicate by two investigators (AA and EGK) using the Cochrane Collaboration risk of bias tool that considers seven domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of assessors; incomplete outcome data; selective reporting of outcomes; and other potential sources of bias.

Each domain will receive a rating of low, high or unclear risk of bias (indicating either lack of sufficient information to make a judgment or uncertainty over the risk of bias). Studies will be finally grouped into the following categories:

• low risk of bias (plausible bias unlikely to seriously alter the results): if all key domains of the study are at low risk of bias,

• unclear risk of bias (bias that raises some doubt about the results): if one or more key domains of the study are unclear, and,

• high risk of bias (bias that seriously weakens confidence in the results): if one or more key domains are at high risk of bias.

Disagreements will be resolved by discussion and consultation with a third author where necessary (AEA).

Strategy for data synthesis

Where studies have used the same type of intervention, we will pool the results using a random-effects meta-analysis analysis in view of the likely variation in population groups and settings. Depending on the variation of the indices used to quantify primary or secondary outcomes we will use weighted or standardized mean differences for continuous outcomes and risk ratios for binary outcomes, and calculate 95% confidence intervals and two sided p values for each outcome. Heterogeneity will be assessed using both the Chi-squared test and the I-squared statistic. If an adequate number of trials are identified, we will carry out analyses for "small-study effects" and publication bias.

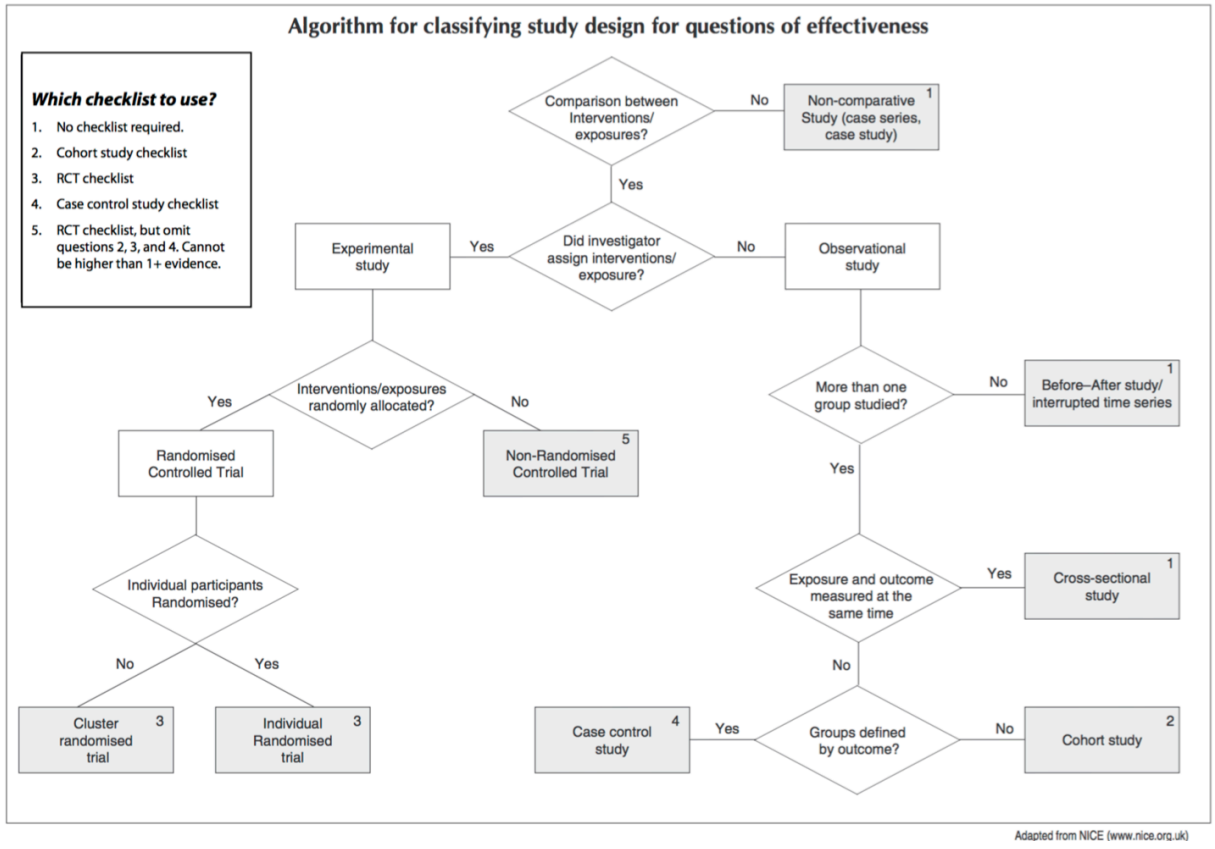
Analysis of subgroups or subsets

If the necessary data are available, subgroup analysis will be performed for gender and displaced canine position.

Dissemination plans

Peer-reviewed orthodontic journal.

Appendix II. Scottish Intercollegiate Guidelines Network (SIGN) algorithm for classifying study design for questions of effectiveness



Appendix III. Strategy for database search (up to November 2015).

Database	Search strategy	Hits
General Sources		
MEDLINE via PubMed http://www.ncbi.nlm.nih.gov/pubmed	((((((((((randomized controlled trial[pt]) OR controlled clinical trial[pt]) OR randomized[tiab]) OR placebo[tiab]) OR drug therapy[sh]) OR randomly[tiab]) OR trial[tiab]) OR groups[tiab])) NOT ((animals[mh] NOT humans[mh]))))) AND ((canine*) OR cuspid*)) AND (((((impact*) OR unerupt*) OR displace*) OR ectop*) OR malpos*)	**322**
Cochrane Central Register of Controlled Trials http://onlinelibrary.wiley.com/cochranelibrary	(orthodon*) AND (canine* OR cuspid*) AND (impact* OR unerupt* OR displace* OR ectop* OR malpos*) in Title, Abstract, Keywords in Trials'	**28**
Cochrane Database of Systematic Reviews http://0-ovidsp.tx.ovid.com.amclb.iii.com	orthodon* {Including Limited Related Terms}	**41**
Scopus https://www.scopus.com/	(TITLE-ABS-KEY(orthodon*)) AND ((TITLE-ABS-KEY(canine*) OR TITLE-ABS-KEY(cuspid*))) AND ((TITLE-ABS-KEY(impact*) OR TITLE-ABS-KEY(unerupt*) OR TITLE-ABS-KEY(displace*) OR TITLE-ABS-KEY(ectop*) OR TITLE-ABS-KEY(malpos*))) AND (LIMIT-TO(SUBJAREA,"DENT"))	**782**
Web of Science™ Core Collection http://apps.webofknowledge.com/	TOPIC: ((“randomized controlled trial” OR “controlled clinical trial” OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups) AND (canine* OR cuspid*) AND (impact* OR unerupt* OR displace* OR ectop* OR malpos*))Refined by: WEB OF SCIENCE CATEGORIES: (DENTISTRY ORAL SURGERY MEDICINE)Timespan: All years. Indexes: SCI-EXPANDED, SSCI, AandHCI, CPCI-S, CPCI-SSH.	**213**

Appendix III. Strategy for database search [up to October 2015]. [Continued]

Database	Search strategy	Hits
Regional sources		
LILACS http://lilacs.bvsalud.org/en/	orthodon$ Type of study: Controlled clinical trial	**121**
IndMed http://indmed.nic.in/indmed.html	(orthodontic OR orthodontics) AND (canine OR canines OR cuspid OR cuspids)	**25**
Scielo http://www.scielo.org/php/index.php?lang=en	orthodon* AND (canine* OR cuspid*) AND (impact* OR unerupt* OR displace* OR ectop* OR malpos*)	**20**
Arab World Research Source http://0-web.a.ebscohost.com.amclb.iii.com	orthodon*	**40**
Deutsche Zentralbibliotekfuer Medizin https://www.livivo.de	orthodon* AND (canine* OR cuspid*) AND (impact* OR unerupt* OR displace* OR ectop* OR malpos*) in Catalogue ZB MED	**53**
Grey literature sources		
Google Scholar https://scholar.google.com	allintitle: orthodontic randomized Excluding patents and citations	**124**
ClinicalTrials.gov http://clinicaltrials.gov/	(orthodontic OR orthodontics) AND (canine OR canines OR cuspid OR cuspids)	**21**
ISRCTN registry http://www.isrctn.com	orthodontic OR orthodontics) AND (canine OR canines OR cuspid OR cuspids)	**9**
OpenGrey http://www.opengrey.eu/	orthodon* AND (canine* OR cuspid*) AND (impact* OR unerupt* OR displace* OR ectop* OR malpos*)	**14**
ProQuest Dissertations and Theses Global http://search.proquest.com	ti((canine* OR cuspid) AND (impact* OR displace* OR ectop* OR malpos*))	**19**

Appendix IV. Details of risk of bias assessment [Domains examined: 1: Random sequence generation; 2: Allocation concealment; 3: Blinding of participants and personnel; 4: Blinding of outcome assessment; 5: Incomplete outcome data; 6: Selective outcome reporting; 7: Other potential threats to validity]

Study	Rating		Reasons for rating
Baccetti *et al.* (2008)	**1.**	Unclear	Insufficient information about the sequence generation process. ["…All PDC subjects were assigned randomly…]
	2.	High	No information about the allocation concealment process. The review authors believe that probably no measures were taken and that there might possibly be a high risk of bias regarding this domain owing to general deficiency in the reporting and possibly conduct of the study.
	3.	Low	Blinding of the participants and personnel was not possible. However, the review authors believe that the outcome is not likely to be influenced by lack of blinding.
	4.	Unclear	No statement that the investigator was blinded with regards to assessing successful eruption of the permanent canine. However, the review authors believe that therisk of bias regarding is unclear owing to general deficiency in the reporting of the study.
	5.	Unclear	Dropouts are described and explained, but not to an adequate extent.
	6.	High	Important outcomes are not adequately reported.
	7.	Unclear	Insufficient information to assess whether an important risk of bias exists
Baccetti *et al.* (2011)	**1.**	Unclear	Insufficient information about the sequence generation process. ["…All PDC subjects were assigned randomly…]
	2.	High	No information about the allocation concealment process. The review authors believe that probably no measures were taken and that there might possibly be a high risk of bias regarding this domain owing to general deficiency in the reporting and possibly conduct of the study.
	3.	Low	Blinding of the participants and personnel was not possible. However, the review authors believe that the outcome is not likely to be influenced by lack of blinding.
	4.	Unclear	No statement that the investigator was blinded with regards to assessing successful eruption of the permanent canine. However, the review authors believe that therisk of bias regarding is unclear owing to general deficiency in the reporting of the study.
	5.	Unclear	Dropouts are described and explained, but not in adequate extent.
	6.	High	Important outcomes are not adequately reported.
	7.	Unclear	Insufficient information to assess whether an important risk of bias exists

Appendix IV. Details of risk of bias assessment [Domains examined: 1: Random sequence generation; 2: Allocation concealment; 3: Blinding of participants and personnel; 4: Blinding of outcome assessment; 5: Incomplete outcome data; 6: Selective outcome reporting; 7: Other potential threats to validity] [Continued]

Study	Rating	Reasons for rating
Bazargani *et al.* (2014)	**1.** Low	The exact method of randomization is mentioned. ["...A computer-generated randomization list was created using SPSS software (version 15.0, SPSS, Chicago, Ill) and stored with a research secretary at the Postgraduate Dental Education Center...."]
	2. Low	The exact method used to conceal allocation is mentioned. ["...Each time a patient gave consent, the secretary was contacted by e-mail and gave the information about which deciduous canine was to be extracted...."]
	3. Low	Blinding of the participants and personnel was not possible. However, the review authors believe that the outcome is not likely to be influenced by lack of blinding.
	4. Low	No statement that the investigator was blinded with regards to assessing successful eruption of the permanent canine. However, the review authors believe that the outcome is not likely to be influenced by lack of blinding.
	5. Low	No dropouts are occurred.
	6. Low	All important outcomes are adequately reported.
	7. Low	The study appears to be free of other sources of bias.
Leonardi et al. (2004)	**1.** Unclear	Insufficient information about the sequence generation process. ["…they were assigned randomly…]
	2. High	No information about the allocation concealment process. The review authors believe that probably no measures were taken and that there might possibly be a high risk of bias regarding this domain owing to general deficiency in the reporting and possibly conduct of the study.
	3. Low	Blinding of the participants and personnel was not possible. However, the review authors believe that the outcome is not likely to be influenced by lack of blinding.
	4. Unclear	No statement that the investigator was blinded with regards to assessing successful eruption of the permanent canine. However, the review authors believe that therisk of bias regarding is unclear owing to general deficiency in the reporting of the study.
	5. Unclear	Dropouts are described and explained, but not in adequate extent.
	6. High	Important outcomes are not adequately reported.
	7. Unclear	Insufficient information to assess whether an important risk of bias exists

Appendix IV. Details of risk of bias assessment [Domains examined: 1: Random sequence generation; 2: Allocation concealment; 3: Blinding of participants and personnel; 4: Blinding of outcome assessment; 5: Incomplete outcome data; 6: Selective outcome reporting; 7: Other potential threats to validity] [Continued]

Study	Rating		Reasons for rating
Naoumova *et al.* (2015)	**1.**	Low	The exact method of randomization is mentioned. ["...For randomization, the permuted block randomization method was used..."]
	2.	Low	The exact method used to conceal allocation is mentioned. ["...allocations were concealed in sequentially numbered, sealed opaque envelopes opened by a dental nurse after the written consent was obtained…."]
	3.	Low	Blinding of the participants and personnel was not possible. However, the review authors believe that the outcome is not likely to be influenced by lack of blinding.
	4.	Low	No statement that the investigator was blinded with regards to assessing successful eruption of the permanent canine. However, the review authors believe that the outcome is not likely to be influenced by lack of blinding.
	5.	Low	Deviations from the randomized protocol are described and explained. Intention-to-treat analysis was used.
	6.	Low	All important outcomes are adequately reported.
	7.	Low	The study appears to be free of other sources of bias.