Clinical Practice Guideline on Treatment of Patients with Clefts of the Lip and Palate

INITIATIVE
Netherlands Association for Plastic Surgery (NVPC)

IN COLLABORATION WITH
Netherlands Association for Ear, Nose and Throat Surgery and Head and Neck Surgery (NVKNO)
Netherlands Association of Orthodontists (NVvO)
Netherlands Association of Oral Diseases and Maxillofacial Surgery (NVMKA)
Netherlands Association for Dentistry (NVT)
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Colophon

CLINICAL PRACTICE GUIDELINE ON TREATMENT OF PATIENTS WITH CLEFTS OF THE LIP AND PALATE

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Summary

The text presented below is a summary of the most important recommendations from the multi-disciplinary, evidence-based Clinical Practice Guideline on Treatment of Patients with clefts of the lip and palate.

This clinical practice guideline was primarily written for and is applicable to the treatment of patients with an isolated cleft of the lip and palate without further anomalies. Therefore, this was the starting point for the evidence synthesis on which this guideline is based. Many of these recommendations will also apply to patients with clefts of the lip and palate in combination with other anomalies - whether they form part of a syndrome or not - though the recommendations may need to be adjusted per patient according to the disease or individual situation.

Readers of this summary should refer to the complete guideline for further information. This summary of recommendations cannot be viewed in isolation. The circumstances and preferences of the patient should be taken into consideration during the medical decision-making process. Treatments and procedures relating to the individual patient are based on communication between patient, physician and other healthcare providers.

Chapter 3 Genetic diagnosis of patients with clefts of the lip and palate

Timing and indication for genetic testing

Patients with a cleft lip with or without a cleft alveolus, a cleft lip and palate or a cleft palate should be referred to an academic Medical Genetics department (in the Netherlands) or similar tertiary centre, preferably before the first operation.

Speed up the referral in the case of growth and feeding problems, associated abnormalities, developmental delay, specific suspicion of a syndrome diagnosis or chromosomal abnormality.

For an infant with only a cleft palate, first perform a single nucleotide polymorphism (SNP) array before the first operation and then consider additional genetic testing in the form of a gene panel or Whole Exome Sequencing. The recommendation for a child with a cleft lip with or without a cleft alveolus, or a cleft lip and palate is to consider the option of additional genetic testing and discuss this with the parents.

Optimum strategy for genetic diagnosis of patients with clefts of the lip and palate

If the decision is made to perform additional genetic testing on patients with non-syndromic clefts of the lip and palate, the recommendation is to perform Whole Exome Sequencing for Single Nucleotide Variations in gene panels in combination with genome-wide Copy Number Variations testing.

Accessory conditions for genetic testing

Always involve a clinical geneticist if genetic testing is performed on a child with clefts of the lip and palate.

Ensure good collaboration between the clinical geneticist and the laboratory specialist. The laboratory specialist must be well-informed about the patient's symptoms and the family history.

Parents should be involved in the decision-making process for genetic testing and should be thoroughly informed about the nature of the testing and the possible results. Special attention should be paid to the possible risk of a syndrome diagnosis that could have consequences in later life and the potential for unclear results or coincidental findings.

Perform an annual evaluation of the results obtained for genetic tests performed within the laboratory, to gain insight into the yield of the diagnostic tests performed.

Chapter 4 Feeding of patients with clefts of the lip and palate

Involve the parents in the decision-making process of finding a suitable feeding method. The aim is to make the drinking process comfortable for both parent and child.

These recommendations apply both to newborns and in the postoperative phase

Start oral feeding as soon as possible in both the postnatal and postoperative phase. Tube feeding (as only feeding method) is not recommended.

Ensure that a speech therapist is present in each cleft team, with knowledge about and experience in the normal development of drinking and eating and the effect of clefts of the lip and palate on these processes. The speech therapist of the cleft team should participate in the speech therapy working group (special interest group) of the NVSCA (in the Netherlands) or similar national cleft society.

In consultation with the parents, choose a suitable, individualised method of administering food to a baby with a cleft lip, cleft lip and alveolar arch, and/or cleft palate. The following factors should be taken into consideration:

- the various feeding methods;
- breast;
- bottles and teats;
- (feeding) postures.

Quality parameters are: growth and height of the child, swallowing air, choking, nasal regurgitation, intake quantity, flow, feeding time and confidence of the parents in good guidance. The wellbeing of the child and the quality of the feeding session are paramount.

Take the capabilities of the parents into consideration during the prenatal preparations and in the support offered to parents regarding potential feeding problems. Where possible, opt for feeding via oral intake. The choice of formula or breast milk is up to the parents.

Chapter 5 Lip and palate closure in patients with clefts of the lip and palate

Module 1: Timing of the lip and palate closure

Perform surgical closure of the lip during the first 6 months of life.

Define a preferred approach within the cleft team for lip closure and palate closure, in order to advise parents in the decision-making process, but also give parents the opportunity to discuss a different approach.

- Check prior to the operation whether the Eurocleft checklist is complete and perform intra-oral X-rays during the procedure if necessary and document any abnormalities in the surgical report.
- Close only the soft palate during the first year of life and close the hard palate at a later stage if the aim is to achieve optimum growth of the maxilla.
- Close the hard palate and the soft palate during the first year of life if the aim is to achieve optimum speech development.

Module 2: Technique for lip and palate closure

During palate closure, move the palate musculature to a more anatomical position (connection placed in the medial line and more posterior) to achieve a better result for speech, for example a Furlow or Langenbeck technique with transposition of the muscles.

Do not use a Furlow extension-plasty in the case of a wide palate cleft, due to the increased risk of fistula formation.

Preferably do not use the Wardill-Kilner pushback technique.

Use everting (suture) techniques to achieve improved wound margin approximation.

Use a (combination of) technique(s) for palate closure that the surgeon is most experienced in, so that the risk of complications is kept to a minimum.

Use a (combination of) technique(s) for lip closure that the surgeon is most experienced in, to ensure an optimum result with regard to function and aesthetics while the risk of complications is kept to a minimum.

Chapter 6 Hearing problems in patients with clefts of the lip and palate

Ask for the results of the neonatal hearing screening for each child with a cleft (lip, alveolar arch alveolar archand) palate.

Check the hearing of children with a cleft (lip, alveolar arch alveolar arch and) palate thoroughly. The recommendation is to perform periodic testing in an audiological centre up to the age of 3-4 years, followed by testing by the ENT physician if indicated. These examinations should be tailored to the surgical protocol.

Check the hearing of children with a cleft (lip, alveolar arch and) palate at least once post-operatively after insertion of tympanostomy tubes, in order to rule out perceptive hearing loss (see Guideline Otitis media with effusion NVKNO, 2012).

Insert tympanostomy tubes in children with a cleft (lip, alveolar arch and) palate only if indicated (see Guideline Otitis media with effusion) and take the audiological findings and speech-language results into consideration (and not only the presence or absence of otitis media with effusion).

Chapter 7 Hypernasality in patients with clefts of the lip and palate

Module 1: Diagnosis of hypernasality

The diagnosis of velopharyngeal insufficiency should be made in a multi-disciplinary setting (at least a surgeon, ENT physician and speech therapist).

Following primary palate closure, the diagnosis of velopharyngeal insufficiency should only be made after six months of specialised speech therapy with inadequate treatment result, on condition that the soft palate appears to be sufficiently long and mobile (during intra-oral inspection) and the child has been able to follow instructions adequately.

The speech therapy examination (Meijer, 2003) to diagnose velopharyngeal insufficiency should be performed by a speech therapist who participates in the national NVSCA guideline task force for speech therapists specialising in clefts of the lip and palate.

To make the imaging studies as complete as possible, preferably also perform an oral inspection, acoustic nasometry, mirror tests and nasal endoscopy to confirm the diagnosis of velopharyngeal insufficiency.

Perform nasal endoscopy if the chances of success for the child are high (usually from three-and-a-half years).

Perform video fluoroscopy as an alternative to confirm the diagnosis of velopharyngeal insufficiency (for example if nasal endoscopy is not successful) or to provide additional diagnostic information about the velum function.

The speech therapist should preferably be present during nasal endoscopy and video fluoroscopy.

Make a photo or video recording of the nasal endoscopy.

One year after the speech-improving surgery, repeat all the examinations that were performed pre-operatively, except possibly the nasal endoscopy/video fluoroscopy, so that the effect of the speech-improving surgery can be determined as objectively as possible.

One year after the speech-improving surgery, repeat the nasal endoscopy/video fluoroscopy if examinations performed after 6 months of specialised speech therapy still indicate the presence of velopharyngeal insufficiency in combination with decreased understandability

Do not perform an MRI as a standard part of the diagnostic process for determining velopharyngeal insufficiency.

Module 2: Treatment of hypernasality

Make a choice for a specific surgical technique based on preoperative speech therapy examination combined with an examination such as nasal endoscopy and/or video fluoroscopy (see module Diagnosis of hypernasality).

Consider an intravelar palatoplasty with repositioning of the palate muscles before performing a pharyngoplasty if the patient has persistent velopharyngeal dysfunction despite previously closed palate.

In the case of persistent velopharyngeal insufficiency despite renewed repositioning of the palate muscles, consider a pharyngoplasty that is based on renewed diagnostic tests such as nasal endoscopy and/or video fluoroscopy.

For a submucous cleft palate, consider a simple palatoplasty over a combined operation consisting of a palatoplasty with pharyngoplasty.

Only use fat injection in the context of a scientific study.

Chapter 8 Bone grafting procedure in patients with clefts of the lip and palate

Module 1: Timing of the bone grafting procedure

Preferably close the cleft in the alveolar arch by means of an early secondary bone grafting procedure.

Base the timing for the bone grafting procedure on the position and the stage of root formation (½ - 2/3) of the cuspid tooth on the cleft side. The presence of a lateral incisor and the moment of eruption of this incisor can bring the timing forward. For certain indications, the position of the central incisor can be of importance.

Decide on the timing of the bone grafting procedure in close consultation with the treating orthodontist.

Consider the tertiary bone grafting procedure only in cases where no (secondary) bone grafting procedure was performed or when insufficient bone is present in the alveolar arch at the site of the cleft for - for example - an implant at a later age. The tertiary bone grafting procedure can also be performed in adulthood.

Module 2: Technique of the bone grafting procedure

Reconstruct the alveolar cleft (the bone grafting procedure) using bone from the iliac crest or the chin (possibly supplemented by a bone substitute).

If a larger volume is required, use bone from the iliac crest, or opt for bone from the chin supplemented by a bone substitute.

Based on the literature, it is not possible to make a recommendation for the choice of the bone substitute to be used.

The use of only a bone substitute for the reconstruction of an alveolar cleft, in other words without an autologous bone transplant, should only be performed in a research context and is as yet not suitable for use in general practice.

Chapter 9 Orthodontic treatment in patients with clefts of the lip and palate

Module 1 : Nasoalveolar moulding

Be reticent about the use of NAM in babies with a complete unilateral or bilateral cleft lip, alveolar arch and palate and only apply NAM in preparation of or in the context of a clinical trial.

Module 2: Maxillary protraction

In general, never apply ventral traction to the maxilla using a face mask on a dentally anchored orthodontic device in children with clefts of the lip and palate with deficient forward growth of the maxilla.

Consider ventral traction with a face mask on a dentally anchored orthodontic device in the case of:

1) slight underdevelopment of the maxilla, or;
2) if the patient and/or parents do not want surgical treatment, or;
3) if the patient has a number of favourable characteristics. The following can serve as a guideline:
   - patient aged between five and nine years;
   - mild skeletal defect ANB < -1^0 with SNB angle normal for age;
   - minimal aesthetic abnormalities of the face;
   - convergent growth pattern with low bottom half of face;
   - AP displacement of the mandible in habitual occlusion (negative overjet);
   - symmetrical condylar growth;
   - no family history of hyperplasia of the mandible;
   - good cooperation in the orthodontic treatment is expected.

If ventral traction with a face mask on a dentally anchored orthodontic device is applied:

Inform the patient and parents that the effect can be limited and that it will only become clear at the end of the growth period whether an osteotomy of the maxilla will be necessary after all.

Module 3: Retention

Use the same form of retention of the position of the teeth as for a patient without clefts of the lip and palate.

In addition, for a patient with a cleft lip, alveolar arch and palate, use a removable orthodontic retention device for the retention of the width of the upper dental arch that is worn at night for the rest of the patient's life.

Check the retention device at least once every two years.

Module 4: Osteoomy versus distractionosteogenesis

Consider a classic Le Fort 1 - either alone or in combination with a setback osteotomy of the mandible - in cleft patients with a sagittal discrepancy between the upper and lower jaw, that is so large that it can no longer be resolved by orthodontic treatment alone. Consider a distraction osteogenesis only in the case of large sagittal discrepancies. Both treatments have specific advantages and disadvantages, which can determine the choice per individual patient and per surgeon.

Chapter 10 Rhinoplasty in patients with clefts of the lip and palate

During primary lip closure, pay attention to the primary correction of the nostril and the position of the caudal septum and columella of the nose.

Preferably delay secondary surgery of the nose for clefts of the lip and palate until growth of the mid-face has been completed and any orthognathic surgery has been completed, in order to limit the total number of procedures.

Chapter 11 Psychosocial guidance for patients with clefts of the lip and palate

Screen the child with clefts of the lip and palate and the parents for psychosocial problems after birth, at the age of 2 to 3 years, 5 years, 10 to 11 years and 17 years.

During this contact, screening should be performed for child factors (wellbeing, possible learning problems, fear of medical procedures and acceptance problems) and family/parent factors (acceptance problems, grief and parenting style).

In addition to conversations, all cleft teams should use the same validated instrument (SDQ, GVL, conversation with parent and/or child).

Based on the results of the screening, offer the parents and child further diagnostic tests or treatment if necessary.

Appoint a behavioural expert with post-academic training (clinical psychologist or special education generalist) and a social worker for less complex problems in each cleft team for the diagnosis of psychosocial problems of the child and family and for the treatment of complex psychosocial problems.

Chapter 13 Dentistry for patients with clefts of the lip and palate

For the cleft team

Include a (paediatric) dentist with an affinity for paediatric dentistry in the cleft team.

An initial consultation with the dentist from the cleft team should take place as soon as

the first deciduous elements have erupted (six to twelve months).

Within the cleft team, check the teeth of children with clefts of the lip and palate at the age of 5 years. This should take place in addition to the periodic monitoring by the general dentist.

Inform the primary care dentist about the treatment pathway implemented by the cleft team and discuss who will provide the dental care.

For the general dentist

Contact the cleft team when treating a child with clefts of the lip and palate in your practice and offer opportunities for consultation with the cleft team when you deem this necessary.

Check the teeth of children with clefts of the lip and palate at least every 6 months.

Introduction

Reason for creating the guideline

Clefts of the lip and palate are one of the most commonly occurring congenital abnormalities in the Netherlands, with a prevalence of approximately 16.6 per 10,000 live births per year (Luijsterburg and Vermeij-Keers, 2011). Clefts of the lip and palate differs from many other congenital defects due to the fact that the cleft is treatable, the treatment is generally finite and children with an isolated cleft generally have the same social chances and opportunities as children without a cleft.

Following the example set by the United Kingdom (UK) and the Scandinavian countries, the care of orofacial clefts in the Netherlands is performed by so-called multi-disciplinary cleft teams. A cleft team generally consists of all the departments of a hospital or institute that are required to provide adequate treatment for a child with clefts of the lip and palate.

At the moment, the care offered by a cleft team usually stretches from antenatal care or care at birth to the age of approximately 22 years. The endpoint of the treatment is determined by the end of the child's growth. Teams are expected to offer individualised care until the treatment, including possible osteotomies etc., has been completed. For adults with late problems resulting from clefts of the lip and palate, there is currently no structured (multidisciplinary) care comparable to the care offered to children with clefts of the lip and palate available in the Netherlands.

The build-up to the development of this clinical practice guideline took place at the start of the development of the clinical practice guideline "Counselling after prenatal detection of clefts of the lip and palate" in 2009. When this guideline was delivered in 2011, it was decided that a follow-up guideline for the postnatal care pathway for orofacial clefts was not only logical, but also highly desirable. The prenatal guideline project demonstrated that the significant practice variation between cleft teams in the Netherlands in the treatment of patients with clefts of the lip and palate was considered confusing and judged as undesirable by patients, parents and healthcare professionals.

Patients and parents do understand that some practice variation will be necessary to give each patient the individualized treatment he or she needs. Patients and parents however do not understand the often unexplained differences in treatment protocols between the Dutch cleft teams in general. Patients and parents find these differences frustrating, because they cannot judge which protocol is preferable or the best for them or their child. They also find it unpleasant that it appears the cleft teams (in the Netherlands) by way of their protocols are in competition with each other. For the patient, it is very important that the professionals should work together to determine what they see as the scientific foundation for their medical actions and define the standard of care the patient and parents may expect.

In summary, both patients and parents would like to see the existing and in their view confusing practice variation in treatment between the cleft teams in the Netherlands

clarified (based on evidence) and - if possible - reduced if the evidence gives reason to do so. In addition, there is a desire to improve on the provision of reliable and independent information about treatment methods.

Objective of the guideline

The objective of this clinical practice guideline is to optimise the care given to patients with clefts of the lip and palate in the Netherlands, substantiated by scientific knowledge from research where possible. This optimisation also includes obtaining insight into the cause of the existing practice variation between the various cleft teams and distinguishing between desirable and undesirable practice variation in the treatment of patients with clefts of the lip and palate. This will result in proposals for a more uniform treatment insofar as this can be scientifically substantiated.

Specific attention will be paid to the following topics:

1. reducing undesirable/unfounded practice variation in the working method and treatment protocols of the Dutch cleft teams, without hampering custom work, innovation or research;
2. making objective / evidence-based information about the treatment of orofacial clefts available and accessible to healthcare providers, patients, parents and other parties;
3. determine to what extent the existing organisation of care needs to change in order to meet the requirements regarding “state of the art” treatment of a child or adult with clefts of the lip and palate and the follow-up to this treatment.

In this manner, the guideline offers a tool to create more uniform care in the field of the postnatal treatment of a child with clefts of the lip and palate and the implementation of this care in the Netherlands.

National registration of patients with clefts of the lip and palate

The Dutch Association for Cleft Palate and Craniofacial Anomalies (NVSCA) has implemented a national anonymous registration process to gain in insight into the number of patients with clefts of the lip and palate who are treated by the Dutch cleft teams. As of 01-01-1997, all patients born in the Netherlands who have not undergone surgery and all adopted children with clefts of the lip and palate - with or without additional congenital defects - who have not had surgery, are included in this registration. As of 01-01-2010, adopted children who have already undergone surgery in their country of origin are also registered. The registration is completely digital.

The NVSCA registration form consists of three parts: a general section, a section in which all the sub-phenotypes of orofacial clefts and other craniofacial abnormalities can be scored based on the abnormal anatomy and morphology, and a section in which the additional abnormalities can be described per organ system. The three parts of the registration form have been validated separately (Rozendaal, 2010, 2012a, 2012b). The NVSCA registration system corresponds largely to the LASHAL documentation and coding system proposed by Kriens (1989). Each year, the NVSCA publishes a general annual report on orofacial clefts, which is sent to all NVSCA members and the team

secretarial offices and each team receives an annual report of the patients that they have registered. More information is available online via www.schisis.nl or www.schisis-cranio.nl.

Delineation of the guideline

The guideline focuses primarily on the treatment of patients with isolated clefts of the lip and palate, including the following subtypes: a cleft lip with or without a cleft alveolus (cheilognathoschisis; cheiloschisis; CL±A), cleft lip, alveolus and palate (cheilognathopalatoschisis; CLAP) and a cleft palate (palatoschisis; CP), without other anomalies in the age range from 0 to 22 years. The literature that was consulted for this guideline was limited to these categories of cleft. These abbreviations are commonly used abbreviations in the English scientific literature.

On average, the last 18 registration years in the Netherlands have seen n = 368 new unoperated patients registered per year, of which 35 were (un)operated adopted children. These patients can be divided as follows across the three categories of orofacial cleft: cleft lip with or without cleft alveolus (25%), cleft lip, alveolus and palate (40%) and cleft palate (35%).

Many of these recommendations will also apply to patients with clefts of the lip and palate in combination with other anomalies - whether they form part of a syndrome or not - though the recommendations may need to be adjusted per patient according to the underlying disease or situation.

A wide range of interventions and treatments related to clefts of the lip and palate take place in the period from birth to the age of 22 years. Most of these treatments and interventions are potentially interesting subjects for a guideline. The guideline task force was forced to prioritise and to select in order to fit the amount of work within the available financial resources. The following factors were taken into consideration in the selection of the topics for this guideline:

a. the wishes from the patients' perspective regarding the need for insight into and - where possible - reduction of undesirable practice variation between cleft teams (for example, variations in feeding, the time of closure of the soft palate or the best technique to close the cleft in the alveolar arch);
b. the wishes from the treating physician's perspective regarding variations in treatment protocols; particularly creating insight into the differences between teams leads to an improved understanding;
c. relevance of problems for children and parents (for example, feeding as a primary necessity of life after birth); and
d. rapid technological developments that need to be acted upon (for example, clinical genetic diagnostics).

This process led to the following list of topics that will be discussed in this guideline: genetic diagnostics, feeding, lip and palate closure (timing and technique), hearing problems, hypernasality (diagnostics and treatment), bone grafting procedure (timing and technique), orthodontics (ventral traction and retention), nose corrections, psychosocial care, dentistry, nasoalveolar molding (NAM) and surgical corrections of the maxilla (orthognathic surgery). In addition, a chapter has been included in the guideline

about the organisation of care for orofacial clefts in the Netherlands. These topics form the basis of the various chapters in this guideline. The guideline is not intended to be comprehensive.

Terms and definitions

A point for discussion in the development of this clinical practice guideline and the formulation of the recommendations was the fact that the various (surgical) interventions can be performed by various disciplines. After all, professionals from several disciplines form the multi-disciplinary cleft team, such as Plastic Surgery, Maxillofacial Surgery and Ear, Nose & Throat Surgery. The distribution of tasks differs per team and depends partially on local customs, training and education. In the United Kingdom, a special training program with a separate certificate has been created to specialise as a “Cleft Surgeon”. This training does not exist in the Netherlands and – as far we are aware - the rest of Europe. The term “Cleft Surgeon” is not a fixed or broadly accepted definition in the Netherlands. Therefore, it is not possible to translate the term “Cleft Surgeon” directly to “Schisischirurg” in the Dutch version of this guideline.
This effectively means that whenever the text refers to - for example - a plastic surgeon for the closure of the lip, the procedure can also be performed by a maxillofacial surgeon or an ENT surgeon, depending on the competencies, training, education, local customs, etc. The guideline task force assumes that the cleft teams will determine for themselves which doctors within the team are skilled and authorised to perform the various procedures. For reasons of practicality and clarity, we have opted to mention in the text and recommendations the specialist who commonly performs a specific procedure in the Netherlands at this moment.

Intended users of the guideline

The guideline is primarily intended for all healthcare professionals who are involved in caring for a child with clefts of the lip and palate: general practitioners, midwives, gynaecologists, paediatricians, ENT physicians, plastic surgeons, maxillofacial surgeons, orthodontists, clinical geneticists, specialised nurses, speech therapists, (paediatric) dentists, medical psychologists, remedial educationalists and social workers. The secondary target group involves patients, parents and their surroundings.

Literature

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Chapter 2 Methodology for guideline development

AGREE II

This guideline was drafted in accordance with the requirements in the report "Richtlijnen 2.0" from the Guidelines Advisory Committee of the Quality Council of the Dutch Association of Medical Specialists. This report is based on the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II) (www.agreetrust.org), which is an internationally widely accepted instrument for the assessment of the quality of guidelines.

Guideline task force

In 2013 a multi-disciplinary guideline task force was appointed by the Netherlands Society of Plastic Surgery (NVPC) for the development of this guideline, consisting of representatives from all the relevant specialties that are involved in caring for patients with clefts of the lip and palate, including a representative from the Dutch Association for Cleft Palate and Craniofacial Anomalies (NVSCA) (see the guideline task force on page 5). The guideline task force members have been mandated by their scientific associations and the NVSCA to take part. The guideline task force spent two years on the creation of the guideline. The guideline task force is responsible for the integral text of this guideline. The guideline development was funded by the Dutch Quality Fund for Medical Specialists (SKMS), with co-funding from the NVKNO, NVvO, NVT and NVMKA.

Professional support

Professional support was provided by the Knowledge Institute of Medical Specialists in the Netherlands (Kennisinstituut, www.kennisinstituut.nl). This non-profit organization provides advice and support for the development of (medical) evidence-based guidelines. For this guideline the Knowledge Institute of Medical Specialists provided two epidemiologists with experience in the development of evidence-based guidelines to support and advice the guideline task force. Their support assured a systematic approach during the development of the guideline. The guideline was developed using an evidence-based approach endorsing GRADE methodology, and meeting all criteria of AGREE-II. Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a systematic approach for synthesizing evidence and grading of recommendations offering transparency at each stage of the guideline development.

Declaration of interests

At the start the guideline task force members declared in writing whether they have had any (financially supporting) relationships in the past five years with commercial companies, organisations or institutions that are related to the subject of the guideline. An overview of this is available in the appendix to this guideline.

Analysis of constraints

The chairman of the guideline task force and the advisor created an inventory of the constraints during the preparatory phase. Constraints were also discussed during an

invitational conference. In this conference - in addition to representatives from the parties in the guideline task force - representatives from the Dutch College of General Practitioners (NHG), the BOSK (Dutch Association for People with Disabilities and their Parents) and Achmea (a Dutch health care insurance company) participated. A report of this is available in the appendix to this guideline.

Patients' perspective

Attention was paid to the patients' perspective in the form of a focus group meeting. An anonymous report has been attached as an appendix to this guideline. The results of the focus group meeting were incorporated in the guideline where possible. In addition, the BOSK (Dutch Association for People with Disabilities and their Parents) assessed the draft guideline during the commentary phase and made suggestions for improvement of the guideline.

Clinical questions and outcome measures

The chairman and the advisor (epidemiologist) created draft clinical questions based on the result of the analysis of constraints. These draft clinical questions were then worked out in more detail by the members of the guideline task force and were confirmed during the guideline task force meeting. The guideline task force then determined per clinical question which outcome measure are relevant to the patient, taking into consideration both the desirable and undesirable effects. The guideline task force ranked these outcome measures as critical, important or unimportant according to their relative significance. Where possible, the guideline task force also defined what they considered a clinically relevant difference for a certain measure of outcome, i.e. when does the improvement in an outcome translate to an improvement for the patient?

Strategy for searching and selecting literature

A professional medical literature specialist first searched for any existing foreign guidelines and systematic reviews in Medline (OVID) and the Cochrane Library. Next, specific search terms were used for each of the clinical questions to search for published scientific studies in (different) electronic databases. The literature lists of the selected articles were also used to search for studies. The initial search focused on studies with the highest level of evidence. The guideline task force members selected the articles found via the search action based on pre-determined selection criteria. The selected articles were used to answer the clinical question. The databases that were searched, the search action or the key words used for the search action and the selection criteria that were applied are described in the chapter relating to the clinical question. The detailed search strategies are listed in an appendix to the guideline.

Quality assessment of individual studies

Individual studies were systematically assessed, based on pre-determined methodological quality criteria, to assess the risk of biased study results. You can find these assessments in the "Risk of Bias" table.

Summary of the literature

The relevant study data from all selected articles were presented clearly in evidence tables. The most important findings from the literature were described in the summary of the literature.

Assessment of the power of the scientific evidence

A) For intervention questions

The power of the scientific evidence was assessed using the GRADE method. GRADE stands for "Grading Recommendations Assessment, Development and Evaluation" (see http://gdt.guidelinedevelopment.org/app/handbook/handbook.html).

GRADE	Definition
High	- it is very unlikely that the literature conclusion will change if further research is performed; - there is great confidence that the true effect of treatment lies close to the estimated effect of treatment as stated in the literature conclusion;
Moderate	- it is possible that the conclusion will change if further research is performed; - there is moderate confidence that the true effect of treatment lies close to the estimated effect of treatment as stated in the literature conclusion.
Low	- it is probable that the conclusion will change if further research is performed; - there is limited confidence that the true effect of treatment lies close to the estimated effect of treatment as stated in the literature conclusion.
Very low	- the conclusion is very uncertain; - there is little confidence that the true effect of treatment lies close to the estimated effect of treatment as stated in the literature conclusion.

B) For questions about the value of diagnostic tests, damage or side effects, etiology and prognosis

The evidential value of the conclusion is determined using the standard EBRO method (Van Everdingen, 2004).

Formulating the conclusions

In the case of intervention questions, the conclusion does not refer to one or more articles, but is drawn based on all studies combined (body of evidence). The guideline task force members took stock of each intervention. In taking stock of each intervention, the guideline task force weighed the benefits and harms for the patient.

For questions about the value of diagnostic tests, damage or side effects, etiology and prognosis, the scientific evidence was summarised into one or more conclusion(s), reflecting the level of the most relevant evidence. To ensure homogeneity, the level of evidence for all conclusions was presented as high/moderate/low/very low, with EBRO level 1 translating to high, level 2 to moderate, level 3 to low and level 4 to very low.

If a systematic literature search was not performed for a clinical question, the quality of the literature was not assessed, and the strength of the evidence was not determined.

Considerations

In addition to the scientific evidence, other aspects are also important in forming a recommendation, such as the (clinical) expertise of the guideline task force members,

patient preferences, costs, availability of facilities or organisational matters. If they were not scientifically studied, these aspects are listed under the heading “Considerations”.

Formulating the recommendations

The recommendations provide an answer to the clinical question and are based on the available scientific evidence and the most important considerations. At least the following four factors are taken into consideration when formulating and grading the recommendation: general quality of the scientific evidence; balance between benefits and harms of the intervention; values and preferences of the professionals and patients; and available resources.

Knowledge gaps

During the development of this guideline, we performed a systematic search for research results that contributed to answering the clinical questions. For each clinical question, the guideline task force determined whether (additional) scientific research was desirable.

Commentary and authorisation phase

The draft guideline was submitted to the (scientific) associations involved for commentary. The comments were collected and discussed with the guideline task force. The draft guideline was amended based on the comments and the definitive version was drawn up by the guideline task force. The definitive guideline was submitted to the (scientific) associations involved for authorisation and this authorisation was provided.

Implementation of the guideline and indicators

During the various phases of the guideline development the implementation of the guideline and the practical feasibility of the recommendations was taken into consideration. This process focused specifically on factors that could promote or inhibit the implementation of the guideline in practice.

The guideline and (subsequent) its English translation were included in the Dutch guideline database (www.richtlijnendatabase.nl), making it accessible to all the relevant professional organisations and patients at no costs. In addition, a summary of the guideline was published in the journals of the participating scientific associations. The guideline can also be downloaded from the websites of the professional associations involved and the NVSCA.

The guideline task force has decided not to develop any new indicators for the current guideline. The guideline task force has advised the (Dutch) scientific associations involved to develop outcome indicators in the near future, when the quality registration for cleft teams by the Dutch Association for Cleft Palate and Craniofacial Anomalies (NVSCA) and the implementations of PROMS - for instance according to the International Consortium For Health Outcomes Measurement (ICHOM) - are supposed to become fully operational. And the cleft teams should be given time to implement the

recommendations of the guideline and to work according to a uniform method, as described in the chapter “Organisation of care”.

Legal significance of guidelines in the Netherlands

A guideline must primarily aim to support healthcare providers in their practice when they do not have a lot of experience yet. In addition, guidelines can serve as a valuable source of information so that healthcare providers can quickly take note of the current state-of-the-art treatments that have some level of evidence. If there is a lack of evidence, the experts of a guideline task force can include their own expertise, provided that they have reached a consensus on this. The resulting recommendations subsequently often have the lowest level of evidential value. The execution of methodologically sound research can increase the evidential value of these expert opinions and recommendations.

Guidelines are no legal requirements, but do contain as much “evidence-based” insights and recommendations as possible that healthcare professionals should ideally and where possible follow in order to offer qualitatively good care. As these recommendations are primarily based on “general evidence for optimum care for the average patient”, healthcare professionals can deviate from the guideline if necessary in individual cases, based on their professional autonomy. In certain situations, a deviation from the guidelines may even be essential, for example when another condition or another medication interferes with the course of action proposed in this guideline. Any deviation from the guideline should be discussed with the patient, if relevant. Deviations from the guideline should always be substantiated and documented in the patient file.

Revision

The guideline task force aims to provide periodic (digital) updates to the guideline.

As the holder of this guideline, the Netherlands Society of Plastic Surgery (NVPC) is the first party responsible for ensuring that this guideline is up-to-date. The other scientific associations who contributed to this guideline or the users of this guideline share the responsibility and shall inform the first party about any relevant developments in their field of expertise.

Literature

Van Everdingen JJE, Burgers JS, Assendelft WJJ, et al. Evidence-based richtlijnontwikkeling. Bohn Stafleu Van Loghum 2004.

Chapter 3 Genetic diagnosis of patients with clefts of the lip and palate

Module: Genetic diagnostics

Clinical question
At which point should genetic testing be performed for children with clefts of the lip and palate?

Sub-questions:
- what is the optimum strategy for genetic diagnosis of orofacial cleft?
- what are the accessory conditions that genetic testing needs to meet for orofacial cleft?
- to what extent do new developments play a role in the policy regarding genetic testing?

Introduction
Clefts of the lip and palate is a congenital abnormality with a complex aetiology and a broad spectrum of causes consisting of - among other factors - several gene mutations, chromosomal abnormalities, teratogens, nutritional deficiencies and infections during pregnancy (Dixon, 2011; Leslie, 2013; Conte, 2016).

The different types of orofacial cleft are categorised as syndromic or non-syndromic, based on additional symptoms and/or developmental delay. More than 275 syndromes have been described in which clefts of the lip and palate is a characteristic symptom (Setó-Salvia, 2014). For a growing number of syndromes, the responsible gene is recognized / identified (Conte, 2016). At present, it is thought that 50% of cleft palates and 70% of cleft lips with or without a cleft alveolar arch and cleft lip, alveolar arch and palate can be considered non-syndromic (Stanier, 2004; Dixon, 2011; Leslie, 2013; Wen, 2015). The cause of non-syndromic orofacial cleft is complex, and it is generally accepted that a combination of genetic and environmental factors plays a role.

However, the line between syndromic and non-syndromic orofacial clefts appears to be blurred.
The abnormalities associated with syndromic orofacial cleft are not always recognisable, or only appear at a later stage (van der Veen, 2006; Rozendaal, 2012, Setó-Salvia, 2014). Rittler (2011) reported that 7 to 9% of the orofacial clefts that are initially thought to be isolated cases are found to have associated abnormalities. Furthermore, various known “syndromic” orofacial cleft genes can also be responsible for non-syndromic orofacial clefts (Jezewski, 2003; Leoyklang, 2006; Leslie, 2015a and b, Moreno, 2009; Rahimov, 2012, Setó-Salvia, 2014, Brito, 2015).

Etiological testing is very important to offer proper care for patients with clefts of the lip and palate. Depending on the underlying cause, clefts of the lip and palate can be associated with specific additional symptoms that require monitoring (Maarse, 2012;

Setó-Salvia, 2014). The prognosis and risk of recurrence are linked to this underlying cause.

This applies both to children with clefts of the lip and palate with additional symptoms and to children who at birth appear to have an isolated orofacial cleft.

At present, there are various options for DNA testing to obtain a diagnosis, including targeted gene testing, gene panel analysis, Whole Exome Sequencing and Array analysis.

The question that requires answering is what the optimum strategy is for genetic diagnosis of orofacial cleft. One particular question that arises is whether - given the new technological developments, the current diagnostic possibilities and the progressive insight - the policy regarding additional genetic testing should still be based on the presence of additional abnormalities and/or the type of cleft.

Searching and selecting

The clinical question was not worked out systematically, due to the methodological limitations. A general search was performed into clinical genetic testing for orofacial cleft. A description of relevant literature and other considerations have been included in the section “considerations”. As a result, the recommendations are based primarily on expert opinion.

Summary of the literature

N/A

Considerations

The distinction between *non-syndromic and syndromic* orofacial clefts is not clear. Additional symptoms can be so mild that they are not immediately recognised, or only become apparent later in life. Furthermore, a non-syndromic orofacial cleft can also be caused by a mutation in known syndromic orofacial cleft genes or by an underlying chromosomal abnormality (Jezewski*,* 2003; Leoyklang, 2006; Moreno, 2009; Oesogawa, 2008; Rahimov, 2012, Setó-Salvia, 2014, Brito, 2015; Leslie, 2015*a and b*). Although the chances of a chromosomal abnormality appear to be associated with the type of cleft (Maarse, 2012), it is important to realise that the aforementioned percentages are largely based on old methods of analysis, in which the interpretation is based on the knowledge at that moment.

Timing of genetic diagnostics

Considering the complex aetiology of clefts of the lip and palate, the large number of syndromes that clefts of the lip and palate can form part of and the fact that relevant family information can form a starting point for an underlying diagnosis, it is recommended that patients with orofacial clefts are referred to the Medical Genetics department of a University Medical Centre. A child with clefts of the lip and palate should preferably be seen by a clinical geneticist before the first surgery. This allows for timely genetic testing and if an underlying diagnosis is confirmed (for example deletion 22q11.2), then the policy regarding surgery can be adapted appropriately. If testing prior

to surgery is not indicated, then a blood sample for genetic testing can be collected under anaesthetic if desirable. Of course, a fast(er) referral is indicated in the case of growth and feeding problems, associated abnormalities, developmental delay, specific suspicion of a syndrome diagnosis or chromosomal abnormality.

The clinical geneticist will take a detailed history and family history and will perform a physical examination to determine whether a (potential) underlying syndrome diagnosis could be the cause of the orofacial cleft. The clinical geneticist will then discuss the options for genetic testing with the parents and will also discuss the impact of determining the risk of recurrence. If the orofacial cleft is associated with additional abnormalities, a positive family history or a suspicion of a specific syndrome diagnosis, then additional genetic testing is always indicated.

In the case of an infant with a cleft palate, the recommendation is to perform a single nucleotide polymorphism (SNP) array first, so that any chromosomal abnormalities that could be relevant for surgery can be confirmed or ruled out in a timely manner. The results of a SNP array are generally available in 4 to 8 weeks. If this does not reveal a cause for the cleft palate, then a second option is to consider additional genetic testing in the form of a gene panel or whole exome sequencing (WES). The result of this test often takes longer (at least 4 months) and in most cases will not be available before the operation.

Additional genetic testing should be considered for infants with a cleft lip, alveolar arch and palate. Cleft palate and cleft lip, alveolar arch and palate carry a higher risk of an underlying syndrome diagnosis or chromosomal abnormality (Maarse, 2012). Potentially associated abnormalities are not always recognisable from an early age (van der Veen, 2006; Rozendaal, 2012, Setó-Salvia, 2014). Although a specific underlying diagnosis can have consequences for the further monitoring and counselling.

In the case of an *isolated* cleft lip with or without a cleft alveolar arch, the clinical geneticist will generally not suggest additional genetic testing, as the risk of associated abnormalities and developmental delay for cleft lip with or without cleft alveolar arch appears to be lower than for cleft lip, alveolar arch and palate and for cleft palate (Maarse, 2012).

By contrast, an *isolated* cleft lip with or without cleft alveolar arch can also be associated with an underlying chromosomal abnormality. One study found that 1.8% of the patients with an isolated cleft lip have a 22q11.2 deletion (Rittler, 2011). Based on the diagnostic options and insights that are currently available, the risk of an underlying aetiological microdeletion/duplication in an isolated cleft lip with or without cleft alveolar arch may be higher.

In addition, one can conclude based on the literature that the analysis of a large number of orofacial cleft genes in cases of an isolated cleft lip with or without cleft alveolar arch could provide a starting point for an underlying diagnosis, can result in health gains (e.g. CDH1) or can be of interest for the counselling and determining the risk of recurrence (e.g. when determining a de novo *IRF6* mutation) (Brito, 2015, Jezewski*,* 2003; Leoyklang, 2006; Leslie, 2015*a and b*, Moreno, 2009*;* Rahimov, 2012, Setó-Salvia, 2014).

As there are currently no studies describing the exact benefit of clefts of the lip and palate gene panel for the various types of orofacial cleft and genetic testing can also be of importance in the case of a cleft lip with or without cleft alveolar arch with regard to counselling, the suggestion is to consider genetic testing for infants with a cleft lip with or without a cleft alveolar arch too and to discuss the option of genetic testing with the parents.

Parents should be thoroughly informed about the nature of the DNA testing, the possible results and the time frame in which the results will become available, so that they can make an informed decision based on this information. The guideline task force is of the opinion that the results of the testing (for example a gene panel for orofacial clefts) should be available within 3 months. During the informed consent procedure, special attention should be paid to the possible risk of a syndrome diagnosis that could have consequences in later life and the potential for unclear results or coincidental findings (Barry, 2012; Dondorp, 2013).

Optimum strategy for genetic diagnosis of orofacial cleft
The literature does not describe an optimum strategy regarding the choice of genetic testing for orofacial cleft. However, in most cases there is no substantiated preference for testing of Single Nucleotide Variations (SNVs) in individual candidate genes or in panels of candidate genes or for testing of Copy Number Variations (CNVs). Therefore, testing with WES for SNVs in gene panels in combination with genome-wide CNV testing is the best way to achieve a genetic diagnosis. This also allows for the data to be re-examined to test newly identified candidate genes.

In the near future, WES will become the indicated method for testing of SNVs and CNVs - both within genes and beyond - summarised in a single test. It is therefore important to have a good collaboration between the clinical geneticist and the laboratory specialist. The laboratory specialist must be well-informed about the patient's symptoms and the family history. This knowledge can be vital to the interpretation of the genetic data.

Accessory conditions for genetic testing
The guideline task force is of the opinion that specific requirements need to be met for performing genetic testing on children with clefts of the lip and palate:

1. parents must be involved in the decision-making process surrounding the genetic testing, with consent from the parents being a requirement to start testing;
2. when performing clefts of the lip and palate gene panel analysis and SNP array, it is important that a clinical geneticist is involved. Parents should be thoroughly informed about the nature of the testing and the possible results.
   Performing genetic tests can result in a syndrome diagnosis being made, which could be accompanied by additional symptoms, for example a syndrome that is associated with a developmental delay or with additional symptoms that only develop later in life. Follow-up later in life is important in such cases. On the other hand, the results may not be clear. There is also a risk of coincidental findings when performing a SNP array analysis;

3. rapid diagnostic testing is indicated in the case of growth and feeding problems, associated abnormalities, developmental delay, specific suspicion of a syndrome diagnosis or chromosomal abnormality;
4. a complete WES can only be requested by a clinical geneticist. WES testing is performed following an informed consent procedure, in which the parents are informed about the possibility of coincidental findings and results that may not be easily interpretable. This test is started once the parents have given consent and have signed an informed consent form.

Considering the rapid developments within the field of genetic testing, it is important that all results of genetic tests performed for cleft lip and palate are evaluated on an annual basis by the laboratories. This will create a clear impression of the yield of genetic testing in the case of cleft lip and palate. An analysis can also be made of the yield of the detailed analysis of orofacial cleft without detected associated abnormalities and positive family history compared to the total costs.

It is then recommended to see patients again at the age of 4 to 6 years for repeat evaluation. We have chosen the age range of 4 to 6 years, because it is then possible to get a better impression of the development of the child. If genetic testing has not been performed yet, it can be reconsidered whether this is indicated. Obtaining a diagnosis can assist in the choice of school or additional testing/guidance. If additional symptoms are detected at an earlier stage (such as a developmental delay, problems with hearing or vision), then a consultation at an earlier stage is indicated.

Finally, the guideline task force recommends annual revision of this chapter. This allows for the proposed policy to be amended every year, based on any new developments in genetic testing and increased understanding.

Recommendations

Timing and indication for genetic testing

Patients with a cleft lip with or without a cleft alveolus, a cleft lip and palate or a cleft palate should be referred to the Medical Genetics department of a University Medical Centre, preferably before the first operation.

Speed up the referral in the case of growth and feeding problems, associated abnormalities, developmental delay, specific suspicion of a syndrome diagnosis or chromosomal abnormality.

For an infant with a cleft palate, first perform a single nucleotide polymorphism (SNP) array before the first operation and then consider additional genetic testing in the form of a gene panel or Whole Exome Sequencing. The recommendation for a child with a cleft lip with or without a cleft alveolar arch, or cleft lip, alveolar arch and palate is to consider the option of additional genetic testing and discuss this with the parents.

Optimum strategy for genetic diagnosis of orofacial cleft

If the decision is made to perform additional genetic testing on patients with a non-syndromic orofacial cleft, the recommendation is to perform Whole Exome Sequencing for Single Nucleotide Variations in gene panels in combination with genome-wide Copy

Number Variations testing.

Accessory conditions for genetic testing

Always involve a clinical geneticist if genetic testing is performed on a child with clefts of the lip and palate.

Ensure good collaboration between the clinical geneticist and the laboratory specialist. The laboratory specialist must be well-informed about the patient's symptoms and the family history.

Parents should be involved in the decision-making process for genetic testing and should be thoroughly informed about the nature of the testing and the possible results. Special attention should be paid to the possible risk of a syndrome diagnosis that could have consequences in later life and the potential for unclear results or coincidental findings.

Perform an annual evaluation of the results obtained for genetic tests performed within the laboratory, to gain insight into the yield of the diagnostic tests performed.

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Chapter 4 Feeding of patients with clefts of the lip and palate

Module: Feeding

Clinical question
What is the best way to administer food immediately after birth and immediately after a procedure in children with a clefts of the lip and palate?

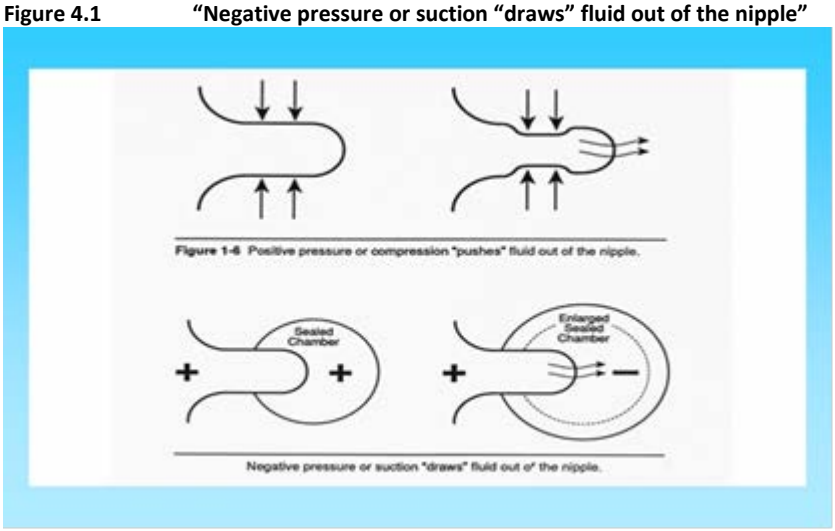
Introduction
Food is a primary necessity for life from birth. The feeding times can be a problematic factor in children with clefts of the lip and palate. The problematic feeding can have a negative effect on growth and the building of a bond between the parent and the child with clefts of the lip and palate. It is therefore very important to offer the parents support - both before and after the birth - to alleviate their concerns about feeding their child.

The guidance offered to parents during the prenatal period is described in detail in the guideline “Counselling after prenatal diagnosis of clefts of the lip and palate”. The support offered to the parents and child to assist in the event of problems with feeding should be given by a speech therapist with knowledge of and experience in the normal development of drinking and eating in children and the effects of clefts of the lip and palate on this development. This speech therapist can offer support on the topic of feeding to (future) parents of a child with clefts of the lip and palate. The speech therapist of the cleft team should participate in the speech therapy working group (special interest group) of the NVSCA.

During the first weeks after birth, the child will spend most of the day sleeping. The rest of the time consists of meeting the child’s needs such as hunger and thirst. The baby is most alert during these moments and the psychosocial factor, namely: building a bond with the parent/carer plays a major role.

During the first weeks of life, babies use reflexes to suck and swallow. An efficient sucking movement is achieved by creating negative intra-oral pressure with a good seal around the nipple/teat, together with lifting the soft palate. (Reid, 2004). This is associated with a rhythmic movement of the tongue and the lower alveolar arch. The nasopharynx is closed as a result and the intra-oral space expands. The lips exert a positive pressure on the teat/nipple, drawing the milk from the nipple (see figure 4.1)

Figure 4.1 "Negative pressure or suction "draws" fluid out of the nipple"



Source: Wolf, 1992

When a child is born with a cleft lip or cleft lip and alveolar arch without a cleft palate (i.e. the palate is intact), then this child will generally be able to feed from a bottle or from the breast without any problems. If the palate is intact, then the child can create a vacuum and produce a sufficiently strong sucking motion. This sometimes requires compensation for the incomplete closure of the lip around the nipple or teat, for example a modified feeding position, a modified teat or by supporting the chin or lips.

If the child is born with a cleft lip or cleft lip and alveolar arch in combination with a cleft palate (i.e. the palate is open) or is born with a cleft palate only, then the abnormal anatomy will usually result in feeding problems. In that case, the baby cannot create sufficient intra-oral negative pressure to draw milk from the breast or the bottle (Reid, 2004). The baby's ability to close the oral cavity and create a vacuum to increase the stability of the nipple or teat is very important in feeding (Watson, 2001; Sell, 2001; Grunwell, 2001). Research demonstrates that a less efficient sucking pattern exists in children with a non-syndromic unilateral cleft lip, alveolar arch and palate in comparison to their peers without clefts of the lip and palate (Maserai, 2007; Besell 2011). Children with clefts of the lip and palate performed shorter sucking movements, had a higher sucking rate, a higher sucking and swallowing frequency and a lower build-up of intra-oral negative pressure. A disrupted sucking-swallowing pattern can result in longer feeding times, delayed growth, lower weight, shorter height and increased fatigue. In addition, the child uses too much energy proportionally to consume a small quantity of milk (Sphrintzen, 1995; Bardach, 1995).

Adequate guidance of feeding is essential for children with a cleft lip, cleft lip and alveolar arch and/or cleft palate. This ensures that the child is fed correctly and that an adequate oral intake is maintained. Pandaya and Boorman (2001) describe a significant decrease in "failure to thrive" in children with clefts of the lip and palate when they receive adequate and intense guidance. It is important to ensure that the child has a good nutritional status, in order to build immunity against infections. This is also important for getting through the surgical phases (Reid 2004, Hughes 2013).

The feeding of a child with clefts of the lip and palate can be frustrating and stressful for the parents. If these moments of togetherness are disrupted by crying and/or agitation

from the baby, this can make the parents feel uncertain and could result in disrupted or inadequate bonding. Good guidance is therefore very important. (Miller, 2011).

Searching and selecting

In order to answer the clinical question, a systematic literature analysis was performed based on the following PICO:

- **P:** orofacial cleft (cleft palate, cleft lip, alveolar arch and palate), postnatal or children under five years of age postoperative (immediately after operation);
- **I:** 1) feeding method;
  2) posture during feeding;
  3) consistency of feeding (treatment by speech therapist, bottle, Special Needs Feeder (Haberman), breastfeeding, tube feeding, spoon feeding, finger feeding, consistency of food).
- **C:** other form of feeding (refer above);
- **O:** amount of food, longitudinal growth and weight gain of child, quality of life, dehiscences, fistulas.

Relevant outcome measures

The guideline task force deems the longitudinal growth and weight gain of the child to be the critical measure of outcome for the decision-making process. The guideline task force deems the amount of food ingested, quality of life, dehiscences and fistulas to be important outcome measures for the decision-making process.

Search and selection (methods)

A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and November 5th, 2014. This search was aimed to identify systematic reviews, RCTs and observational studies. Detailed search characteristics are shown in the appendix.

Studies that investigated patients with cleft lip/alveolus and/or palate were selected if they compared two different feeding techniques. The feeding interventions had to be studied immediately after birth or after surgery for cleft palate. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: weight gain, or increase of height, or quality of life or risk of postoperative complications.

The initial search identified 65 references of which 17 were assessed full text. After assessment of full text nine studies were excluded and eight studies were included. Reasons for exclusion are described in the Exclusion Table (see appendix).

Summary of the literature

Description of studies

A total of eight studies are included in this literature summary: two systematic reviews (Besell, 2011; Goyal, 2014), four randomized controlled trials (RCTs) (Ausgornwan, 2013; Hughes, 2013; Ize-Iyamu, 2001; Kim, 2009) and two observational studies (Jones, 1988; Turner, 2000).

Besell (2011) is a systematic Cochrane review that studies the effect of feeding interventions on growth and development of infants with cleft lip and/or palate. Several articles that were already selected in the literature search were included in this review (Brine 1994, Darzi 1996, Masarei 2007a, Prahl 2005, Shaw 1999). Therefore, these articles are not individually discussed in this literature summary. A total of five RCTs (n=292) were included in this summary, comparing squeezable and rigid bottles (two studies), breast-feeding versus spoon feeding (one study) and maxillary plate versus no maxillary plate (two studies). The studied outcomes were weight gain, increase of height, head circumference and parent satisfaction. When possible, the outcomes of two studies were pooled for meta-analysis.

Goyal (2014) is a systematic review studying the effects of obturators and other feeding interventions in infants with clefts. Although several of the selected articles were already included in the systematic review of Goyal, 2014 (Brine, 1994; Ize-Iyamu, 2011; Maserei, 2007a; Maserei, 2007b; Shaw, 1999; Turner, 2001), we chose also to describe these articles individually (unless they were already described in Besell, 2011). The reason for this is that even though a systematic literature search is performed in this review, the results are not summarized systematically by outcome. A total of 26 articles (four RCTs, 22 observational), studying the effectiveness of feeding interventions in children with clefts, were identified by a systematic literature search and included in this review.

Ausgornwan (2013) is a RCT that compares the risk of wound dehiscence in patients receiving breast/bottle feeding (n=96) versus spoon/syringe feeding (n=96) after primary cleft lip repair.

Hughes (2013) is a pilot study (RCT) that compares the effect of nasogastric feeding (n=18) with oral feeding (n=23) on morphine requirements and amount of ingested food after primary cleft palate repair. Babies underwent palate repair (type of surgery not described) at the age of five to ten months. Patients were followed for the first 24 hours after surgery.

Ize-Iyamu, 2001 is a RCT that compares syringe feeding (n=38) with cup-and-spoon feeding (n=19) in babies with cleft lip and palate in terms of feeding time and weight gain. Furthermore, the babies with clefts were compared to 55 non-cleft babies of the same age. Babies were followed from the age of one to 14 weeks.

Kim (2009) describes a RCT in which the effects of bottle feeding (n=42) after cheiloplasty are compared to those of feeding from a spoon, cup or syringe (n=42) in terms of oral intake, weight gain and risk of postoperative complications. Cleft palate repair was performed using the 2-flap palatoplasty technique at the age of approximately 8 months. Patients were followed until two months after the operation.

Jones (1988) describes a retrospective observational study in which the weight gain of children with a cleft lip/alveolus and/ or palate is compared when they are treated on an outpatient basis (two centers, n=94) or hospitalized until the time of primary cleft repair (one center, n=108). In the first two centers mother and baby were cared for in the community and followed up at regular intervals by the cleft team in outpatient clinics prior to admission for primary surgery. In the third center an inpatient mother-and-baby

ward was established, where infants with clefts were cared for by mothers and nursing staff until the time for primary repair. Patients were followed until the age of four months.

Turner (2000) describes a prospective observational study in which the effectiveness of a palatal obturator on feeding time, amount of ingested milk, weight gain and growth is compared with lactation education and the use of a Haberman bottle in eight babies with a cleft of the hard and soft palate. A 5-phase (A, B1, C1, B2, C2) withdrawal design was used with each infant serving as its own control. In phase A the baseline minutes to feed were obtained in three consecutive feedings. In the B1 phase the baseline minutes to feed were obtained for three feedings with the Haberman bottle. In the C1 phase minutes to feed with a palatal obturator and breast feeding were obtained for three feedings. In the B2 phase the obturator was again removed for three feedings and total time with Haberman was recorded. In phase C2 the time to feed of three feedings with obturator and Haberman was obtained. At the conclusion of the 5-phases parents completed a 10-question satisfaction questionnaire. Infant height and weight were recorded at birth, and at subsequent visits at two and three weeks, four months, one year and two years.

Results

Weight

Besell (2011) reports that two studies were pooled to compare rigid and squeezable bottles (n=131). After two months the difference in weight gain was -0,05 kg (95% CI: -0,25 to 0,15) in the rigid versus squeezable bottle group (weight gain was 0,05 kg higher in the squeezable bottle group on average). After three months the difference in weight gain was -0,10 kg (95% CI: -0,42 to 0,23) in the rigid versus squeezable bottle group. After six months the difference in weight gain was -0.15 kg (95% CI: -0,53 to 0,22) in the rigid versus squeezable bottle group.

One study reported the effects of breast feeding versus spoon feeding (n=40). The weight gain was higher by an average of 0,47 kg (95% CI: 0,20 to 0,74) in the breastfeeding group six weeks after surgery.

Two studies were pooled to compare the use of a maxillary plate versus no plate (n=72). After two months the difference in weight gain was -0,02 (95% CI: -0,35 to 0,30) in the maxillary plate versus no plate group (weight gain was 0,02 kg higher in the plate group). After six months the difference in weight gain was -0,57 (95% CI: -1,14 to 0,00) in the maxillary plate versus no plate group. After 12 months the difference in weight gain was 0,10 (95% CI: -0,53 to 0,73) in the maxillary plate versus no plate group.

Ize-Iyamu, 2001 reports that the syringe fed babies gained 0,2 kg in the first six weeks of life, 0,8 kg in the sixth to tenth week and 0,7 kg in the 10th to 14th week if they were fed with breast milk. The syringe fed babies that received a combination of breast milk and formula gained 0,3 kg in the first six weeks, 0,6 kg in the sixth to tenth week and 1,2 kg in the tenth to 14th week. The cup-spoon fed babies gained 0,3 kg in the first six weeks, 0,4 kg in the sixth to tenth week and 0,4 kg in the tenth to 14th week if they were fed with breast milk. The cup-spoon fed babies that received a combination of breast milk and formula gained 0,3 kg in the first six weeks, 0,5 kg in the sixth to tenth week and 0,6 kg in the tenth to 14th week. In the group that received breast milk only, the weight gain

was significantly (p<0,05) higher in the syringe fed babies in the sixth to tenth week. In the breast/formula fed babies the weight gain was significantly higher in the syringe group in the tenth to 14th week.

Kim (2009) reports that the weight gain was 6,4% in the bottle-fed infants and 5,1% in the cup/spoon fed infants after one months (p=0,47). After two months the weight gain was 10,3% in the bottle-fed infants and 9,3% in the cup/spoon fed infants (p=0,33).

Jones, 1988 describes that the average weight gain in the first four months was 163 g/week and 151 g/week in the centers where patients were treated on an outpatient basis and 134 g/week in the center where the patients were treated on an inpatient basis (p>0,05).

Turner (2000) describes that after two years weight was within the -2 SD by World Health Organization Standards for Growth Measurement, although all eight patients had a negative Z-score for weight. The average value was -0,8 (95% CI: -1,4 to -0,2).

Growth

Besell (2011) reports that two studies were pooled to compare rigid and squeezable bottles (n=131). After two months the difference in height was -0,0 cm (95% CI: -0,84 to 0,84) in the rigid versus squeezable bottle group. After six months the difference in height was 0,20 cm (95% CI: -0,59 to 0,98) in the rigid versus squeezable bottle group (the patients in the rigid bottle group were on average 0,20 cm taller than those in the squeezable bottle group). After 12 months the difference in height was 0,21 cm (95% CI: -0,72 to 1,14) in the rigid versus squeezable bottle group. After two months the difference in head circumference was -0,40 cm (95% CI: -0,99 to 0,19) in the rigid versus squeezable bottle group (the head circumference was 0.40 cm bigger in the squeezable bottle group). After six months the difference in head circumference was -0,28 cm (95% CI: -0,70 to 0,14) in the rigid versus squeezable bottle group. After 12 months the difference in head circumference was -0,66 cm (95% CI: -1,16 to -0,17) in the rigid versus squeezable bottle group.

Two studies were pooled to compare the use of a maxillary plate versus no plate (n=72). At two to six months the difference in height was -1,05 cm (95% CI: -2,20 to 0,11) in the maxillary plate versus no plate group (patients in the maxillary plate group were taller by 1,05 cm). After six months the difference in height was -0,78 cm (95% CI: -3,68 to 2,12) in the maxillary plate versus no plate group. After 12 months the difference in height was -1,29 cm (95% CI: -3,86 to 1,28) in the maxillary plate versus no plate group. At three months the difference in head circumference was 0,30 cm (95% CI: -0,66 to 1,26) in the maxillary plate versus no plate group (patients in the no plate group had a bigger head circumference by 0,30 cm). At 12 months the difference in head circumference was 0,25 cm (95% CI: -1,03 to 1,53) in the maxillary plate versus no plate group.

Goyal (2014) describes that the following feeding interventions have been described in literature and found effective in supporting normal growth in infants with clefts: a squeezable bottle with an orthodontic nipple, a squeezable Mead Johnson Cleft Lip/Palate Nurser. The following interventions have also been described as being potentially effective in supporting growth: the Haberman Feeder and type P teat, disposable syringe (without needle), Benifex cleft lip/palate nurser, cup feeding and

spoon feeding. There is contradictory evidence regarding the use of obturators. Some studies suggest that they do not facilitate feeding or weight gain, while others suggest that obturators may improve feeding efficiency. A pragmatic approach to feeding, plus using a combination of various interventions is recommended. Although a systematic search is performed, the evidence and outcome measures are not summarized systematically and no meta-analyses are performed.

Turner (2000) describes that after two years weight was within the -2 SD by World Health Organization Standards for Growth Measurement, although all eight patients had a negative Z-score for weight.

Feeding time and oral intake

Hughes (2013) reports that the amount of post-operative feed in the first 24 hours after surgery was 50 mL/kg in the oral feeding group and 147 mL/kg in the nasogastric feeding group. The mean difference between groups was -88 mL/kg (95% CI: -115 to -61 mL/kg).

Ize-Iyamu, 2001 reports that average feeding time was 10 mL/ 1.25 minute for the syringe-fed babies and 10 mL/2.08 minute for the cup-and-spoon fed babies (p-value not reported).

Kim (2009) describes that there were no differences in oral intake between the bottle-fed and the cup/spoon fed infants for the first five days after surgery. The oral intake on the 6th day was higher in the bottle-fed infants (798mL versus 586 mL, p=0,042).

Turner (2000) describes that the average feeding time was 48 minutes at baseline, 34 and 32 minutes in phase B1 and B2, respectively (with Haberman) and 15 and 16 minutes in phase C1 and C2, respectively (with obturator) (p<0,05). The average volume of milk consumed was 37 and 37 mL in phase B1 and B2, respectively and 67 and 76 mL in phase C1 and C2, respectively (p<005). The average volume of milk consumed per minute was 1,4 and 1,2 mL in the B1 and B2 phase respectively and 3,8 and 5,2 in the C1 and C2 phase respectively (p<0,05).

Quality of life

Ausgornwan (2013) describes the subjective observation of the authors and opinions of the parents. The overall experience is that parents are more satisfied with breast/bottle feeding and children are more relaxed, when compared to spoon/syringe feeding.

Besell (2011) reports that in the squeezable versus rigid bottle comparison one study reported quality of life using a 24-hour parental log (crying, feeding, sleeping, playing time). No statistically significant difference between bottle types were shown for any of these outcomes.

Turner (2000) describes that out of the six out of eight mothers of the participating infants were highly satisfied with the obturator plus Haberman feeding method and two showed good satisfaction.

Postoperative complications

Ausgornwan (2013) reports that there was no significant difference between the breast/bottle (0 dehiscences) and the spoon/syringe group (1 dehiscence) regarding

wound dehiscence (p=0,32). Furthermore, there was no significant difference in the risk for swelling, bleeding and skin inflammation.

Hughes (2013) reports that there was no significant difference (p>0,10) between painful episodes in the first 24 hours postoperatively, in the group receiving oral feeding (median 5, range 0 to 14) and nasogastric feeding (median 4,5, range 0 to 13). Morphine and other analgesic intake was similar in both groups.

Kim (2009) describes that there was no significant difference (p=0,99) in postoperative complications (bleeding, respiratory problems, wound dehiscence) in the patients that were bottle-fed (12%) or cup/spoon fed (13%) after palatoplasty. Oronasal fistula occurred in four patients in the bottle-fed group and five patients in the cup/spoon fed group (p-values not reported but >0,05).

Grading the evidence
Regarding Besell (2011), the evidence for the comparisons squeezable – rigid bottle and obturator – no obturator were downgraded by one grade due to high heterogeneity between the pooled studies. Regarding the comparison breast – spoon feeding, the evidence was downgraded by two grades for imprecision and poor allocation concealment.

The level of evidence of Turner (2000) was downgraded by one level from low to very low due to imprecision.

The level of evidence of Goyal, 2014 was downgraded by two levels (from high to low) due to unsystematic reporting of outcomes.

The level of evidence of Kim, 2011 was downgraded by one level (from high to moderate) due to risk of bias due to allocation concealment.

The level of evidence of Jones, 1988 was downgraded due three to the retrospective nature of the study.

The level of evidence of Ize-Iyamu, 2011 was downgraded by two levels due to imprecision and allocation bias.

The level of evidence of Hughes 2013 was downgraded by two levels due to short length of follow-up and imprecision.

The level of evidence of Ausgornwal, 2013 was donwngraded by three levels (from high to very low): two levels for imprecision (low event rate), one for lack of allocation concealment.

Conclusions

Moderate GRADE	There is a moderate level of proof that for infants with a cleft lip/alveolus and palate or a cleft palate only the use of using squeezable bottles for feeding results in a similar gain in weight gain and height as feeding from rigid bottles in normal children. *Besell, 2011*

Low GRADE	We found little proof that in infants with a cleft lip/alveolus and palate or a cleft palate only breastfeeding results in a higher weight gain when compared to spoon-feeding. *Besell, 2011*

Moderate GRADE	There is a moderate level of evidence that in infants with a cleft lip/alveolus and palate or a cleft palate only the use of maxillary plate for feeding results in a similar weight gain in weight and height as not using a maxillary plate. *Besell, 2011*

Very Low GRADE	We found very little proof that using a palatal obturator in combination with lactation education and a Special Needs Feeder (Haberman bottle) leads to a reduced feeding time and increased volume intake, when compared to using a Haberman bottle feeder and/or lactation instructions without an obturator in infants with a cleft of the hard and soft palate. *Turner, 2000*

Low GRADE	We found little proof that that the combined use of different feeding interventions (such as palatal obturator, Haberman feeder, breast milk pump and lactation education) may successfully meet the feeding needs of both mother and child. *Goyal, 2014*

Moderate GRADE	There is a moderate level of evidence that bottle feeding after palatoplasty has a similar effect on weight gain, oral intake and complication rate as feeding with a spoon, cup or syringe. *Kim, 2011*

Very Low GRADE	We found very little proof that that there is no difference in weight gain between infants with a cleft palate that were treated on an outpatient basis or infants with a cleft palate that were hospitalized in a mother-and-baby ward until the time for primary cleft repair. *Jones, 1988*

Low GRADE	We found little proof that that infants with a cleft lip/alveolus and palate that are fed with a syringe after birth have a faster feeding time and higher weight gain than those who are fed with the cup and spoon method. *Ize-Iyamu, 2001*

Low GRADE	We found little proof that that nasogastric feeding leads to higher enteral intake than oral feeding in the first 24 hours after primary cleft palate repair surgery. *Hughes, 2013*

Very low GRADE	We found very little proof that that patients undergoing breast/bottle feeding have a similar risk of wound dehiscence as patients fed by syringe/spoon after cleft lip repair. *Ausgornwan, 2013*

Considerations

We can conclude that not much research has been performed into the most optimum way of feeding babies with clefts of the lip and palate and that the research that is available has a low level of scientific evidence. It is not yet clear how the normal sucking and swallowing pattern develops in children with clefts of the lip and palate compared to the sucking and swallowing pattern of babies without clefts of the lip and palate (Palmer, 1993). Interventions are performed based on expert opinion, but there is no solid substantiation for this. Babies with clefts of the lip and palate are usually excluded from studies examining the sucking and swallowing pattern. In studies by Palmer it is generally assumed *that the sucking and swallowing pattern in babies with clefts of the lip and palate is fundamentally different, but there is no evidence of this.*

In two studies, the standard bottle and teat were compared to the Special Needs Feeder (squeezable). Both studies used weight, height and head circumference as outcome measures. No significant differences were found in weight, height or head circumference at various times during the study. The aspect “quality of life” was deemed better in the group with the Special Needs Feeder. However, this difference was not significant. An adjustment to the Special Needs Feeder was required less often than for the standard bottle (Shaw, 1999; Brine, 1994).

One study that compared breastfeeding to spoon feeding in babies after lip closure found a postoperative difference in favour of the breastfeeding group. However, the follow-up period was only six weeks. There was no difference in admission time in the hospital for both groups (Darzi, 1996; Besell, 2011).

Two studies (Prahl, 2005; Gorstein, 1994) measured the effect of using a plate to cover the palate until the closure of the soft palate. The outcome measures were weight compared to height, height compared to age and weight compared to age (Z score).

Neither of the studies found any significant difference. However, the study by Prahl (Prahl, 2005) did report a significant difference for children with a complete cleft lip, alveolar arch and palate compared to the standard values for Dutch children without clefts of the lip and palate. The children were lighter and shorter in their first year of life compared to the standard values for Dutch children. The presence or absence of a plate to cover the palate was not significant in this regard. This difference had disappeared in subsequent years.

More physiological functional research is required to gain insight into the sucking and swallowing pattern of babies and children with clefts of the lip and palate. Research is also required to determine the incidence of feeding problems with the risk factors such as postoperative recovery, compared to normal children. The results of these studies should clarify whether there are any differences compared to a normal sucking and swallowing pattern in healthy babies and children and what these differences are. Further research should also be performed after birth and postoperatively to determine the way in which children with clefts of the lip and palate are able to compensate for the anatomical abnormalities during the swallowing process. The long-term effects of the abnormal sucking pattern on the further development of the swallowing process should also be examined.

In the context of the sensorimotor development, it is important to normalise the sucking and swallowing pattern and the eating pattern as soon as possible by using a natural form of feeding. If tube feeding is necessary, then this should be given for the shortest possible period, preferably combined with oral feeding or oral stimulation.

Children with a cleft lip may struggle to enclose the nipple/teat. This makes it more difficult for them to suck milk from the breast/teat.

If the child has a cleft palate (with or without a cleft lip and/or cleft alveolar arch), then the child is unable to suck with sufficient force. This means that a vacuum cannot be created, as a result of the open connection between the nose and mouth. There is no chance of succeeding with placing the baby on the breast or using a regular bottle, due to the limited ability to suck.

In addition, children with a cleft palate have a higher risk of nasal regurgitation when feeding. A special needs feeder, such as the Special Needs Feeder (Haberman) by Medela (plastic bottle with valve and special teat) is useful in such cases. By squeezing the teat when the child is sucking and by using the 1-2-3 system, it is possible to support the child's sucking strength.

Children with reflux symptoms who have been prescribed thicker milk can try the Nuby (Natural Touch Softflex) teat.

For children with a cleft lip, cleft lip and alveolar arch and/or cleft palate and their parents, it is very important that they receive good guidance about feeding starting soon after birth. The speech therapist from the cleft team should be contacted if there are any feeding problems. This speech therapist has knowledge about and has experience in the normal development of drinking and eating and the effect of clefts of the lip and palate on these processes. In addition, the speech therapist is aware of the different

feeding methods and the use of the various materials and feeding postures. Quality indicators for the feeding process are: longitudinal growth and body weight, aerophagia, dysphagia, nasal regurgitation, intake quantity, flow and feeding time. Parents and carers should be able to rely on good guidance, in which the wellbeing of the child and the quality of the feeding session are paramount. If there are no specific problems, then another healthcare professional can take on delegated tasks from the speech therapist.

In conclusion, we can state that there is no obvious preference of a single feeding method; this depends on the child, the parents and the type of orofacial cleft (Goyal, 2014). Important starting points are:

- ensure that a speech therapist is present in each cleft team, with knowledge about and experience in the normal development of drinking and eating and the effect of clefts of the lip and palate on these processes. The speech therapist of the cleft team should participate in the speech therapy guideline task force of the NVSCA (refer to chapter about organisation of care);
- individualised care should be offered with regard to feeding of a child with clefts of the lip and palate. Every parent and every child requires different advice. The speech therapist should have knowledge about and be able to use the existing Special Needs Feeders;
- during the pregnancy (after the 20-week ultrasound) and/or after birth, the cleft team will provide information about the care pathway for clefts of the lip and palate. This includes information about the (im)possibilities of breastfeeding and bottle feeding by the speech therapist, or by a member of the cleft team from a different discipline in accordance with the instructions from the speech therapist.

Recommendations

Involve the parents in the decision-making process of finding a suitable feeding method. The aim is to make the drinking process comfortable for both parent and child.

These recommendations apply both to newborns and in the postoperative phase

Start oral feeding as soon as possible in both the postnatal and postoperative phase. Tube feeding (as only feeding method) is not recommended.

Ensure that a speech therapist is present in each cleft team, with knowledge about and experience in the normal development of drinking and eating and the effect of clefts of the lip and palate on these processes. The speech therapist of the cleft team should participate in the speech therapy working group (special interest group) of the NVSCA (in the Netherlands) or similar national cleft society.

In consultation with the parents, choose a suitable, individualised method of administering food to a baby with a cleft lip, cleft lip and alveolar arch and/or cleft palate. The following factors should be taken into consideration:

- the various feeding methods;
- breast;
- bottles and teats;
- (feeding) postures.

Quality parameters are: growth and height of the child, swallowing air, choking, nasal regurgitation, intake quantity, flow, feeding time and confidence of the parents in good

guidance. The wellbeing of the child and the quality of the feeding session are paramount.

Take the capabilities of the parents into consideration during the prenatal preparations and in the support offered to parents regarding potential feeding problems. Where possible, opt for feeding via oral intake. The choice of formula or breast milk is up to the parents.

Literature

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Chapter 5 Lip and palate closure in patients with clefts of the lip and palate

Module 1: Timing of the lip and palate closure

Clinical question

Which considerations (benefits and disadvantages) play a role in determining the timing of closure of the cleft palate and the cleft lip in children with clefts of the lip and / or palate.

Introduction

The cleft palate makes it impossible for patients with clefts of the lip and palate to separate the nasal cavity from the oral cavity. This results primarily in problems with speech and feeding. Closure of the (soft and/or hard) palate aims to resolve these symptoms. Earlier closure results in earlier resolution of the symptoms, but can result in growth abnormalities of the maxilla.). Abnormal growth of the maxilla can result in underdevelopment of the mid-face, which can have an effect on the anterior-posterior relation of the mandibule and the maxilla and on prominence of the nose. Lateral growth of the alveolar segments of the maxilla can also be inhibited by operation of the palate, meaning that the molars no longer align properly, causing cross-bite. It is therefore very important to know at which age closure of (a part of) the palate is best performed.

There is less of a discussion about the timing of lip closure. Considering the aesthetic aspects, the lip is generally closed during the first year of life, often in the first months of life and this can be accompanied by a primary correction of the nose (see chapter on nose corrections for orofacial cleft). It is important to substantiate the importance of the optimum timing for lip closure using the existing literature.

Searching and selecting

In order to answer the clinical question, a systematic literature analysis was performed based on the following PICO:

- **P**: patient with at least a cleft palate;
- **I**: palate closure before the age of 18 months / lip closure before the age of three months;
- **C**: palate closure after the age of 18 months / lip closure after the age of three months;
- **O**: growth and shape of the maxilla, , speech, hearing, aesthetic result, early complications (fistula), late complications.

Relevant outcome measures

The guideline task force deemed the shape of the lip, growth of the maxilla and velopharyngeal insufficiency critical outcome measures for the decision-making process.

Search and selection (Method)
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and December 3rd 2014. This search was aimed to identify systematic reviews, RCTs, CCTs, and observational studies.

Studies that investigated patients with cleft lip and palate were selected if they compared stage palatal closure before 18 months of age / lip closure before three months of age to stage palatal closure palate after 18 months / lip closure after three months of age. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: early complications (fistula), late complications (maxillary growth), speech, aesthetic results. For the outcomes speech and hearing, a follow-up until at least the age of four years, and a follow-up length of at least one year was deemed sufficient. For the outcome maxillary growth, a follow-up time until at least the age of nine years was deemed sufficient. When papers reported a shorter follow-up time they were excluded.

The initial search identified 516 references of which 40 were assessed on full text. After assessment of full text 22 studies were excluded and 18 studies were included.

Summary of the literature
Description of studies
A total of 18 studies was included in this literature summary: three systematic reviews (Liao, 2006; Nollet, 2005; Yang, 2010), three randomized controlled trials (RCTs) (Richard, 2006; Wada, 1990; Williams, 2011), two prospective observational studies (Fudalej, 2011; Ysunza, 1998) and eight retrospective observational studies (Bartzela, 2010; Friede, 2001; Gundlach, 2013; Kirschner, 2000; Landheer, 2010; Randag, 2014; Rohrich, 1996) and two observational studies where it was not reported whether they were prospective or retrospective (Grobbelaar, 1994; Zemann, 2011).

Bartzela (2010) is a retrospective observational study in complete bilateral cleft lip/palate that compares the effect of three different center protocols on maxillary growth (dental arch relationship) in patients with bilateral cleft lip and palate. In center A (n=56) patients underwent soft palate (velum) closure (center's own technique) at the age of 8.5 months and hard palate closure with alveolar bone grafting at the age of 8.5 years. In center B (n=37) patients underwent modified von Langenbeck soft palate closure at 14 months and von Langenbeck hard palate closure at the age of 9.9 years. In center C (n=107) the hard palate was closed on one side at 3.4 months and on the other side at five months, soft palate closure (von Langenbeck) at 19 months and bilateral alveolar bone grafting was performed at the age of 10 years. Dental casts were evaluated at the age of 6, 9 and 12 years.

Friede (2001) is a retrospective observational study that examines cephalometric growth in patients with unilateral complete cleft lip and palate that underwent early one-stage hard palate closure (n=29) in one center versus two-staged palate closure (n=30) in another center. In the center that performed early hard palate closure the patients underwent the vomer flap procedure at three months together with lip closure and then a pushback procedure at 22 months. In the center that performed late hard palate closure the patients underwent velum repair at eight months and then hard palate

closure at 8.5 years together with bone grafting of alveolar cleft. Lateral röntgencephalograms of these patients at the age of 10 to 16 years were analysed retrospectively.

Fudalej (2011) is a prospective observational study that compares dental arch relationship in patients who underwent a one-stage surgical protocol including lip and palate closure in one operation (n=61) versus a three-stage surgical protocol including lip closure, soft palate closure and delayed hard palatal closure in three operations (n=97) in patients with complete unilateral cleft lip and palate. Dental casts of the children were compared at the age of 11.2 for the one-stage closure and 8.7 years for the three-stage closure.

Grobbelaar (1994) is an observational study that assessed the effects of timing and time of cleft palate repair on speech in patients with a cleft in only the soft palate. A total of 184 patients were included in this study who underwent a Dorrance repair (n=25), Wardill (n=41), Perko (n=19), von Langenbeck (n=79) or Furlow Z-plasty (n=20). It was the policy of the unit to repair cleft palates before the age of one year. Palates were repaired after one year of age when patients were referred at a later age or failed to attend the hospital on the booking date and thus had to be rescheduled. A total of 78 patients were operated before six months of age and 107 after six months. Articulation, intelligibility and resonance were assessed. The follow-up period was from 3 to 24 years with a mean of 9.6 years.

Gundlach (2013) is a retrospective observational study in patients with complete unilateral cleft lip, palate and alveolus, in which the effects of one-stage versus two-stage palatoplasty on speech development and maxillary growth are described. Plaster casts from 85 patients were evaluated (n=36 at 8 years of age, n=49 at 18 years of age). The treatment results of three centers were compared. In two centers (A and B, n=50) the palate was closed in two stages and in one center (C, n=35) in one stage. In center A and B labioplasty was performed at six months according to the waveline procedure and intravelar veloplasty by Kriens at age 15 to18 months in center B and three years at center A. In center C labioplasty was performed at three months according to the Triangular Flap Method and veloplasty at 12 to 18 months by the Two Flap technique, a modification of Tennison's Stensil Method. Maxillary arch dimensions measured on plaster casts, taken at the age of 8 and 16 years, were studied. The speech development was not precisely described in this paper, but in the discussion an earlier publication of speech development in this population (1987) is mentioned.

Kirschner (2000) describes a retrospective observational study that examines speech outcome in children with complete unilateral cleft lip and palate, who underwent palate repair between three to seven months of age (n=40) or later than seven months of age (n=50). Surgical procedures were performed by two surgeons using a modified Furlow technique. Speech evaluations were conducted using the Pittsburg Weighted Values for Speech symptoms associated with velopharyngeal incompetence by two speech pathologists. Patients were followed for a mean of 7.9 ± 3.2 years.

Landheer (2010) is a retrospective observational study that studies the clinical outcomes of cleft (lip and) palate patients in terms of fistula rate and aims to determine whether patient or surgery characteristics determine this outcome. The medical records of 275

cleft palate patients were examined, and a multivariate analysis was performed to look for predictors of formation of fistulas. One of the examined determinants was one-stage (n=121) versus two-stage (n=154) palate repair. All patients underwent the cleft palate repair in two stages, unless the operating surgeon considered the cleft narrow enough to close in one operation. The soft palate was closed at six to nine months. The hard palate was closed by a modified von Langenbeck procedure at four to seven years; when the speech therapist felt that the open hard palate may influence speech. The majority of operations was performed by two plastic surgeons. The mean duration of follow-up was nine years.

Liao (2006) is a systematic review in which the effect of timing of hard palate repair on facial growth in patients with cleft palate and lip is studied, with special reference to cranial base, maxilla mandible relation and incisor relation. A total of 15 studies (n=1439), all retrospective and non-randomized, were included in this review.

Nollet (2005) is a systematic review and meta-analysis, that assesses determinants for treatment outcome in patients with unilateral cleft lip and palate. A total of 15 studies (n=1236) were included in this review. Patients were evaluated by the Great Ormond Street London and Oslo Yardstick (GOSLON) score, which assesses the dental arch relationship in terms of anterior-posterior, transverse and vertical discrepancies in persons with unilateral cleft lip and palate. For this score a very good dental arch relationship is scored as one and a very poor one as five.

Randag (2014) is a retrospective observational study that describes the effect of one-stage versus two-stage palate closure on speech and risk of postoperative complications in patients with a complete unilateral or bilateral cleft lip and palate. A total of 24 patients underwent one-stage palate closure at ten months, and 24 patients underwent two-stage closure at 11 and 18 months. Both patient groups underwent lip closure at 3-6 months. Soft palate was closed using intravelar veloplasty. Hard palate was closed using the von Langenbeck technique: a two-flap palatoplasty or a hybrid palatoplasty depending on the width of the cleft. Speech analysis was performed by analysing spontaneous speech and performing an articulation test. Patients were followed until the age of 2.5 years.

Richard (2006) describes an RCT in which the effects of operating the soft palate first (n=23, at follow-up 16) versus operating hard palate first (n=24, at follow-up n=19) on facial growth are studied in unilateral complete cleft lip and palate patients. The anterior operation consisted of a lip repair by Millard rotation advancement, a nasal correction using the McComb procedure and a hard palate repair by a single layer vomerine flap. The posterior operation consisted of a soft palate repair with medial von Langenbeck incisions. The two operations were undertaken three months apart with the first operation at 19 months of age. Preoperative maxillary models, speech and velopharyngeal function and ontological examinations were performed. Patients were followed until the age of four to six years.

Rohrich (1996) is a retrospective observational study that describes the effect of early (at an average age of 11 months, n=21) versus late (at an average age of 49 months, n=23) hard palate closure on speech and maxillary growth in patients with a complete cleft of the alveolus and secondary palate. Out of the total of 44 patients, 13 had

bilateral cleft types. In all patients the alveolar cleft repair (Millard rotation-advancement) was undertaken at an average age of 3.4 months. The timing of soft palate repair was 11 months in both groups. Patients in the early closure group underwent a modified three- or four-flap Wardill-Kilner procedure. In the late closure group, the soft palate closure was performed with short Veau flaps, followed by a second-stage hard palate closure with a vomer flap. All operative procedures in both groups were performed by the same plastic surgeon. Speech analysis of specific parameters was assessed by the speech pathologist. Maxillofacial growth evaluation based on soft-tissue profile measurements, cephalometric analysis and dental impression of upper and lower arches was assessed by the orthodontist. Palatal assessment based on a detailed palatal examination and history of fistulas was assessed by the plastic surgeon. Hearing status was assessed by an otologic history, examination and audiogram by the otologist. Patients were followed until an average of 17.5 years (12.8 years of follow-up).

Wada (1990) is a randomized trial that describes the effects of one-stage palatal closure (unilateral cleft n=14, bilateral n=8) versus two-stage palatal closure (unilateral n=16, bilateral n=7) in patients with uni- and bilateral cleft lip and palate. Also, the maxillary growth was compared with 11 healthy controls. Lip repair was performed at five months of age. One-stage repair was performed at 20 months using mucoperiosteal palatal pushback procedure. Two-stage repair was performed with primary veloplasty at 20 month and double overlapping palatal hingeflap procedure at five years ten months. Maxillofacial cast models were examined. The children are followed until the age of ten years.

Williams (2011) describes a RCT in which different surgical techniques and different timings of surgery for cleft palate were compared in terms of speech outcome and risk of palatal fistulae in patients with a complete unilateral cleft lip and palate. A 2x2x2 factorial clinical trial was used in which each subject was randomly assigned to one of eight groups: one of two different lip repairs (Spina versus Millard), one of two different palatal repairs (von Langenbeck versus Furlow) and one of two different ages at time of palatal surgery (9 to 12 months versus 15 to 18 months). All surgeries were performed by the same 4 surgeons. A total of 181 patients were operated at 9 to 12 months (Spina - Furlow = 35, Millard – Furlow = 43, Spina – Langenbeck = 51, Millard – Langenbeck = 52) and 195 at 15-18 months (Spina - Furlow = 48, Millard – Furlow = 47, Spina – Langenbeck = 46, Millard – Langenbeck = 54). Children were followed for at least the age of four years.

Yang (2010) describes a systematic review that evaluates the effect of one-stage versus two-stage palate repair with delayed hard palate closure in patients with cleft lip and palate. A total of nine studies (n=812), all retrospective and non-randomized, are included.

Ysunza (1998) describes a prospective observational study in which closure of the primary and secondary palate at six months of age (n=35) was compared to the same procedure at 12 months of age (n=41) in terms of speech outcome in patients with unilateral complete cleft of primary and secondary palate. Minimal incision palatopharyngoplasty was used in all cases. Operations were performed by two

surgeons. All patients were followed until they were four years of age and underwent a speech evaluation and maxillofacial assessment.
Zemann (2011) is an observational study that describes the effect of one-stage (n=22) in one center versus two-stage (n=32) palatal repair on facial growth in another center in patients with unilateral cleft lip, alveolus and palate. In the center that performed one stage palate closure the patients underwent lip repair at three months by Millard and one-stage palatal closure within 12 months by Veau. In the center that performed two-stage palate closure the patients lip repair was performed within six months by Tennison-Randall, soft palate repair at 12 months by intravelar velaplasty and hard palate repair at 30 months by Veau. Lateral röntgencephalograms of these patients at the age of 6-10 years were analysed retrospectively.

Results

Maxillary growth

Bartzela (2010) describes that maxillary growth was similar in all three centers at the age of 9 and 12 years. Apparently delaying hard palate closure or employing maxillary orthopaedics did not affect maxillary growth with long follow-up.

Friede (2001) reports that children that had undergone early hard palate closure generally had more retrognathic faces (more maxillary retrusion and thus less facial convexity) than those who underwent late hard palate closure. Furthermore, the ANB angle only became negative in the patients who underwent early hard-palate closure and only in the older (14 to 16 years) age groups. The anterioir vertical development of the maxilla was most satisfactory in patients who underwent delayed closure of the hard palate. Overall, the midfacial development was more favourable in the delayed hard palate closure group (exact data not reported, p-values not reported).

Fudalej (2011) describes that the dental arch relationship was better in the group that underwent the two-stage palatal closure. However, the palatal morphology was more favourable in the one-stage palatal closure group, when compared to the two-stage closure.

Liao (2006) describes that the studies included in this systematic review show conflicting results. A total of 13 studies describe the effect of timing of hard palate repair on maxillary growth. Three studies concluded that the variation in timing of the hard palate repair does not affect the length of the maxilla significantly, whereas one study opposes this view. One study reports that the effect of timing depends on the type of cleft and another that the results depend on the age at time of assessment. Seven studies conclude that variation in timing of hard palate repair does not affect protrusion of the maxilla, whereas another two oppose this view and one more study states that this depends on the age at assessment. Methodological deficiencies and heterogeneity of the studies prevented pooling of results and possibility to draw major conclusions.

Gundlach (2013) describes that in center C (one-stage palatoplasty) the patients had more constricted palates than in the centers with two-stage palatoplasty. In center A (two-stage palatoplasty at three years) the prevalence of anterior cross-bite was lowest.

Nollet (2005) describes in a meta-analysis that patients whose hard and soft palate was closed before the age of three (early) presented significantly poorer GOSLON scores

(mean 2.9±0.4) than patients whose palate was closed at a later age (mean 2.3±0.2, p=0.002). The percentage of patients with a GOSLON score of four and five (poor or very poor relationship) was 29% in the early palate closure group and 26% in the late palate closure group (p=0.002). However, Nollet 2005 also notes that well-designed randomized clinical trials are required for further investigation of the optimal timing for palatal closure, since the methodological quality of the included studies is low and heterogeneity between studies is high.

Richard (2006) describes that there was no significant difference in overall facial growth between the different types of palatal closure sequencing.

Rohrich (1996) describes that there was no significant difference in maxillary arch width between the late and early closure groups. Both groups demonstrated anterior maxillary collapse and a relatively normal arch relationship at the molar level without maxillary collapse; with no significant difference between the groups. Both groups also demonstrated a degree of maxillary and midfacial hypoplasia, again with no significant difference between the groups.

Wada (1990) reports that in unilateral cleft palate patients maxillary growth after two-stage palatal closure was comparable to those of non-cleft controls regarding depth and height of the maxilla, while after one-stage closure aberrant maxillary development was observed. For patients with bilateral clefts, maxillary growth was similar in the one-stage and two-stage palatal closure groups.

Yang (2010) reports that the results of the included studies are conflicting. Two studies evaluate the effect of stage of palate repair on the length of the maxilla. One study concludes that the stage of palate repair does not affect the length of the maxilla, whereas the other study opposes this view. Eight studies evaluate the effect of stage of palate repair on the protrusion of the maxilla. Seven studies conclude that the stage of palate repair does not affect the protrusion of the maxilla, whereas one study opposes this view. The difference in the palate repair timing between the stages varies considerably between studies (1-96 months). Pooling of results is not possible due to the heterogeneity of included studies. Furthermore, definitive conclusions about maxillary growth cannot be drawn based on the results of current literature.

Ysunza (1998) reports that there was no significant difference in orthodontic parameters (intercanine and intermolar width for both arches, maxillary length) between patients operated at SIX months and at 12 months. Both groups showed anterior maxillary collapse and a relatively normal interarch relationship at the molar level.

Zemann (2011) reports that there was no statistically significant difference in cephalometric parameters between patients undergoing one-stage versus two-stage palate closure. However, in the one-stage closure center there was considerably normal sagittal facial growth, with tendency to forward growth of the mandible. In the two-stage closure group there was a slight decrease in sagittal maxillary growth and mandibular growth with unchanged jaw relationship.

Speech

Grobbelaar (1994) describes that there was significantly ($p<0.05$) more velopharyngeal incompetence in the patients undergoing palatalum closure after six months (9/107), compared to those before 6 months of age (5/73).

Gundlach (2013) mentions in the discussion that an earlier publication noted no significant difference in speech success rates between center C where the hard palate was closed in one stage at 12 to 18 months (74%) and center A where the palate was closed in two stages at three years (70%).

Kirschner (2000) describes that there were no differences observed between patients who underwent palate closure before and after seven months of age in terms of resonance, articulation and velopharyngeal function (exact data not reported, shown in figures).

Randag (2014) reports that the one-stage palate closure group had a significantly higher number of correctly produced initial consonants (9.7±4.5 versus 7.0±3.8, $p=0.03$). There was no difference between the groups in frequency of inadequate language production, resonance problems, nasal air emission and intelligibility.

Richard (2006) reports that there was hypernasal resonance significant enough to warrant surgery in five patients in the posterioir-anterior group and four in the anterior-posterior group. This difference was not statistically significant.

Rohrich (1996) describes that 10% of the patients in the late closure group had articulation errors versus 5% in the early closure group (p-value not reported). Furthermore, nasal resonance was normal in 30% of the late closure group versus 81% in the early closure group ($p<0.001$). There was more hypernasality in the late closure group ($p<0.01$, data not reported). Speech intelligibility was impaired in 35% of the patients in the late closure group versus 5% in the early closure group ($p<0.02$). The number of subjects with a normal articulation pattern was similar in both groups (data not reported).

Williams (2011) reports that of the patients operated early (9 to 12 months) 78% had hypernasality and 57% had nasal air emission versus 74% and 55% operated late (15 to 18 months) respectively. The odds ratio for hypernasality was 1.46 (95% CI: -0.84 to 2.54, $p=0.12$) and for nasal air emission 1.16 (95% CI: 0.72 to 1.85, $p=0.49$) for patients operated early versus patients operated late.

Ysunza (1998) reports that articulation scales (as measured by the BELE articulation scale) were significantly better in patients operated at six months (mean 5.4 ± 1.0) compared to patients operated at 12 months (mean 9.0 ± 1.1).

Hearing Status

Richard (2006) reports that there was no significant difference in hearing status between the patients in the posterior-anterior group and the anterior-posterior group.

Rohrich (1996) describes that there was no statistically significant difference in the prevalence of severe hearing loss between the late and early closure group as evaluated audiometrically (data not reported).

Esthetic results

No studies were identified that met the inclusion criteria and reported esthetic results as an outcome measure.

Early complications

Landheer (2010) describes that out of the 154 patients with 2-stage repair 42 (25 hard palate, six soft palate, 11 combined) developed fistulas and out of 121 patients with 1-stage repair 58 (31 hard palate, 11 soft palate, 17 combined) developed fistulas. Most fistulas occurred in patients with Veau IV cleft types: 2-stage closure 12/48 (25%) and 1-stage closure 1/8 (13%). Odds ratio of fistula rate was 2.3 (95% CI: 1.2 – 4.3) for 2-stage repair versus 1-stage repair.

Randag (2014) describes that there was no significant difference between the one-stage (4/24) and two-stage (1/24) group in postoperative haemorrhage. No differences were found in other short-term postoperative complications (data not reported).

Richard (2006) reports that there were 10 symptomatic fistulae in the anterior-posterior group and six in the posterior-anterior group ($p>0.05$).

Rohrich (1996) describes that the overall fistula rate was six (29%) in the early closure group versus 14 (61%) in the late closure group ($p<0.05$).

Williams (2011) describes that 44/181 patients operated early (9 to 12 months) developed a fistula, versus 37/195 in the late (15 to 18 months) operation group. The odds ratio for fistula formation in the early versus late group was 1.37 (95% CI: 0.84 to 2.22, $p=0.21$).

Late complications

Landheer (2010) describes that the majority of recurrent fistulas occurred in the one-stage repair group. However, this difference was not statistically significant (data not reported).

Rohrich (1996) describes that the persistent fistula rate at time of examination was 1(5%) in the early closure group versus 8 (35%) in the late closure group ($p<0.05$). No pharyngeal flaps were performed in any of the studied patients.

Grading the evidence

Due to the large variation in study design, type of intervention, measurement of outcome and length of follow-up it was not possible to pool the results.

Most studies were graded as very low level of evidence due to study design type and imprecision.

Conclusions

Moderate GRADE	There is a moderate level of evidence that delayed hard palate closure (>3 years) results in a better dental arch relationship than early palatal closure in patients with unilateral cleft lip and palate. *Nollet, 2005*

Moderate GRADE	There is a moderate level of evidence that there is no difference in speech development or risk of fistula formation in patients with complete unilateral cleft lip and palate undergoing palatal closure using the Furlow technique or von Langenbeck technique (combined with Spina or Millard lip closure) at the age of 9 to 12 months, and those undergoing one of the same procedures at the age of 15 to 18 months. *Williams, 2011*

Low GRADE	There is a low level of evidence that sequencing of cleft closure (anterior – posterior versus posterior – anterior) has no difference on facial growth in patients with unilateral complete cleft lip and palate. *Richard, 2006*

Very low Grade	There is a very low level of evidence that in patients with a unilateral complete cleft lip, alveolus and palate minimal incision palatoplasty at six months of age is related to a better speech development when compared to minimal incision palatoplasty at 12 months of age. Maxillary growth does not differ between both groups. *Ysunza, 1998*

Very low Grade	There is a very low level of evidence that when the outcomes of soft palate (velum) repair at 11 months plus hard palate repair at 49 months are compared to soft and hard palate repair at 49 months in patients with a complete cleft of the lip, alveolus and secondary palate: - the effects on maxillary growth are similar - the effects on hearing loss are similar - the speech impediment is greater in the late hard palate closure group - risk of temporary and persistent fistulae is greater in the late hard palate closure group. *Rohrich, 1996*

Very low Grade	There is a very low level of evidence that in children with a cleft (lip, alveolus and) palate a soft and hard palate repair at six to nine months is related to a decreased risk of fistula formation when compared to soft palate repair at six to nine months and hard palate repair (modified Langenbeck procedure) at four to seven years. *Landheer, 2010*

Very low Grade	There is a very low level of evidence that there is a lower risk of velopharyngeal insufficiency in patients with an isolated cleft in the soft palate, who underwent palate closure before six months of age, compared to those who underwent palate closure after the age of six months. *Grobbelaar, 1994*

Very low Grade	There is a very low level of evidence that in children with complete unilateral cleft lip, alveolus and palate there is no difference in speech development between patients undergoing palatal closure using the modified Furlow technique before the age of seven months, and those undergoing the same procedure after seven months. *Kirschner, 2000*

Very low Grade	There is a very low level of evidence that there is a better speech development in patients with a complete unilateral or bilateral cleft lip, alveolus and palate undergoing one-stage palate repair at ten months (intravelar veloplasty combined with von Langenbeck or two-flap palatoplasty or a hybrid palatoplasty), compared to those undergoing 2-stage palate repair at 11 and 18 months (same procedures). There is no difference in risk of short-term complications between these two groups. *Randag, 2014*

Very low Grade	There is a very low level of evidence that closing the hard palate in one stage at one year or less is interferesing more with the maxillary growth than closing the hard palate at a later age study in patients with complete unilateral cleft lip, alveolus and palate and alveolus. *Gundlach, 2013*

Very low Grade	It is not clear what effect one-stage versus two-stage palate repair with delayed hard palate closure has on facial growth on patients with cleft lip and palate. *Liao, 2005; Yang, 2010*

Very low Grade	There is a very low level of evidence that two-stage palatal closure (primary veloplasty at 20 month and double overlapping palatal hingeflap procedure at five years ten months) leads to a better maxillary development compared to one-stage palatal closure (mucoperiosteal palatal pushback procedure at 20 months) in patients with a unilateral cleft lip and palate. *Wada, 1990*

Very low Grade	There is a very low level of evidence that two-stage palatal closure (primary veloplasty at 20 month and double overlapping palatal hingeflap procedure at five years ten months) leads to a comparable maxillary development as one-stage palatal closure (mucoperiosteal palatal pushback procedure at 20 months) in patients with a bilateral cleft lip and palate. *Wada, 1990*

Very low Grade	There is a very low level of evidence that in unilateral complete cleft lip and palate, children with delayed hard palate repair (velum repair at eight months, hard palate closure at 8,5 years together with bone grafting of alveolar cleft) have a better maxillomandibular development compared to children treated with early hard palate closure (vomer flap at three months together with lip closure with pushback procedure at 22 months) closing of posterior palate. *Friede, 2001*

Very low Grade	There is a very low level of evidence that in patients with unilateral cleft lip, alveolus and palate the facial growth is similar in patients that underwent one stage palatal closure (lip repair at three months by Millard, one-stage palatal closure within 12 months by Veau) and late palate repair (lip repair within six months by Tennison-Randall, soft palate repair at 12 months by intravelar velaplasty, hard palate repair at 30 months by Veau). *Zemann, 2011*

Very low Grade	There is a very low level of evidence that one-stage surgical protocol (lip and palate at six to 12 months) is associated with a more favourable palatal morphology but a less favourable dental arch relationship when compared to a three stage surgical protocl(lip, soft palate at 12 to 14 months and hard palate repair at nine to 11 years) in patients with unilateral complete cleft lip and palate. *Fudalej, 2011*

Very low Grade	There is a very low level of evidence that delaying hard palate repair and using infant orthopaedics does not affect maxillary growth in patients with complete bilateral cleft lip and palate. *Bartzela, 2010*

Considerations

A lot of research has been performed into the timing of the surgical closure of the hard palate, usually with little evidential value. The available literature reveals that there is no evidence to support a single conclusive protocol regarding the early or late closure of the hard palate that is both better for speech development and not worse for the growth of the maxilla. In addition to timing, there are usually various other – often unquantifiable – unknown factors affecting the growth of the maxilla, such as: the technique of palate closure and the additional scars (skills and expertise) and genetic predisposition (family history and racial features). There is no literature reporting on the effects of the aforementioned factors in combination with timing and technique of palate closure.

There are no known studies that demonstrate that early closure of the hard palate results in improved maturation of the face in adulthood than later closure of the hard palate. In contrast, several studies did conclude that the growth of the maxilla is disrupted by early closure. Catch-up growth of the maxilla is not described and therefore not expected. There are also various studies that conclude that early closure of the hard palate does not result in growth abnormalities. However, the follow-up time for both treatment options is often short and in the case of early closure it is not possible to rule out that growth retardation can occur at a later stage, particularly during the growth spurt in puberty. The guideline task force is therefore of the opinion that the hard palate should only be closed at a later stage if the aim is to achieve optimum growth of the maxilla.

Several studies concluded that late closure of the hard palate results in speech problems. Other studies concluded that later closure of the hard palate (ultimately) does not result in speech problems. There are no known studies that demonstrate that late closure of the hard palate results in improved speech compared to closure during the first year of life. No comparative studies have been performed to assess speech development at a later age in which the patients who have undergone late closure of the hard palate were compared with children who have undergone early closure of the hard palate. As a result, it is not possible to investigate whether children who have undergone late closure of the hard palate are able to catch up. The guideline task force is therefore of the opinion that the hard palate should be closed at an early stage, just like the soft palate, if the aim is to achieve optimum speech development. Closure before 12 months is consistent with an early treatment aimed at achieving optimum speech development.

Considering the lack of scientific evidence, there is no treatment protocol that guarantees optimum results for both development of speech and growth of the maxilla. The guideline task force is therefore of the opinion that this dilemma should be

discussed with the parents. However, the guideline task force does recommend that each cleft team should define a preferred approach (standard care pathway/treatment protocol).
We found no evidence to support an optimum time for closure of the lip. The guideline task force recommends surgical closure of the lip during the first 6 months of life.

Timing in the Netherlands:
The cleft protocols of the 13 cleft teams in the Netherlands were summarised on the website of the NVSCA in mid-2015:
Lip closure:

- unilateral cleft: 12 of the 13 teams perform lip closure at approximately three months, one team performs lip closure at six months;
- bilateral cleft: at least two teams describe a protocol that differs from the procedure for unilateral cleft, with lip adhesion performed at three months in the case of an obvious tilt of the premaxilla, followed by definitive closure of the lip at nine months.

Conclusion: in the Netherlands, all teams close the lip during the first year of life, with the majority performing the closure at around three months.

Palate closure: soft palate

- unilateral cleft: 11 of the 13 teams close the soft palate around the age of nine months, of which one team in the Netherlands performs the closure at the age between six and 12 months; one team performs closure of the soft palate at six months and one team at the age of three months;
- bilateral cleft: same protocol;
- isolated cleft palate: same protocol.

Conclusion: In the Netherlands, all teams close the soft palate during the first year of life, with the majority performing the closure at around nine months.

Palate closure: hard palate

- unilateral cleft: there is significant variation ranging from three months to 12 years, with almost every team describing its own protocol; one team closes the hard palate completely at three months, two teams perform vomer flap surgery at three months followed by closure of the oral layer at nine to 24 months; one team closes at six to 12 months, three teams at nine months, one team at 18 months, two teams at three years, one team at three to seven years, one team at seven to nine years and one team at nine to 12 years;
- bilateral cleft: same as the protocol for unilateral cleft, only two teams already perform a unilateral vomer flap surgery at three months;
- isolated cleft palate: eight teams use the same protocol; one team closes at nine months instead of nine to 12 years for a complete orofacial cleft, one team at six to 12 months instead of six months for a complete orofacial cleft, one team closes an isolated cleft palate at 12 years instead of three to seven years and two teams close at nine to 24 months without performing a vomer flap procedure at three months.

Conclusion: There is significant variation in the time of closure of the hard palate (ranging from three months to 12 years), particularly between the teams, but also varying per type of cleft.

Combination treatments:

- unilateral cleft: three teams combine lip closure at three months with a (partial) hard palate closure (vomer flap), one team combines a lip closure at six months with a soft palate closure; three teams always combine closure of the hard and soft palate at nine months, two teams combine these procedures at nine months only if indicated (otherwise they delay closure of the hard palate to no later than 24 months);
- bilateral cleft: the same as for the unilateral cleft, with two teams combining the final lip closure with the palate closure in the case of definitive lip closure following lip adhesion;
- isolated cleft palate: one team combines closure of the soft and hard palate at nine months (four total).

Conclusion: ten of the 13 teams perform a combination of procedures on the lip, soft palate or hard palate at some point in their own treatment pathway.

The literature demonstrates that there is generally very little evidence to support many of the components of orofacial cleft treatment. There are different philosophies about diagnosis and treatment, but compelling evidence to support a certain strategy is missing. The lack of consensus is most striking in the case of hard palate closure. A degree of modesty is therefore appropriate when defending a protocol. Another team's protocol should not be deemed flawed if this is not supported by a high degree of scientific evidence. However, a cleft team should explain clearly to patients and parents why they have opted for a certain protocol. Of course it is permitted to mention reasons for rejecting a different protocol, as long as it is stated clearly that each protocol has its benefits and disadvantages and that the perfect protocol unfortunately does not exist (yet). Honesty and modesty, passion and cooperation and the sharing of results ensure that cleft teams can offer patients and parents the best foundation for optimum care.

Recommendations

Perform surgical closure of the lip during the first 6 months of life.

Define a preferred approach within the cleft team for lip closure and palate closure, in order to advise parents in the decision-making process, but also give parents the opportunity to discuss a different approach.

- Check prior to the operation whether the Eurocleft checklist is complete and perform intra-oral medical photographs during the procedure if necessary and document any abnormalities in the surgical report.
- Close only the soft palate during the first year of life and close the hard palate at a later stage if the aim is to achieve optimum growth of the maxilla.
- Close the hard palate and the soft palate during the first year of life if the aim is to achieve optimum speech development.

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Module 2: Technique for lip and palate closure

Clinical question
Is there a preference for a surgical technique to close the soft palate (velum) (Veau class 1 and 2) in children with a cleft palate (with or without a cleft lip alveolar arch)?

Sub-question:
- Is there a preference for a surgical technique to close a cleft lip?

Introduction
The aim of closing the soft palate is to improve the speech, followed closely by promoting good hearing development. It is therefore important to assess the timing and technique used in closure of the soft palate based on the results that these factors have on speech development and hearing problems. Many techniques have been described up till now. Due to the complications associated with certain closure techniques, newly implemented techniques were sometimes abandoned. An example of such a significant complication is scarring and fibrosis of the closed posterior section of the palate, resulting in reduced growth and mobility. Other complications include speech problems and fistula formation. It is important to know which closure technique for the soft palate results in the lowest number of immediate postoperative complications and the fewest speech and hearing problems in the long term.

Searching and selecting
In order to answer the clinical question, a systematic literature analysis was performed based on the following PICO:
- P: orofacial cleft patient with cleft lip and/or palate
- I: closure of lip and/or soft palate
- C: various techniques for closure of lip and/or soft palate
- O: speech (open nasal speech or not), hearing, feeding (eating pattern; weight), postoperative complications appearance (patient, doctor and parent satisfaction).

Relevant outcome measures
The guideline task force deemed that speech, hearing and feeding are critical outcome measures for the decision-making process regarding the soft palate.
The guideline task force deemed that appearance (patient, doctor and parent satisfaction) and postoperative complications were important outcome measures for the decision-making process regarding lip closure.

Search and selection (Method)
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and December 3rd, 2014. This search was aimed to identify systematic reviews, RCTs, CCTs, and observational studies.
Studies that investigated patients with cleft lip and palate were selected if they compared two different operative techniques in terms of closure of the soft palate.

Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: esthetics (patient, parent and/or doctor satisfaction), speech, feeding capability, postoperative complications. For the outcomes speech and hearing, a follow-up until at least the age of 4 years, and a follow-up length of at least 1 year was deemed sufficient. When papers reported a shorter follow-up time they were excluded.

The initial search identified 519 references of which 39 were assessed on full text. After assessment of full text, 25 studies were excluded and 14 studies were included, 9 for soft palate, 4 for lip.

Summary of the literature

Description of studies

Palatum molle / soft palate (velum)

A total of 9 studies was included in this literature summary that described soft palate surgery: 3 randomized controlled trials (RCTs) (Abdel – Aziz, 2011; Henkel, 2004; Williams, 2011), 3 prospective observational trials (Grobbelaar, 1995; Hassan, 2007; Witt, 1999) and 1 retrospective observational trial (McWilliams, 1995).

Also, 2 studies were included in which it was not clear whether the surgery was performed for soft or hard palate closure; one RCT (Spauwen, 1992) and one retrospective observational study.

Abdel-Aziz and Ghandour, 2011 is an RCT that compares the effects of the Furlow double opposing Z-plasty (n=22) and the Wardill – Kilner V-Y (n=24) pushback technique in terms of velopharyngeal outcome and speech in patients with a cleft of the soft palate and no other congenital anomalies. Age at surgery was 11-36 months. All cases were followed for at least 1 year. Flexible nasopharyngoscopy and perceptual speech resonance evaluation were used to assess the velopharyngeal closure and speech outcome respectively.

Henkel, 2004 is a randomized controlled trial in which the effects of soft palate closure using the wave-line technique in the intravelar veloplasty (n=12) are compared to the classic intravelar veloplasty (n=12) in terms of speech outcomes in patients with complete cleft of the soft palate. Patients were randomly assigned to one or the other group following a previously determined succession. Surgery was performed at the age of 10-12 months. Speech was investigated at the age of 4 years by a speech pathologist blinded for the technique.

Spauwen, 1992 performed an RCT comparing Furlow (n=10) to the von Langebeck technique (n=10) in patients with any kind of palate cleft, 10 in both groups. Speech was evaluated. Follow-up time was 2.5 years.

Williams, 2011 describes a RCT in which different surgical techniques and different timings of surgery for complete cleft palate were compared in terms of speech outcome and risk of palatal fistulae in patients with a complete unilateral cleft lip and palate. A 2x2x2 factorial clinical trial was used in which each subject was randomly assigned to 1 of 8 groups: 1 of 2 different lip repairs (Spina versus Millard), 1 of 2 different palatal repairs (von Langenbeck versus Furlow) and 1 of 2 different ages at time of palatal

surgery (9-12 months versus 15-18 months). All surgeries were performed by the same 4 surgeons. A total of 181 patients were operated at 9-12 months (Spina – Furlow = 35, Millard – Furlow = 43, Spina – Langenbeck = 51, Millard – Langenbeck = 52) and 195 at 15-18 months (Spina – Furlow = 48, Millard – Furlow = 47, Spina – Langenbeck = 46, Millard – Langenbeck = 54). Children were followed for at least the age of 4 years.

Carroll, 2013 is a retrospective observational study that examines the association between palate repair technique and hearing outcomes in children with all types of cleft palate. Four different techniques were used: double reverse Z-plasty (Furlow, n=24), V to Y pushback (Wardil-Kilner, n=24), 4-flap (n=70) and the von Langenbeck technique (n=20). The number of middle ear infections was assessed and audiological measurements were performed 3-6 years post repair.

Grobbelaar, 1995 is a prospective observational study that compared speech outcomes in patients with a soft palate cleft, operated by Dorrance repair (n=25), Wardill repair (n=41), Perko repair (n=19), Furlow Z-plasty (n=20) and a von Langenbeck repair (n=79). Articulation, intelligibility and resonance were assessed by at least one speech therapist. All the children underwent videofluoroscopy. The follow-up period was 3-24 years, with a median of 9.6 years.

Hassan and Askar, 2007 compared the Wardill-Kilner technique (two layer repair without intravelar veloplasty n=33) to the Kriens technique (three layer repair with intravelar veloplasty n=37) in patients with nonsydromic cleft palate (Veau type I or II, submucous clefts excluded) in terms of Eustachian tube and velopharyngeal competence. Patients were stratified by cleft type. Patients underwent surgery at the age of 19-23 months and were followed for 2 years.

McWilliams, 1995 described a retrospective observational study in which cleft patients (type of cleft not described in more detail) who underwent palatal closure by Furlow (n=63) are compared to those who underwent palatal closure by another procedure (n=20) in terms of speech and usage of pharyngeal flaps. The non-Furlow group had palate repair consisting of either a two-flap or four-flap Wardill-type closure (n=12) or a von Langenbeck type repair (n=6), both of which included a intravelar veloplasty. Two subjects had procedures that were not specified, but included intravelar veloplasties. The repair in the non-Furlow group was performed at a mean age of 10.3 ± 4.3 months. In the Furlow group 24 patients had soft palate closure at the time of initial lip repair/adhesion. Hard palate clefts were performed 3-12 months later. The rest of the palate closures were performed in one stage. The repair in the Furlow group was performed at a mean age of 7.7 ± 4.1 months. Patients were followed for at least 5 years. Speech was assessed using the Pittsburg Weighted Values for Speech Symptoms Associated with velopharyngeal incompetence.

Witt, 1999 is a prospective observational study that assesses the long-term stability of speech (velopharyngeal ratings) in patients with cleft palate (type of cleft not specified) who underwent palatoplasty with intravelar veloplasty (n=14) compared to those who underwent palatoplasty without intravelar veloplasty (n=14). Palatoplasty was performed at the median age of 14.6 months. Speech and language evaluation was conducted at the age of 6 and 12 years.

Lip closure

Five studies comparing different lip closure techniques were identified, three randomized studies (Chowdri, 1990; Da Silva Amartunga, 2004, Williams. 2011); 1 prospective observational study (Reddy, 2010) and one retrospective observational study (Halli, 2012).

Chowdri, 1990 is a randomised comparative study performed in India in which rotation advancement lip repair as described by Millard (n=58) is compared to triangular flap lip repair as described by Randall (n=50) in terms of esthetic results and compliucations. Age at lip repair was 3 years. Patients were followed for 1-6 years. Esthetics were evaluated independently by 3 examiners, each scoring surgical results on a 0-10 scale for 10 aspects of lip and nose, making a total assessment of 100 points for the 10 components studied.

Da Silva Amaratunga, 2004 describes an RCT in which the esthetic results of unilateral lip repair are compared for Millard's method (n=18), Cronin's method (n=21) and a combination of the two methods (n=20). Lip repair was performed at the age of 2-6 months. The results of the repair were assessed 3 months after surgery. Esthetic results were assessed using the Cleft Lip Component Symmetry Index (0-100, with 100 points indicating perfect symmetry).

Williams, 2011 describes a RCT which is mentioned in the section on palatal closure above. In this study not only the surgical techniques for closure of palate where compared but also the surgical closure of lips with 2 different technigues. A 2x2x2 factorial clinical trial was used in which each subject was randomly assigned to 1 of 8 groups: 1 of 2 different lip repairs (Spina versus Millard), 1 of 2 different palatal repairs (von Langenbeck versus Furlow) and 1 of 2 different ages at time of palatal surgery (9-12 months versus 15-18 months). All surgeries were performed by the same 4 surgeons. A total of 181 patients were operated at 9-12 months (Spina – Furlow = 35, Millard – Furlow = 43, Spina – Langenbeck = 51, Millard – Langenbeck = 52) and 195 at 15-18 months (Spina – Furlow = 48, Millard – Furlow = 47, Spina – Langenbeck = 46, Millard – Langenbeck = 54). Children were followed for at least the age of 4 years.

Halli, 2012 is a retrospective observational study that compares cleft lip repair with Acrylate glue (n=30) and Prolene sutures (n=30) in terms of esthetic results. Age at lip closure was not reported. Five observers looked at postoperative photographs of the patients at 18 months of age and scored esthetics with a visual analogue scale.

Reddy, 2010 describes a large prospective cohort study comparing 3 different lip techniques for correction of the cleft lip. A cohort of 400 Millard technique corrections is compared to 400 Pfeifer incisions and 400 Afroze technique lipclosures. The latter technique is a combination of the Millard technique at the cleft side and the Pfeifer technique at the non-cleft side. Outcome measurements were performed 2 years postoperatively and consisted of the white roll, vermillion border, scar, cupids' bow, lip length, nostril symmetry, and appearance of alar dome and base.

Results

Palatum molle / soft palate

Speech

Abdel-Azziz and Ghandour, 2011 describe in 46 patients that velopharyngeal closure and speech outcome were better after Furlow Z-plasty than after the V-Y pushback procedure. Auditory perceptual assessment for nasality was 0.88 ± 1.01 in the Furlow group and 0.27 ± 0.55 in the V-Y pushback group (p=0.035). Nasal emission was 0.92 ± 1.1 in the Furlow group versus 0.36 ± 0.73 in the V-Y pushback group (p=0.049). Glottal articulation was 1.13 ± 1.04 in the Furlow group and 0.50 ± 0.74 in the V-Y pushback group (p=0.029). There was no significant difference in pharyngealization of fricatives and speech intelligibility between the groups.

Henkel, 2004 shows in 24 patients that compensatory grimacing when speaking was observed in 1/12 patients in the wave-line veloplasty group versus 8/12 in the classic intravelar veloplasty group ($p<0.05$). A sound difference was observed in speech with a closed and open nose in 12/12 of the wave-line veloplasty group and 8/12 in the classic intravelar veloplasty group ($p<0.05$). Articulation of alveolar sounds was judged normal in significantly more subjects in the wave-line veloplasty group (6/10 (2 children too playful for examination)) versus the classic intravelar veloplasty group (3/12, $p<0.05$). They concluded that the waveline technique seems to be superior, however group size is small.

Spauwen, 1992 shows in 20 patients that there was a significant difference in nasality and nasal escape favouring the Furlow technique. No differences were found in articulation, comprehension, language production or hearing. There was a similar size of cleft type distribution (Veau type I and II) over the groups. Although this study is small sized, a power analysis performed before inclusion showed that this number of 20 patients could be enough for answering the primairy question about VPI.

Williams, 2011 reports in 376 subjects that patients operated by the Von Langenbeck technique had an 0.54 OR (95% CI 0.31 – 0.95, p=0.014) for hypernasality and a 0.72 (95% CI: 0.45 – 1.15, p=0.12) OR for nasal air emission when compared to the Furlow technique.

Grobbelaar, 1995 describes in 184 patients that the Furlow Z-plasty and Perko repairs yielded the best results, when compared to Dorrance, Wardill and von Langenbeck repairs. Normal speech was recorded in 100% of the Perko and Furlow Z-plasty patients, and in 22/25 of the Dorrance, 40/41 of the Wardill and 75/79 of the Langenbeck patients. No hypernasality was recorded in the Perko and Furlow Z-plasty groups, and also in in 20/25 of the Dorrance, 39/41 of the Wardill and 73/79 of the Langenbeck patients.

McWilliams, 1995 describes in 101 subjects that the Furlow patients had a total speech score of 1.70 ± 2.12 when compared to the non-Furlow patients: 3.20 ± 3.04 (p=0.04) (0 = no speech impediment, 5 = very severe speech impediment). However, when this difference was controlled for cleft type, it was no longer significant. Furthermore, 98% of the Furlow patients had no articulation errors compared to 85% in the non-Furlow group (p=0.014). In the Furlow group 79% of the patients had no hypernasality compared to 40% in the non-Furlow group (p=0.001). Also, the hypernasality scores were lower in the Furlow group (0.32 ± 0.74) compared to the non-Furlow group (1.30 ± 1.34, p=0.001).

Witt, 1999 describes in 28 subjects that the speech outcomes were comparable in the group that recieved intravelar veloplasty during palatoplasty and the group that did not. There was no velopharyngral dysfunction in 7/14 intravelar veloplasty patients and 4/14 non-intravelar veloplasty patients (p=0.25).

Hassan and Askar, 2007 describe 15 of 70 patients in total had VPI: in total 6/33 patients after three layer closure (Kriens) experienced VPI compared to 9/37 after two layer closure technique. But, no conclusive distinction could be made between two layer closure versus three layer closure regarding VPI.

Hearing

Carroll, 2013 describes in 138 subjects that the double-reverse Z-plasty was associated with the lowest median pure tone average (PTA) of 10.0 dB ($p = 0.046$) at 6 years. There was no difference in median PTA between children with and without comorbid diagnoses (such as Pierre Robin Sequence, arthrogryposis) at either 3 years or 6 years of age ($p = 0.075$, $p = 0.331$). A multivariate model showed that extent of the cleft influenced technique choice ($p = 0.027$), but only technique choice was associated with significant differences in PTA and only at 6 years post-repair.

Hassan, 2007 found in 70 subjects that patients who underwent the Kriens technique (three layer technique with intravelar veloplasty) had a greater probability for resolution of secretory otitis media, in the early postoperative period, less time required for extrusion of the grommet tube, and lower incidence of recurrent secretory otitis media.
Spauwen, 1992 found no difference in hearing after Furlow compared to Von Langenbeck in 20 subjects.

Cephalometric and maxillary growth

No RCTs and observational studies were found that described the influence of surgical techniques of palatal closure on cephalometric and maxillary growth.

Postoperative complications

Abdel-Azziz, 2011 reports that in total 0/22 fistulas were found in the Furlow group versus 2/24 in the V-Y pushback procedure group (no p-value reported).

Henkel, 2004 reports that 1 patient in the wave-line group developed wound dehiscence in the oral mucosa that healed secondarily without complications (p-value not reported). All other patients healed without complications.

In Williams, 2011 only fistula rates were compared and were found not to be different between the Spina and Millard repair technique. In total 37/269 (14%) patients operated by von Langenbeck developed fistula, versus 44/190 (23%) in the Furlow operation group. The odds ratio for fistula formation in the von Langenbeck versus the Furlow group was 1.93 (95% CI: 1.12 – 3.14, p=0.008). The esthetic result of the different lip-closure techniques were not compared in this study.

Hassan, 2007 reports in 70 patients that there was a tendency for increased incidence of palatal fistula in the three layer closure technique group (Kriens) (6/33) compared to the two layer closure technique group wall kilmer) (4/37)., however not reaching significance.

McWilliams, 1995 describe in 101 subjects that 8 (13%) of the patients in the Furlow group required pharyngeal flaps versus 9 (45%) in the non-Furlow group (p=0.002). When this comparison was controlled for age at surgery and cleft results, the difference was still significant (p=0.001).

Esthetics
No RCTs and observational studies were found that described the influence of surgical techniques of palatal closure on esthetics in patients with cleft soft palate.

Food intake
No RCTs and observational studies were found that described the influence of surgical technique of palatal closure on food intake in patients with cleft soft palate

Lip closure
Esthetics
Chowdri, 1990 report that the esthetic scores were similar in the patients treated with rotation advancement repair (71 ± 10) and triangular flap repair (73 ± 12, p>0.50). There was also no significant difference for the lip-scores alone (p>0.10) or the nose-scores alone (p>0.80) between the two surgical techniques. Regarding postoperative complications, this study reports that 5/58 (9%) of the patients in the rotation flap advancement group developed scar hypertrophy compared to 2/50 (4%) in the triangular flap group (p>0.10). Furthermore, 4 patients in the rotation advancement group developed wound dehiscence, compared to 0 patients in the triangular flap group (p-value not reported).

Da Silva Amaratunga, 2004 reports that the Cleft Lip Component Symmetry Index score of philtral height, vermillion height, and Cupid's bow height achieved with the combined method was comparable to that achieved with Cronin's method and was superior to that obtained with Millard's method (p<0.01). Further, the combined method achieved a Cleft Lip Component Symmetry Index score for the philtral width that was not significantly different from that of Millard's method and better than that of Cronin's method (p<0.01).

In Williams, 2011 only fistula rates were compared and were found not to be different between the Spina and Millard repair techniques. The esthetic result of the different lip-closure techniques were not compared in this study.

Halli, 2012 describes that the mean score of ranks was higher in the Glue repair group (15.96) compared to the suture repair group (15.04, p<0.05), ergo the esthetic results were better in the glue repair group.

Reddy, 2010 describes in 1200 subjects that the esthetic outcomes were best in patients who underwent cleft lip repair with the Afroze incision, when compared to the incision by Millard or wave-line by Pfeifer. The odds ratio for a good outcome was significantly higher for the Afroze incision regarding the white roll match (p<0.001), vermillion match (p=0.004), scar appearance (p=0.022), Cupid's bow (p<0.001), Lip length (p=0.001), and nostril symmetry (p<0.001). The odds ratio for a good outcome was similar for the

Afroze incision compared to other incisions regarding the Alar dome (p=0.16) and Alar base (p=0.14).

Grading the evidence
Due to the large variation in study design, type of intervention, measurement of outcome and length of follow-up it was not possible to pool the results. Most studies were unable to adequately control for known confounding factors and were graded as very low level of evidence due to study design type and imprecision.

Conclusions
Soft palate (velum) closure

Moderate GRADE	There is a moderate level of evidence that the double-opposing Z-plasty Furlow procedure is associated with a better velopharyngeal function but also higher risk of fistulae when compared to the von Langenbeck repair with intravelar veloplasty in patients with complete unilateral cleft lip, alveolus and palate. *Williams, 2011*

Low GRADE	There is a low level of evidence that speech results are better in patients with a complete cleft of the soft palate treated by wave-line technique in intravelar veloplasty when compared to classic intravelar veloplasty. *Henkel, 2004*

Very Low GRADE	There is a very low level of evidence that cleft palate repair using the Furlow double Z-plasty leads to a better velopharyngeal closure and speech outcome when compared to the Wardill-Kilner V-Y pushback technique in patients with cleft soft palate. *Abdel-Aziz, 2011*

Very Low GRADE	There is a very low level of evidence that cleft palate repair using the Kriens technique leads to a better postoperative functional outcome of the Eustachian tube when compared to the Wardill-Kilner V-Y pushback technique in patients with cleft palate. *Hassan, 2007*

Very low GRADE	There is a very low level of evidence that speech outcome is similar in patients with cleft palate who received palatoplasty with intravelar veloplasty or those who received palatoplasty without intravelar veloplasty. *Witt, 1999*

Very Low GRADE	There is a very low level of evidence that in cleft patients a Furlow palatal repair is associated with a better speech outcome and lower risk of pharyngeal flaps, when compared to other techniques of soft palatal repair. *McWilliams, 1996*

Very Low GRADE	There is a very low level of evidence that cleft soft palate repair using the Furlow Z-plasty or Perko repair leads to a better speech development when compared to a Dorrance or a Wardill repair in patients with cleft soft palate. *Grobbelaar, 1995*

Soft palate or hard palate closure (not clear from study description)

Very low GRADE	There is a very low level of evidence that for cleft palate repair double reverse Z-plasty closing soft palate alone when hard palate is already closed is associated with better hearing outcomes when compared to the 4-flap, V-Y plasty and the von Langenbeck procedure closing soft and hard palate in a single operation in patients with all types of cleft palate. *Carroll, 2013*

Very Low **GRADE**	There is a very low level of evidence that cleft palate repair using the Furlow double Z-plasty leads to a less nasal speech, but similar articulatory skills, language production, language comprehensionand hearing when compared to the von Langebeck technique in patients with complete cleft palate. *Spauwen, 1992*

Lip closure

Low GRADE	There is a low level of evidence that using the Afroze incision for repair of unilateral cleft lip yields better esthetic results than using the Millard incision or the Pfeifer wave line incision. *Reddy, 2010*

Low GRADE	There is a low level of evidence that the esthetic results and risk of postoperative complications are comparable in patients with unilateral cleft lip who underwent a rotation-advancement repair as described by Millard or a triangular flap repair as described by Randall. *Chowdri, 1990*

Low GRADE	There is a low level of evidence that the esthetical results for unilateral cleft lip repair were best in a combination of Millard's method and Cronin's method, when compared to Millard's method or Cronin's method alone. *Da Silva Amaratunga, 2004*

Very low GRADE	There is a very low level of evidence that cleft lip repair with Acrylate results in better esthetic results than cleft lip repair with prolene sutures. *Halli, 2012*

Considerations

Closure technique for palate

Several surgical techniques are widely accepted as a primary closure technique for the palate, including: von Langebeck, Veau-Wardill-Kilner pushback, Bardach 2-flap technique and Furlow double Z-plasty. Despite the differences between these methods, most of these techniques perform the same intrinsic muscle mobilisation, namely an intravelar veloplasty, in which the palatal muscles are closed medially and moved to a more posterior position. A great deal of research has been performed into the results of various techniques for palate closure, usually with little proof due in part to the lack of randomisation, lack of prospective study design or follow-up. However, there are publications that favour the Furlow technique. As more data has been published on the Furlow technique, this seems to create a bias. There are no studies with the same level of evidence about the other techniques.

The largest prospective study in this field was performed by Williams (2011), who designed a study including children with a complete unilateral cleft lip, alveolar arch and palate. If speech development is used as the most important measure of outcome for a functionally good result of palate closure, then the Furlow technique that is used for closure of the soft palate appears to be the best technique compared to the von Langebeck technique (with intravelar palate muscle reposition) for Veau I and Veau II orofacial clefts. A significantly lower number of VPI symptoms was found in the Furlow group. However, one important finding was also the increase in the number of fistulas in the Furlow group, accompanied by a significant increase in fistula formation in the case of broad palate defects. A significant difference in fistula percentage was observed for palate defects with an average width of more than 1.0 cm compared to those with an average width less than 1.0 cm. More relaxation incisions were performed using the von Langenbeck technique compared to the Furlow technique, but more fistulas were observed in the population of patients in both groups where relaxation incisions were not used. The age at which the palate was closed (9-12 months versus 15-18 months) did not result in any difference in fistula percentage. Finally, it became clear that there was a marked difference between the 4 surgeons who performed both techniques, with the surgeon who had the most experience in the Furlow technique causing the lowest number of fistulas (Williams, 2011). In addition, it became clear that the surgeon "with the most fistulas" did not use everting mattress sutures to close the palate.

The remaining three smaller randomised studies reflect their results of techniques used for the closure of the soft palate only (Abdel –Aziz and Ghandour (2011) and Henkel (2004)) and the complete palate (Spauwen, 1992). The group of Abdel-Aziz compared the Furlow technique to the Wardill Kilner pushback technique. This study also concluded that the Furlow technique is the superior technique with regard to speech development. However, fistula formation does not occur with the Furlow technique, which is primarily due to the less major dissection during closure of the soft palate only. Henkel (2004) compared a modified technique to the classical straight closure by creating a more wave-like incision, which effectively equates to an elongation-plasty such as the Furlow technique. This extended Wave line technique also resulted in improved speech development without fistulas. Fistula formation did not occur in either study, which is primarily due to the less major dissection during closure of the soft palate only. In a small RCT, Spauwen describes that the patients treated with a Furlow plasty had better speech development compared to those treated with the von Langebeck technique. It is not clear for this group whether the closure involves the entire palate, the soft palate only or also the hard palate. The study did state that the Furlow technique requires a longer surgical learning curve and is better used for smaller clefts as insufficient tissue would otherwise be available, thereby increasing the risk of ischaemia.

The guideline task force concluded that more research has been conducted into the Furlow technique, possibly resulting in a bias compared to other techniques. Having said that, one can conclude from the aforementioned literature overview that the double opposing Z-plasty (i.e. Furlow technique) appears to be an adequate technique for the correction of a soft palate cleft, in which the width of the cleft and the experience that the surgeon has in this procedure appear to be deciding factors in performing this technique. The guideline task force is of the opinion that the repair of the muscular sling in the palate forms the foundation of good speech development and that this muscular sling can also be achieved using techniques other than the Furlow technique.

Closure technique for lip

Numerous variations on the different lip closure techniques have been developed over time. When the techniques described by Millard, Pfeifer and others are compared to the current techniques based on these original techniques, then it becomes apparent that comparisons are increasingly difficult to make. However, a large retrospective study performed by Reddy (2010) did reveal a difference in aesthetic quality of the scars and the lip following correction using the Afroze technique. Again, this is a modification of existing techniques and in this case a combination of the Millard technique on the cleft side and a Pfeifer technique on the non-cleft side.

The guideline task force is of the opinion that no conclusive advice can be given about the choice of technique for closure of the lip. The technique for closure of the lip strongly depends on surgical preference and has been modified increasingly over the years based on the surgical learning curve of the surgeon. The techniques as initially described by Millard and Pfeifer and others have now been modified to such an extent that they are becoming increasingly similar. Surgical skills and modification of existing techniques by individual surgeons, as well as the low urgency due to the fact that the results are generally good, make it ethically impractical to examine lip closure in a randomised controlled study design. When selecting surgical techniques, the guideline

task force recommends using an optimum result with regard to function and aesthetics with a minimal risk of complications as a starting point.

Recommendations

During palate closure, transpose the palatal musculature to a more anatomical position (suture created in the median line and the muscle placed in a more posterior position) to achieve a better result for speech, for example a Furlow or Langenbeck technique with transposition of the muscles.

Do not use a Furlow palatoplasty in the case of a wide palate cleft, due to the increased risk of fistula formation.

Preferably do not use the Wardill-Kilner pushback technique.

Use everting (suture) techniques to achieve improved wound margin approximation.

Use a (combination of) technique(s) for palate closure that the surgeon is most experienced in, in order to reduce the risk of complications.

Use a (combination of) technique(s) for lip closure that the surgeon is most experienced in, to ensure an optimum result with regard to function and aesthetics while the risk of complications is kept to a minimum.

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Chapter 6 Hearing problems in patients with clefts of the lip and palate

Module: Hearing problems

Clinical question
Which considerations (benefits and disadvantages) play a role in the treatment of hearing loss in children with a cleft (lip, alveolar arch and) palate?

Introduction
Children with a cleft (lip, alveolar arch and) palate often experience hearing problems. This is usually caused by otitis media with effusion as a result of the reduced functioning of the Eustachian tube caused by reduced functioning of the velar musculature as a result of the orofacial cleft. In addition, permanent conductive hearing loss can occur as a result of congenital abnormalities in the auditory ossicles. This usually occurs in a previously undiagnosed syndromal form of orofacial cleft. The same also applies to sensorineural (perceptive)hearing loss. This is also more common in syndromal forms of orofacial cleft. However, there are many syndromal forms of orofacial cleft that are not recognisable immediately after birth. So far, there is no consensus about the best timing and the best method for the treatment of hearing loss.

Searching and selecting
In order to answer the clinical question, a systematic literature analysis was performed based on the following scientific question(s):

- What are the (un)favourable effects of early insertion of tympanostomy tubes compared to a wait-and-see approach in children with a cleft (lip, alveolar arch and) palate or alternative forms of treatment?

The clinical question was translated into a scientific query. The guideline task force is aware of the fact that this query can only answer part of the clinical question.

- **P:** Children with a cleft (lip, alveolar arch and) palate;
- **I:** Early standard treatment of hearing loss by means of tympanostomy tubes inserted immediately during the first cleft surgery at the age of a few months, followed by routine replacement of the tympanostomy tubes after every episode of otitis media with effusion;
- **C:** Later start of treatment or alternative forms of treatment and selective insertion of tympanostomy tubes;
- **O:** Long-term results relating to hearing, ear status, speech.

Relevant outcome measures
The guideline task force deems hearing and a normal status of the tympanic membrane and middle ear to be important outcome measures for the decision-making process, as well as a high degree of understandable speech.

The guideline task force did not define these outcome measures *a priori*, but used the definitions from the studies. With regard to hearing, a normal hearing pattern with a hearing threshold better than 20 dB was considered a clinically relevant effect.

Search and study selection (methods)
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 2000 and March 12, 2014. This search was aimed to identify systematic reviews, RCTs, CCTs, and observational studies. Detailed search characteristics are shown in appendix X.

The initial search identified 109 references of which 15 reviews / RCTs and 94 other studies. After studying the abstracts, 28 were assessed on full text. Two systematic reviews were found to be relevant for answering the above stated review question. 25 studies (9/15 reviews/RCT's and 19/94 other studies) seemed to be relevant for answering the other aspects of the clinical question on hearing loss, but not eligible for GRADE assessment. Furthermore, some national established guidelines (CBO, FENAC, ENT) were used. The evidence tables and risk of bias assessment are added as an appendix.

Summary of the literature
Two systematic reviews by Kuo (2014) and Ponduri (2009) were included. Kuo (2014) studied the effectiveness of ventilationtube insertion (VTI) for OME in children with cleft palate. Kuo (2014) found in a systematic review (9 publications in which Gani, 2012; Kobayashi, 2012; Shaw, 2003; and Maheswar, 2002) evidence for a faster solution of hearing impairment by grommets than with conservative treatment in two studies, but not in three other studies. In one study (Hubbard, 1985) also positive long-term effects on speech development are found, but this could not be statistically confirmed in two other studies (Kobayashi, 2012; Shaw, 2003). Almost all studies report on more frequent otologic complications in children with than without grommets. Kuo concluded that all nine studies included in the review were observational cohort studies, which were initially graded as low-quality evidence according to the GRADE approach. For each outcome the studies (outcomes related to hearing, speech and language development, frequency of treatment, and complications or sequelae) were unable to adequately control for known confounding factors. Although the results of this study are evidence based, the studies included in the analysis are underpowered cohort studies, and the evidence for each outcome is of very low strength.

Ponduri (2009) performed a systematic review of randomized controlled trials, controlled clinical trials, case series, and prospective and historical cohort studies to determine whether early routine grommet insertion in children with cleft palate has a beneficial effect on hearing and speech and language development compared with conservative management. They found many confusing and contradictory results in these studies concerning early routinely grommet insertion versus grommet insertion in selected cases. Most studies were either small or of poor quality or both. However, they concluded that there was insufficient evidence on which to base the clinical practice of early routine grommet placement in children with cleft palate.

In order to detect sensorineural hearing impairment (SNHI) earlier than before, neonatal hearing screening by Otoacoustic emissions (OAE's) and Automated auditory brainstem responses (AABR) is introduced in the Netherlands since 2007-2008 (Ploeg, 2014). After detection at a very young age, HI can be diagnosed at Speech and Hearing Centres (6-8 weeks) (Guideline Dutch Federaton of Audiological Centres, 2014). SNHI will be treated by hearing equipment, while conductive hearing impairment can be treated by grommets immediately or by temporary hearing equipment until surgery is more convenient. Since otitis media with effusion often is temporary, also a wait-and-see policy is possible. Because there is still no scientifically proven deleterious effect of temporary conductive HI on speech language development in otherwise healthy children (Roovers, 2000), one can also choose to treat depending the speech development. By now, it is clear that grommets are the first choice of treatment when the otitis media with effusion is persistent (Dutch ENT Guideline for persistent otitis media with effusion 2012).

In children with cleft (lip) palate C(L)P otitis media with effusion is especially prevalent between 2 and 6 years of age and gradually diminishes between 7 and 13 years (Sheahan, 2003; Kuo, 2013). With or without otitis with effusion, hearing is often quite normal. Audiological research in non-cleft children proved an often only mild conductive HI in otitis media with effusion (Anteunis and Engel,2000).

There is a debate whether the grommets should be placed routinely (often already during first surgery at the age of a few months) (Valtonen, 2005; Klockars, 2012; Merrick, 2007), or only in selected cases depending the severity of the HI (Andrews, 2004; Kobayashi, 2012). There is no scientifically demonstrated difference between these two treatment options in outcome results with respect to hearing (Kuo, 2013; Tuncbilek, 2002; Phua, 2009) and speech language development (Kobayashi, 2012) in the long run. Even with a conservative treatment policy 28 till 98% (Shaw, 2003; Szabo, 2010) of the children are treated with grommets.

Because the otitis media with effusion often recurs soon after extrusion of the grommets, the effect of grommets seems only symptomatic and not causal (Broen, 1995; Kuo, 2013; Sheahan, 2003).

From the literature it is seems clear that there are negative long-term deleterious effects (tympanosclerosis, atelectasis, fixation of the middle ear ossicles, eardrum perforations) when grommets are inserted often (Phua,2009; Kuo, 2013; Kuo, 2015). There seems to be a relation with the number of insertions. Especially T-tubes are notorious for persistent eardrum perforations after extrusion (Hornigold, 2008). Cholesteatoma can be seen in 1.5 – 6.9% of children with C(L)P (Spilsbury, 2013) and in 8 – 13% reconstructive middle ear surgery is indicated (Sheahan, 2003; Goudy,2006).

With respect to the relation between type of cleft surgery and hearing and ear results, the conclusions are not clear; in a systematic review, Antonelli (2001) cannot demonstrate a difference in hearing results after palate surgery between the techniques of Furlow and Von Langenbeck, while Carroll (2013) finds a small positive correlation in ear results after palate surgery with the Furlow technique versus the Von Langenbeck and the Wardill-Killner techniques, respectively. However, after the age of 6 years this difference was not present anymore.

18-28% of children with C(L)P do not pass the neonatal hearing screening (Chen, 2008; Andrews, 2004; Szabo, 2010). In most cases, there is otitis media with effusion, but one should be cautious for permanent SNHI, often part of a syndrome that is frequently not clearly visible. Syndromes are present in 30-50% in cleft palate (Andrews, 2004) and in 14% in CLP. The chance of a permanent HI in C(L)P children who fail the neonatal hearing screening is estimated to be 5,4 times higher than in children without cleft (Chen, 2008). It is suggested therefore to first insert grommets after failing the neonatal hearing screening in cleft children in order to improve the audiological investigations and detect SNHI earlier (Jordan, 2014).

Hearing equipment

Instead of grommets, hearing equipment can be suggested as an alternative. The audiological results are comparable with those of grommets, but there are less complications and less long-term negative sequelae (Maheshwar, 2002; Gani, 2012). However, hearing equipment as an alternative is not often suggested to the parents (Tierney, 2013). A model-based cost-effectiveness analysis showed that grommets are the most cost-effective on the long term, followed by hearing equipment and that a wait and see policy is the least cost-effective (Mohiuddin, 2014).

Conclusions

Very low GRADE	There is very little proof that VTI (ventilationtube insertion) may improve hearing outcomes in the children with cleft palate in the long run. *Kuo, 2014*

Very low GRADE	There is very little proof that early routine VTI may benefit children with cleft palate in the development of speech and language. *Kuo, 2014; Ponduri, 2009*

High	Conductive hearing impairment caused by otitis media with effusion is almost ubiquitous in children with C(L)P.

Moderate	Hearing results of early routinely insertion of grommets are not different than in a conservative treatment with grommets.

Low	There seems to be a correlation between the frequency of grommet insertion and the long-term sequelae.

Low	There is no difference in audiological results between treatment of HI due to persistent otitis by grommets or by hearing equipment.

Low	Treatment of otitis media with effusion by grommets results in more long-term sequelae than treatment by hearing equipment.

Low	Permanent hearing impairment (conductive and/or sensorineural) is more prevalent in children with than without C(L)P.

Considerations

Children with a cleft (lip, alveolar arch and) palate have a higher risk of failing the neonatal hearing screening than children without clefts of the lip and palate. This is due on the one hand to the frequent otitis media with effusion and on the other hand to the greater risk of permanent sensorineural hearing loss as a result of syndromes. For this reason, the neonatal hearing screening for children with clefts of the lip and palate has been changed from 2 x Oto-Acoustic Emissions (OAE) screening followed by measurement in a 3rd stage of Automatic Auditory Brainstem Responses (AABR) for children without clefts of the lip and palate to 1 x OAE screening followed by measurement in a 2nd stage of AABR. Please bear in mind here that the threshold for OAE screening is 20-25 dB and the threshold for AABR screening is 40 dB.

It is presumed that mild hearing loss to 35 dB in otherwise healthy children generally does not result in delayed speech-language development during the first year of life. To date, there is also no irrefutable evidence that (recurrent) otitis media with effusion (the most common cause of mild hearing loss in the Netherlands) has a negative effect on the speech-language development of otherwise healthy children.

Conversely, hearing loss is often established as a contributing factor in children with delayed speech-language development. In view of these findings, there is an extensive discussion about the insertion of tympanostomy tubes. This discussion is even more pronounced in regard to children with clefts of the lip and palate, due to the anatomical abnormalities that are also present, which can also have a negative effect on normal speech-language development. In some cleft teams, tympanostomy tubes are therefore always inserted during the first surgery and replaced after each episode of otitis media with effusion, whilst in other cleft teams the tympanostomy tubes are inserted selectively. There are also major differences in the frequency of insertion of tympanostomy tubes during the further course of treatment of orofacial clefts. However, there is now mounting evidence that this can result in long-term negative effects on ear and hearing status, without any significant difference in results between frequent insertion of tympanostomy tubes and a more conservative approach.

Therefore, one can consider working together closely with audiological centres, where age-appropriate hearing diagnostics can be performed from a very early age. The results can then be included in the (indication for) treatment of middle ear problems. From the age of 4 to 5 years, audiological diagnostics can also be performed with adequate reliability at the ENT (outpatient) clinic. A proposal can be made here to treat conductive hearing loss caused by otitis media with effusion with loss greater than 25-30 dB. Faster intervention can be considered in the case of delayed speech-language development.

As there is also a greater risk of sensorineural hearing loss due to an as yet undiagnosed syndrome, close cooperation - in the area of audiological and genetic testing - between the ENT physician, the audiological centre and the clinical geneticist is strongly recommended.

Recommendations

Ask for the results of the neonatal hearing screening for each child with a cleft (lip, alveolar arch and) palate.

Check the hearing of children with a cleft (lip, alveolar arch and) palate thoroughly. The recommendation is to perform periodic testing in an audiological centre up to the age of 3-4 years, followed by testing at the ENT (outpatient) clinic if indicated. These examinations should be tailored to the surgical protocol.

Check the hearing of children with a cleft (lip, alveolar arch and) palate at least once post-operatively after insertion of tympanostomy tubes, in order to rule out sensorineural (perceptive) hearing loss (see Dutch Guideline Otitis media with effusion (NVKNO, 2012, available on www.richtlijnendatabase.nl).

Insert tympanostomy tubes in children with a cleft (lip, alveolar arch and) palate only if indicated (see Guideline Otitis media with effusion) and take the audiological findings and speech-language results into consideration (and not only the presence or absence of otitis media with effusion).

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Chapter 7 Hypernasality in patients with clefts of the lip and palate

Module 1: Diagnosis of hypernasality

Clinical question
What is the best diagnostic strategy for determining and analysing velopharyngeal insufficiency (VPI) in children with a cleft (lip, alveolar arch and) palate?

Introduction

Children with a cleft (lip, alveolar arch and) palate can experience speech and resonance problems that are not consistent with normal speech development. These speech and resonance problems are usually caused by velopharyngeal insufficiency (VPI). VPI is defined as an inability of the velum and the lateral and posterior walls of the pharynx to separate the oral cavity and nasal cavity whilst speaking and/or swallowing (Collins, 2012). VPI is a relatively common problem in children with clefts of the lip and palate involving at least the palate and can occur both before and after surgical correction of the palate (Collins, 2012). The cause of this is usually a soft palate (velum) that is too short or not mobile enough, but it can also be caused by control problems or a combination of factors. Another possibility for the development of speech and resonance problems is the presence of a (remaining) opening in the hard palate.

As a consequence of VPI, children have difficulty achieving oral control of the air flow during speech. In addition to other factors, this oral air flow is required to produce various speech sounds correctly. VPI results in hypernasality (of the vowels) and/or nasality or nasal snoring (on the consonants). Compensation strategies can also develop in the speech, in the form of - for example - glottal realisations or glottal amplifications, pharyngeal productions, backing and/or active nasal productions.

The diagnostic phase in which the speech and/or resonance problems and the (degree of) VPI are diagnosed consists of a range of available examinations and there is significant practice variation between the cleft teams in this area. The following examinations are used in the Netherlands: speech therapy examination (including mirror tests), nasal endoscopy, (acoustic) nasometry and video fluoroscopy. The diagnosis of hypernasality aims to determine which examinations should at least be performed in order to make a reliable diagnosis of VPI. Factors such as reliability, objectivity, burden on the child and the cost-benefit ratio play a role in this decision. Greater uniformity in making the diagnosis of VPI is desirable, with a view to achieving the best possible end result of the treatment and being able to compare the treatment results between the various cleft teams.

Searching and selecting

In order to answer the clinical question, a systematic literature analysis was performed based on the following PICO:

- **P:** non-syndromal cleft (lip, alveolar arch and) palate patients with a closed palate and speech and resonance problems (in particular hypernasality, velopharyngeal insufficiency);
- **I:** diagnosis of velopharyngeal insufficiency by means of speech therapy examination, nasometry, nasal endoscopy, video fluoroscopy, MRI;
- **C:** comparison of the diagnostic instruments;
- **O:** diagnosis of velopharyngeal insufficiency (VPI, hypernasality, gap size).

Relevant outcome measures
The guideline task force defines the diagnosis of velopharyngeal insufficiency (hypernasality) as a critical measure of outcome. VPI refers to a non-functional closure between the nasopharynx and the oropharynx when speaking, making normal speech and/or resonance impossible.

Search and selection (Method)
Medline (OVID), Embase and the Cochrane Library were searched with relevant search terms between January 2007 and 27 November 2014. Reviews, RCTs and observational studies were included. The search strategy can be found in the appendix.

Studies were selected based on the following selection criteria: Clinical research comparing two diagnostic methods to diagnose velopharyngeal insufficiency (hypernasality) in children with a cleft palate with a suspicion of speech impairment (specifically open nasality, velopharyngeal insufficiency).

A total of 245 papers were found with the literature search. Based on the title and abstract, 71 papers were selected. None were selected based on the full text (see the exclusion table in the appendix).

Summary of the literature
No relevant papers comparing two diagnostic methods for diagnosing velopharyngeal insufficiency (hypernasality) in children with cleft palate with a suspicion of speech impairment were found.

Conclusions
Not applicable.

Considerations
The most reliable diagnostic strategy for confirming velopharyngeal insufficiency (VPI) remains unclear due to a lack of scientific studies that reliably compare the different diagnostic strategies. Therefore, in the following section, the guideline task force would like to propose a diagnostic strategy for which a consensus exists within the guideline task force. This strategy describes which examinations are a minimum requirement for the reliable confirmation of the diagnosis of velopharyngeal insufficiency. It also describes which disciplines should at least be involved in making the diagnosis of VPI and at which points in the entire treatment course this diagnostic strategy can be implemented. In conclusion, a flow diagram has been created to clarify matters.

If a child with clefts of the lip and palate is suspected to have VPI, then a speech therapy examination will first be performed by a speech therapist from clefts of the lip and palate team, preferably in combination with oral inspection to rule out severe defects or an extremely short velum and to get a first impression of the mobility of the velum.

During this first appointment, the speech therapist will perform initial measurements of the speech, resonance and intelligibility of the child. If, after this examination, the speech therapist suspects VPI and the child is cooperative enough and able to follow instructions, speech therapy will be started. In some cases, this is sufficient to achieve good speech, resonance and intelligibility.
If a period of six months of specialised speech therapy does not produce adequate effects on speech and resonance and the child was able to follow instructions during the treatments, the child will return for further examinations within the cleft team.

The aim of these further examinations is to collect enough relevant information about the VPI affecting the child in question with clefts of the lip and palate, that the cleft team is subsequently able to:

a) make a well-founded decision about whether or not to recommend a speech-improving procedure.
b) determine the most effective technical variant of the speech-improving procedure.

The age at which the further examinations are started varies on average between 3½ and 5 years and depends on the intelligibility, the level of cognition, the language level and the cooperation of the child. If the child is registered with the cleft team at a later age, then the first visit should not only include a speech therapy examination, but also an examination to exclude a too short soft palate or submucous cleft palate. As these children almost always meet the criterion of half a year of specialised speech therapy with inadequate effect, the diagnostic strategy described above and the flow schedule provided below are also followed.

Available examinations
The following examinations for diagnosis and analysis of VPI are known to and available in the Dutch orofacial care:

A: Speech therapy examination by the speech therapist of the cleft team
The aim of the speech therapy examination is to describe the intelligibility, the speech problems and the resonance (usually hypernasality) resulting from a possible VPI (Kummer, 2011). The speech therapy examination for children born with clefts of the lip and palate was developed in 2003 (Meijer, 2003). In the Netherlands, this examination is performed exclusively by speech therapists who work in a cleft team and therefore form part of the National Guideline Task force for Cleft Speech Therapists, affiliated with the Netherlands Association for Orofacial Clefts and Craniofacial Abnormalities (NVSCA). The quality of the speech therapy examinations that are performed is guaranteed by means of consensus training (twice a year) within this guideline task force. A study is currently being conducted, funded by the Netherlands Association for Plastic Surgery, to validate this speech therapy examination. The speech therapy examination consists of evaluating

the speech at word level, sentence level and spontaneous speech level, evaluating the resonance and the presence of any grimaces and performing mirror tests. The intelligibility is ultimately assessed on a five-point scale. Research by Klinto (2011) reveals that the evaluation of the speech at word level gives the most reliable assessment of the child's best performance. When assessing running speech, the repetition of sentences is a reliable testing method for children with clefts of the lip and palate. This study examined 20 children with and 20 children without clefts of the lip and palate at the age of five years.

B: Oral inspection

If the speech therapy examination reveals indications for the presence of VPI, then an oral inspection of the palate should preferably be performed. If possible, both examinations should take place on the same day. If the child has already undergone surgery of the soft palate, then the aim is to estimate the length and the mobility of the soft palate, the mobility of the velum, the position of the musculus levator veli palatini and the presence of adenoids and tonsils. The aim of this is to check for the existence of a bifid uvula or any other indications of a submucous cleft palate.

Another objective is to inspect the hard palate for the presence of a fistula. Or, if the hard palate has not been closed yet, the size of the opening. An opening in the hard palate can have a negative effect on hypernasality and in some cases is the main cause of it.

If there is a fistula present in the hard palate, then the advice is to close this fistula during (a part of) the speech therapy examination, the nasometry and the nasal endoscopy, so that the effect of the fistula on the hypernasality can be objectified. The temporary closure can be achieved with wafer paper or edible paper, for instance.

C: Mirror test

A part of the speech therapy examination for children with clefts of the lip and palate is the mirror test. (Meijer, 2003). The aim of the mirror test is to detect nasal emission with several standard items (papa, pipi, kaka, kiki, ffff, ssss, ie, oe and the sentence "Piet zit op de stoep"). These are items that contain denasal consonants and vowels. Whilst the child is repeating these items - after the child has started - a mirror is placed under the child's nose, so that any emission of air becomes visible in the form of condensation on the mirror. The mirror is removed from under the nose before the end of the series of repetitions. If left in place, the exhaled breathe will be visible on the mirror and the measurement will not be reliable. If condensation is visible on the mirror during one or more of these items, then this is an indication that VPI is present.

D: Acoustic nasometry

In addition to the speech therapy examination, including the mirror tests, the speech therapist should preferably also perform acoustic nasometry. This is an objective measurement (Karnell, 2011; Sweeney and Sell, 2008; Brunnegard e.a. 2012). It is advisable to use standard texts for this measurement (van de Weijer and Slis, 1991; van der Heijden, 2011). The standards texts and benchmarks that are used by the speech therapists in cleft teams in the Netherlands have been included in the appendix.

The reliability of the measurement depends partly on the cooperation (and age) of the child. The child must be able to repeat the standard sentences and must accept the helmet that needs to be worn during the nasometry measurements. Research by Van

der Heijden (2011) revealed that the majority of children aged six years and older are able to cooperate well in the acoustic nasometry. Children aged six years and older cooperated significantly better than children aged younger than six years. In children aged four and five years, the cooperation is very dependent on the situation. This study examined 159 children aged between four and six years.

Not every cleft team in the Netherlands currently has access to a nasometer. The teams that do have a nasometer, use various types of nasometers manufactured by the company Kay Pentax. The different types of nasometers by the brand Kay Pentax exhibit only small differences in nasometry values, which cannot be observed subjectively (Kay Pentax Instruction Manual Nasometer II, 2010). As such, it is likely that the nasometry values are comparable between the Dutch cleft teams, provided that the nasometry is performed according to the same procedure and expressions and a Kay Pentax nasometer is used. It would be preferable for each cleft team to have its own nasometer, because this is one of the few objective measurements that can confirm abnormal resonance.

If the diagnosis of VPI has been confirmed and a (surgical) treatment will follow, then acoustic nasometry can be repeated before and after the treatment.
The child's speech pattern must be taken into consideration when interpreting the nasometry values. If a child exhibits compensatory speech before the speech-improving surgery, this could have a positive effect on the nasometry values. Despite nasometry being an objective measurement, the data from the speech therapy examination should always be included in order to obtain a reliable assessment of the speech and resonance and the improvement in both.

E: Nasal endoscopy

The plastic surgeon, ENT physician and/or speech therapist performs the nasal endoscopy (Karnell, 2011) in order to assess the velum function (musculus levator veli palatini), as well as the functioning of the surrounding muscles and the possible presence of an (enlarged) adenoid to compensate for possible VPI. It is advisable to use the standard expressions for this examination (see appendix). The nasal endoscopy should be recorded on video as documentation, but more importantly to be able to have a multidisciplinary discussion and interpretation of the images in the cleft team.

The physician can use nasal endoscopy to assess whether non-functional closure occurs between the nasopharynx and the oropharynx during speech. If this is the case, then this confirms VPI. Depending on the size of the opening, the functioning of the musculus levator veli palatini and the surrounding muscles, the further course of action should be determined in a multi-disciplinary context. Speech therapy examination and nasal endoscopy provide information about the anatomical and functional foundation of the child and these examinations contribute to the decision-making process for a speech-improving procedure (Rayan, 2014). Nasal endoscopy provides a detailed image of the anatomy of the pharynx, the presence or absence of an adenoid, the dynamics of the musculus levator veli palatini and the surrounding muscles during speech and is also able to detect very small defects. In addition, the child is not exposed to radiation and the costs are low. However, there are also various disadvantages. The child has to cooperate and the size of the opening cannot be determined reliably (Howard, 2011). However, it is not possible to measure the size of the opening reliably using images from

nasal endoscopy, making it impossible to perform an objective comparison of the size of the opening before and after surgery. There is also the possibility that speech will be affected as a result of irritation caused by the nasal endoscope in the nose, or as a result of reduced sensory feedback if a local anaesthetic is used.
The chances of a successful nasal endoscopy depend on the doctor's experience and the child's cooperation. Therefore, it is advisable to perform this examination with two people present and to make image and sound recordings of the examination. Practical experiences teach us that nasal endoscopy can be quite scary for the child. It is therefore important that the child and the parents receive proper instructions before the procedure, so that they are adequately prepared. Usually a child will be sufficiently cooperative from the age of about three-and-a-half to four years.

F: Video fluoroscopy

If nasal endoscopy was unsuccessful or not possible (yet), then video fluoroscopy can be performed as an alternative. The advantages of video fluoroscopy are that it is simple and quick to perform and can be used for very young children. Video fluoroscopy can be used to get an impression of the velum function from different angles (Karnell, 2011). This examination therefore also provides information about any non-functional closure between the nasopharynx and the oropharynx during speech and can be used as a pre-surgical and post-surgical measurement. However, there are also various disadvantages: this is a two-dimensional image and the costs are high (Howard, 2011). In addition, the radiation dose that is required can be deemed a disadvantage by the child's parents or carers. The child's cooperation is also required for this examination. The child must be able to repeat sounds, words and sentences. It is also very important that the child sits still during the examination to ensure optimum imaging. This can be achieved by creating a head support, which must include eye protection. The speech therapist should preferably be present during this examination.

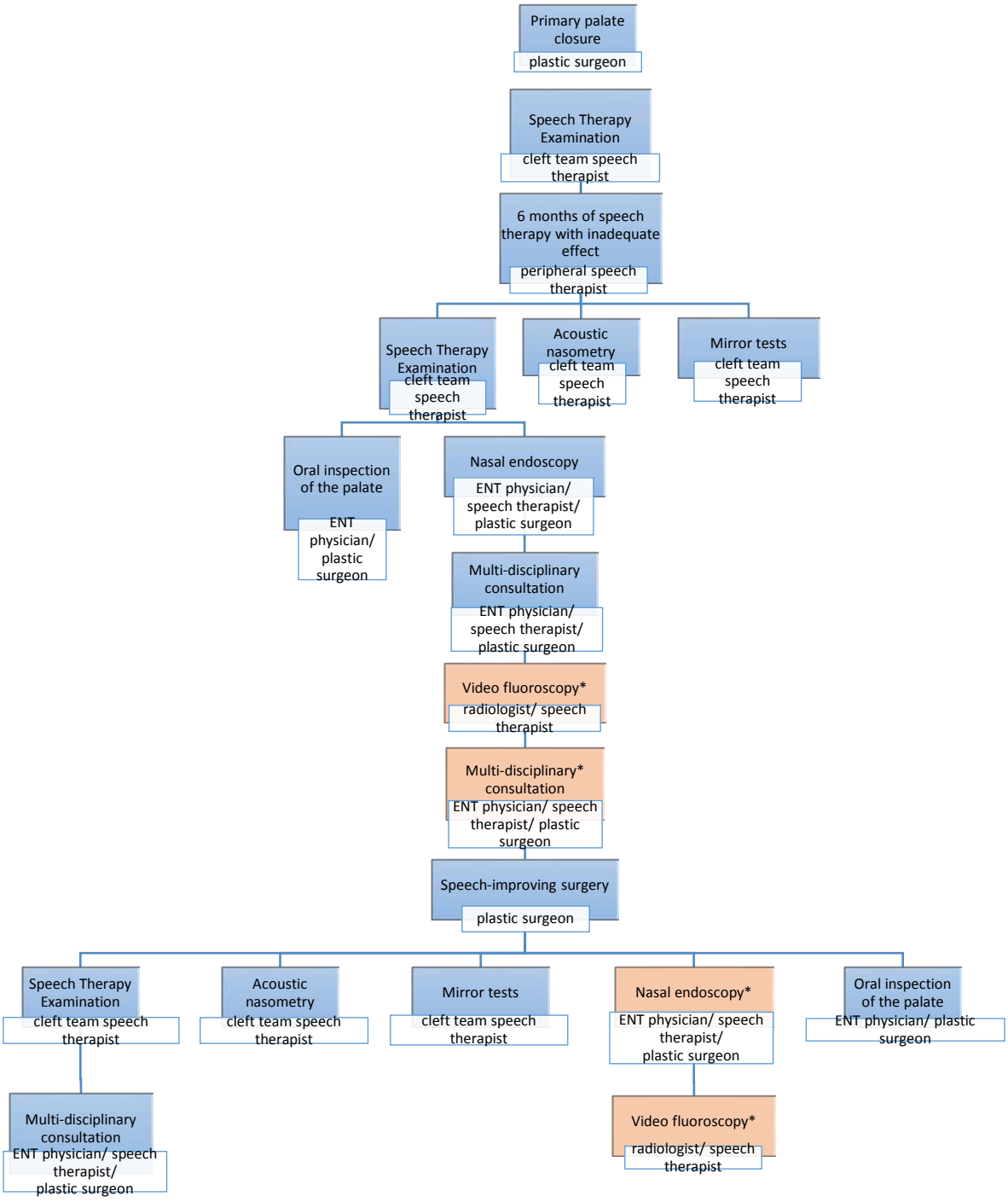
In general, the advice is to give both parents and child good information and instructions about the execution, the course and the aim of an examination.

G: Functional MRI

There are indications that functional MRI could become a useful additional technique in the future to diagnose VPI (Kuehn, 2001; Howard, 2011; Perry, 2014). Study protocols have already been developed for the use of MRI with the aim of confirming the diagnosis of VPI. However, further investigation is required to make this protocol applicable in daily clinical practice (Perry, 2014). The benefits of the MRI that are described include: the reproducibility of the examination, the non-invasive nature of the examination, no ionising radiation is required and an MRI provides detailed information about the musculus levator veli palatini. Disadvantages include the high costs, the length of the examination and the noise (Howard, 2011).

MRI is not used in the Netherlands (yet) to diagnose VPI. This appears to be due in part to the costs associated with the examination.

Schematic representation of diagnostic strategy for VPI



* Optional examinations/activities are marked in orange. If nasal endoscopy was unsuccessful or not possible (yet), then video fluoroscopy can be performed as an alternative.

Recommendations

The diagnosis of velopharyngeal insufficiency should be made in a multi-disciplinary setting (at least a surgeon, ENT physician and speech therapist).

Following primary palate closure, the diagnosis of velopharyngeal insufficiency should only be made after six months of specialised speech therapy with inadequate treatment result, on condition that the soft palate appears to be sufficiently long and mobile (during intra-oral inspection) and the child has been able to follow instructions adequately.

The speech therapy examination (Meijer, 2003) to diagnose velopharyngeal insufficiency should be performed by a speech therapist who participates in the national task force for orofacial cleft speech therapists.

To make the imaging studies as complete as possible, preferably also perform an oral inspection, acoustic nasometry, mirror tests and nasal endoscopy to confirm the diagnosis of velopharyngeal insufficiency.

Perform nasal endoscopy if the chances of success for the child are high (usually from three-and-a-half years).

Perform video fluoroscopy as an alternative to confirm the diagnosis of velopharyngeal insufficiency (for example if nasal endoscopy is not successful) or to provide additional diagnostic information about the velum function.

The speech therapist should preferably be present during nasal endoscopy and video fluoroscopy.

Make a photo or video recording of the nasal endoscopy.

One year after the speech-improving surgery, repeat all the examinations that were performed pre-operatively, except possibly the nasal endoscopy/video fluoroscopy, so that the effect of the speech-improving surgery can be determined as objectively as possible.

One year after the speech-improving surgery, repeat the nasal endoscopy/video fluoroscopy if examinations performed after 6 months of specialised speech therapy indicate the presence of velopharyngeal insufficiency with insufficient understandability.

Do not perform an MRI as a standard part of the diagnostic process for determining velopharyngeal insufficiency.

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Module 2: Treatment of hypernasality

Clinical question
What is the best surgical treatment strategy for velopharyngeal insufficiency (VPI) in children with clefts of lip and palate?

Introduction

The aim of surgical treatment of velopharyngeal insufficiency (VPI) is to restore a functional closure between the nasopharynx and the oropharynx, so that normal articulation and speech can follow. Various procedures for the secondary treatment of velopharyngeal insufficiency have been described, with reposition of the palate musculature to a more anatomical position (connection placed in median and more posterior position) at the top of the list, even if this procedure has already been performed previously.

Additional techniques include pharynx posterior wall flaps (attached cranially or caudally), sphincter pharyngoplasties (such as Orticochea), a combination of extension of the palate and a cranially attached pharynx flap (modified Honig), extension plasty of the palate (Furlow Z plasty or unilateral/bilateral buccal flaps) and pharynx posterior wall augmentation (e.g. fat injection therapy or Hynes). Each treatment option has its advantages and disadvantages. The aim of this clinical question is to determine which surgical treatment strategy is preferable in the case of velopharyngeal insufficiency in a patient with clefts of the lip and palate for which primary palate closure has already been performed.

Searching and selecting

In order to answer the clinical question, a systematic literature analysis was performed based on the following scientific question:

- **P:** Non-syndromal cleft (lip, alveolar arch and palate) patients with a closed palate with velopharyngeal insufficiency;
- **I:** Pharyngoplasty; palate plasty; pharynx augmentation; fat injection therapy;
- **C:** Comparison of surgical options;
- **O:** Speech; presence of (open) nasality (gap size); revision surgery; and postoperative complications or side effects (sleep apnoea, dehiscence/detachment of flap).

Relevant outcome measures

The guideline task force did not define these outcome measures a priori, but used the definitions from the study. The guideline task force deemed success percentage of the procedure (defined as postoperative (open) nasality) as a critical measure of outcome for the decision-making process, and speech and complications or side effects as important outcome measures for the decision-making process.

Search and study selection (methods)

A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and April 9, 2014. This search was aimed to

identify systematic reviews, RCTs, controlled clinical trials, and observational studies. Detailed search characteristics are shown in the appendix.

Studies that included patients with repaired cleft lip and palate were selected if they compared surgical interventions to correct velopharyngeal insufficiency. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: speech, hypernasality, hyponasality, adverse effects and/or complications.

Results selection
The initial search identified 315 references. After selection 11 studies were found describing VPI and assessed full-text. Nine studies were excluded because these studies did not meet the inclusion criteria (see appendix). One of these 9 studies was a systematic review/ meta analysis (Collins, 2012). However, in adition to this review two RCT studies were described which do meet the inclusion criteria. The evidence table and risk of bias assessment table are added as an appendix.

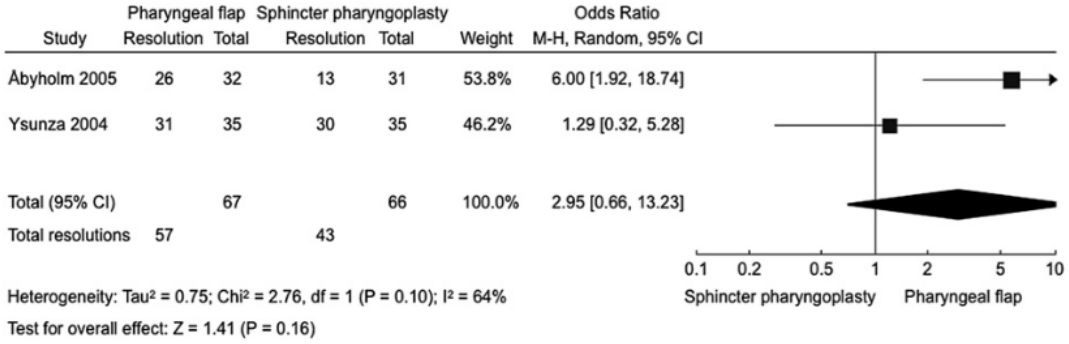
Summary of the literature
Study characteristics
The study by Ysunza (2004) concerned a 7-year prospective study to assess the planning and results of pharyngeal flaps and sphincter pharyngoplasties for correcting velopharyngeal insufficiency. The customized pharyngeal flap and sphincter pharyngoplasty were performed according to findings of videonasopharyngoscopy and multiview videofluoroscopy. The study population consisted of 70 patients with complete unilateral cleft lip and palate with no other medical conditions, which was randomly divided into two groups. Palate repair was performed before 8 months of age in all patients. Age ranged from 4 years and one month to 7 years and 10 months (median: 5 years, 2 months) in the group with a pharyngeal flap, and from 4 years and 5 months to 7 years and 7 months (median: 5 years 4 months) in the group with sphincter pharyngoplasty. Outcomes were evaluated postoperatively and after four months. No loss to follow up was reported.

The study by Åbyholm (2005) is a randomized clinical trial comparing pharyngeal flap and sphincter pharyngoplasty for correcting velopharyngeal insufficiency in 97 patients with a repaired cleft palate with no other medical conditions were randomly divided in two groups. Patients, aged 3 to 25 years old, were evaluated at both three months and one year.

Results
<u>VPI resolution</u>
Whereas Ysunza (2004) reports no significant difference in VPI resolution between the groups, Åbyholm (2005) found a significant difference in favour of pharyngeal flap (P = 0.005). The pooled odds ratio for VPI resolution calculated by Collins (2012) was found to be 2.95 (95% CI: 0.66 - 13.23) in favour of the pharyngeal flap. In figure 1 the forest plot from Collins (2012) is shown. The meta-analysis by Collins (2012) included the selected studies by Ysunza (2004) and Åbyholm (2005). Collinset (2004) pooled the data of the two studies (133 patients) to calculate a pooled odds ratio for VPI resolution. This figure shows the number of patients with resolution of VPI after pharyngeal flap and sphincter pharyngoplasty procedures at follow-up times of 3 to 4 months for the RCTs of

Åbyholm and Ysunza. Odds ratio and 95% confidence intervals for each study and for the meta-analysis as a whole are shown.

Figure 8.1 Pooled odds ratio for VPI resolution (Collins, 2012)



Although Åbyholm (2005) found a high level of clinical improvement for both surgical interventions, at 3 months postsurgery, elimination of hypernasality was found in twice as many patients after flap surgery (significant). At 12 months post-surgery, however, Åbyholm found no statistically significant difference in VPI resolutions between the sphincter and pharyngeal flaps procedures, resp. 78% vs. 83% (P = 0.45).

Postoperative complications

Both studies reported no differences in postoperative complications between the groups. Åbyholm reported low complication rate, low reoperation rate, and no significant differences between the two procedures. In addition, Åbyholm found that both procedures rarely resulted in clinically significant sleep apnea directly after surgery or on long-term incidence. This was assessed by carrying out overnight polysomnograms 1 month prior to surgery, and repeated 4 to 6 weeks and 1 year after surgery.

Grading the evidence

Grading the evidence started at the level of high evidence. Downgrading with three levels was, however, necessary as the sample size needed for statistical significance was not achieved, and due to heterogeneity of results. The number of patients, and for some outcomes like complications the number of events was very low.

Conclusions

Very low GRADE	We found very little proof that pharyngeal flap and sphincter pharyngoplasty are equally effective in treating velopharyngeal insufficiency. *Ysunza, 2004; Åbyholm, 2005*

Very low GRADE	We found very little proof that pharyngeal flap and sphincter pharyngoplasty result in comparable complications in treating velopharyngeal insufficiency. *Ysunza, 2004; Åbyholm, 2005*

Considerations

The most optimum surgical method to correct VPI remains controversial, due to a lack of good randomised controlled, prospective studies that compare the various surgical techniques. In addition, the aforementioned studies and those listed below lack clinical follow-up of sufficient length (at least three years) in order to estimate the value of the surgical result over time. Furthermore, there is no consensus about the objective diagnostic tools for good comparison of the surgical techniques. An important part of the differential diagnosis of VPI, in the case of a previously corrected palate, should also consist of the theory that the previously performed palate closure technique with intravelar veloplasty has not healed optimally. The restored muscle sling may have become dehiscent or formed new adhesions with the posterior wall of the hard palate. Indications to support this include complicated palate healing or scar formation with reduced mobility. However, there is no research that compares repeat intravelar veloplasty to other speech-improving operations.

Considering the limited number of scientific studies, the guideline task force wants to include in the next section the comparative studies in which another surgical technique or combined techniques are described.

Carlisle (2011) performed a retrospective analysis of 46 patients with clefts of the lip and palate (cleft palate not specified (80%) submucous cleft palate (20%, including velocardial facial syndrome) and VPI in which sphincter pharyngoplasty (SP; n=20) was compared to sphincter pharyngoplasty combined with an extension plasty according to Furlow (SP+; n=26). One measure of outcome for this study was the chance of revision surgery due to persistent hypernasality. The two groups were not comparable as far as indication was concerned and differed in such a way that the SP+ group consisted of patients with a greater distance from velum to pharynx posterior wall, as recorded by nasal endoscopy. The results of this study showed that more revision surgery was required in the group with SP than in the group with SP+ (25% versus 4%).

A retrospective comparative study by Meek (2003) describes a population of 93 patients with VPI, in which a caudally (n=53) or cranially (n=40) attached pharynx posterior wall flap was performed. The choice of the pedicle was determined pre-operatively, depending on the presence of an enlarged adenoid and the distance from velum to posterior wall. From a speech therapy perspective, all patients exhibited an improvement in the field of articulation, emission and hypernasality. The improvement of the VPI was significantly larger if surgery was performed before the sixth year of life. No difference was demonstrated between both techniques. An important limitation of this study is the large difference in phenotyping of the patients (a group consisting of: congenital short palate, complete cleft lip and palate to submucous palate).

Both studies revealed that the choice of the plasty depends on the preoperative examination and the perioperative findings regarding the velum, the adenoids and the distance to the pharynx posterior wall. In this way, good results have been achieved both with combined procedures and with caudally and cranially attached plasties.

Ysunza (2001) studied 203 patients, of which 72 children were ultimately included with a non-syndromal submucous cleft palate and VPI. All children were subjected to an oral examination, speech therapy examination, nasal endoscopy and video fluoroscopy.

Patients were randomised into 2 groups: a standard minimal incision palatopharyngoplasty (MIPP) was performed in the control group (n=37) and in the experimental group the MIPP was combined with an individualised surgery based on the preoperative diagnostics (n=35; 32 pharyngeal flap, 3 sphincter plasty). Both techniques produced the same results for complete closure (86% in group 1 versus 89% in group 2) and velopharyngeal distance. None of the patients had sleep apnoea after surgery. This is due partly to screening for enlarged tonsils that were first removed surgically before continuing with a pharynx or palate plasty. Considering the minimal differences between the two surgical techniques, the advice from the authors is to opt for the least invasive technique without additional pharynx plasty and to correct residual VPI in a second instance with a more individualised pharynx plasty.

The guideline task force deems that there is insufficient evidence to support the combined surgery on palate and pharynx to correct VPI in comparison to a single procedure. The advice is to separate the operations, with a redo of the palate being advised as the first step.

Keuning (2009) performed an observational longitudinal study involving 130 patients with residual VPI following previous palate surgery, in which a cranially attached pharynx posterior wall flap was performed. The case mix in this study was large, consisting partially of unilateral cleft lip, alveolar arch and palate, partially of bilateral cleft lip, alveolar arch and palate, partially of submucous or isolated cleft palate and also including syndromal patients. A revision surgical procedure was required in 15% of patients and very few complications occurred. Considering the fact that the authors achieved similar results with the cranially attached pharynx posterior wall flap compared to previously described other techniques, they mainly emphasised the surgical aspects of the technique. The working hypothesis was studied to determine whether a more experienced surgeon has fewer complications and therefore a better functional result. The authors emphasise that the outcome of the plasty is often difficult to estimate, due in part to the concept of tube formation/shrinkage and shortening of the flap in the pharynx area. The advice is to cover the raw surface of the pharynx flap in order to reduce tubing (Keuning, 2009; Rintala and Haapanen, 1995).

The study demonstrated that no distinction can be made according to surgical experience, with the youngest surgeon scoring fewer complications than the oldest. They concluded that the individual technical skills of the surgeon are more important in minimising complications than the surgical experience.

Autologous fat injections (lipofilling)

A relatively new intervention to treat VPI is autologous fat injection (lipofilling). A systematic review (Bishop, 2014) examined the literature about pharynx posterior wall augmentations; from artificial additions such as silicone and Gore-Tex to biological materials such as cartilage and lipofilling. Eleven studies about lipofilling were included, of which 3 provided a description of selective augmentation of the pharynx posterior wall and the other 8 studies provided a description of augmentation of the soft palate/pharyngeal arches and pharynx posterior wall. None of these 11 studies was a comparative study. Meta-analysis was not possible due to the strong heterogeneity of the population. No comparable diagnostic resources were used and no clearly comparable objective postoperative assessments were given. All studies used the same

technique to obtain the fat (Coleman set). The amount of remaining volume of the injected fat in short and long term was not consistently reported, except for the study by Filip (2011), which found an association between the volume of fat injected as visible on MRI and a reduction in the velopharyngeal distance. However, this study did not report on the actual clinical change in the VPI.
A preferred location for injection of the fat was not defined. Only 1 complication was reported, namely an increase in fat with increase in the child's weight over a period of 31 months. This resulted in obstructive sleep apnoea symptoms. The conclusion that the authors provided based on this systematic review is that fat injection appears to be a simple, relatively cheap technique with few complications. However, important information is missing about patient selection, volume and location of fat injection, as well as the amount of resorption of the injected fat depot and the result compared to other existing surgical techniques.

The guideline task force deems that there is currently no proven effectiveness for the use of lipofilling in the treatment of VPI. The guideline task force is therefore of the opinion that VPI correction by means of lipofilling should only be used if there are no other surgical options.

General considerations
In the absence of a proven effective universal surgical approach for VPI, the choice of a technique will have to be based mainly on a good preoperative evaluation of the form of VPI, based on the examination as described in the module Diagnosis of VPI. This preoperative and perioperative examination should be recorded and repeated postoperatively if necessary. Not only to check the success or failure of the treatment, but also as a registration and the option for comparison. The age at which surgical correction of VPI can best take place will have to be determined jointly by the treating physicians, using the child's ability to follow instructions during speech therapy exercises as a guideline. This ability to follow instructions can be tested during the speech test, which should form part of the standard preoperative diagnostic tests.

Considering the limited defined differences between the pharynx posterior wall flap and pharynx sphincteroplasty, both techniques appear to be comparable with regard to clinical effectiveness.

One cause of the limited differences between techniques could very well be the limited sample size of the various studies and the diversity of conditions of the included patients resulting in VPI. In order to demonstrate a difference of 20% between various techniques in a study with an expected drop-out rate of 10% of the study population, a group size of 292 patients is required (Åbyholm, 2005). As many identical studies as possible should be started in order to achieve these numbers, knowing that the number of patients included per hospital is low.

Recommendations

Make a choice for a specific surgical technique based on preoperative speech therapy examination combined with an examination such as nasal endoscopy and/or video fluoroscopy (see module Diagnosis of hypernasality).

Consider an intravelar palatoplasty with repositioning of the palate muscles before performing a pharyngoplasty if the patient has persistent velopharyngeal dysfunction despite previously closed palate.

In the case of persistent velopharyngeal insufficiency despite renewed repositioning of the palate muscles, consider a pharyngoplasty that is based on renewed diagnostic tests such as nasal endoscopy and/or video fluoroscopy.

For a submucous cleft palate, consider a simple palatoplasty over a combined operation consisting of a palatoplasty with pharyngoplasty.

Only use fat injection in the context of a scientific study.

Literature

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Chapter 8 Bone grafting procedure in patients with clefts of the lip and palate.

Module 1: Timing of the bone grafting procedure

Clinical question
Which considerations (benefits and disadvantages) play a role in determining the moment (timing) of the bone grafting procedure in a patient with a unilateral or bilateral cleft lip, alveolus (and palate)?

Introduction
Patients with a cleft lip, alveolus (and palate) will at some point undergo alveolar bone grafting of the cleft and any existing oronasal communication will be closed. A bony bridge is created between both maxillary segments, which are stabilised and thereby support the base of the ala nasi on the cleft side. This also allows the canine and/or lateral incisor to erupt on the cleft side. Timing and technique of this procedure are important.

As far as the timing is concerned, in the Netherlands we usually opt for early secondary closure, i.e. when the root of the cuspid tooth is 1/2 to 2/3rd formed and before it erupts into the cleft. In practice, this is usually between the age of 9-12 years. If the procedure is carried out based on the eruption of the lateral incisor, the procedure can sometimes be performed earlier in life. Other, less common time points for the closure of the alveolar cleft and bone grafting are: primary alveolar cleft closure / alveolar cleft grafting during closure of the lip and/or soft palate and late secondary closure, after the canine has erupted on the cleft side, but still in the mixed dentition phase. Tertiary closure of the alveolar arch cleft takes place in adulthood.

Searching and selecting
In order to answer the clinical question, a systematic literature analysis was performed based on the following scientific question with accompanying PICO:

Is there a preference regarding the timing for bone grafting surgery in a patient with a cleft of the lip and palate?

- **P:** Patients with an alveolar cleft;
- **I:** Early secondary closure of the alveolar cleft by means of a bone grafting procedure;
- **C:** Other time points for a bone grafting procedure: 1. primary closure of the alveolar cleft during lip closure / gingivoperiostoplasties, 2. late secondary closure and 3. tertiary closure;
- **O:** Eruption (disorder) of the canine on the cleft side (important), amount of bone left in the alveolar cleft (important), persisting fistula, need for revisionary surgery, physiological shape of the alveolar process, pre/post-operative orthodontics: expanding the arch, growth, pain and quality of life.

Relevant outcome measures
The guideline task force deemed the amount of bone remaining in the alveolar cleft, continuity of the maxillary arch and absence of oro-nasal communication to be critical outcome measures for the decision-making process; and eruption of the canine and/or lateral incisor on the cleft side and growth of the maxilla as important outcome measures for the decision-making process.
The guideline task force did not define these outcome measures *a priori*, but used the definitions from the studies.

Search and study selection (methods)
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and March 12, 2014. This search aimed to identify systematic reviews, RCTs, CCTs, and observational studies. Detailed search characteristics are shown in the appendix.

Studies that investigated patients with cleft lip, alveolus and palate were selected if they compared early secondary autogenous bone grafting to bone grafting performed at other developmental moments, like primary, late secondary, or tertiary. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: eruption of the canine at the cleft side, bone height and amount of bone between the nasal floor and the alveolar crest, fistulae, necessity for revisional grafting, orthodontics related to bone grafting, physiological shape of the alveolar process, periodontal condition of the teeth adjacent to the cleft, growth and quality of life measures. Studies that presented test results (p-value) without the size of the effect or association were excluded.

The initial search identified 445 references of which 15 were assessed full text. Ten studies, all with a non-randomized observational study design, seemed to be relevant but two did not present data on the effect size or association for the outcomes of interest. Finally, eight studies were included. The evidence tables and risk of bias assessment are added as an appendix.

Summary of the literature
Study characteristics
Out of eight included studies, six studies compared early secondary bone grafting to late secondary bone grafting prospectively (Rawashdeh, 2007) or retrospectively (Freihofer et al, 1993; Jia, 2006; Miller, 2010; Nishihara at al, 2014; Sindet-Pedersen, 1985). For these studies, sample sizes ranged from 21 to 313 participants. Nishihara (2014) limited the inclusion to patients with a unilateral cleft. Miller (2010) compared bone grafting before and after eruption of the central incisor. This study and the other studies included patients with unilateral and bilateral clefts.

Two of the included studies compared secondary with tertiary bone grafting (Dempf et al, 2002, Trindade et al, 2012). Dempf at al (2002) performed a retrospective study comparing early secondary bonegrafting with bone from the iliac crest during the mixed dentition period (mean age 10.6 yrs) with tertiairy bonegrafting (mean age 21.3 yrs) in a mixed group of unilateral and bilateral clefts. The length of follow-up is not stated.

Trinsdade-Suedam et al (2012) did a prospective study (n=52) in which they compared two groups of patients with alveolar bone grafting using iliac crest bone with a unilateral cleft lip and palate after 2 and after 6-12 months. Group A received secondary bonegrafting during the mixed dentition period before or after eruption of the permanent canine (age 10-13 years), group B had their bone grafting procedure in the permanent dentition (age 15-28 years). Both studies had a considerable number of drop-outs (37.0 and 39.3%).

All treatments were performed using autogenous bone grafts harvesting the particulate bone from the iliac crest. All results have a high risk of confounding by indication. This means that the indication for treatment may be related to the risk of future health outcomes. The resulting imbalance in the underlying risk profile between treated and comparison groups can generate biased results.

Results

Early secondary bone grafting compared to late secondary bone grafting

There was no difference in eruption of the canine adjacent to the cleft measured 1 to 4 years after bonegrafting with iliac crest bone in the study of Nishihara et al (2014). Bony fill was studied by Rawashdeh (2007) in a mixed group of unilateral and bilateral clefts using the Kindelan grading scale. No statistics were performed to test for differences between groups. Descriptive results on rates per Kindelan grading were overall comparable between both groups (example: Grade 1 after early secondary grafting was reported for 90% (unilateral) and 56.2% (bilateral) versus 80% (unilateral) and 57.1% (bilateral) after late secondary grafting). Freihofer (1993) measured success rate of the treatment defined as no oronasal communication and with at least 50 % of the bone graft height. They found that early secondary bone grafting gave significantly better results than late secondary bone grafting for both unilateral and bilateral clefts. Sindet-Pedersen (1985) evaluated the marginal bone-level for teeth adjacent to the cleft. They also concluded that early secondary bone grafting before eruption of the canine gave significantly better results.

Nishihara (2014) reported the number of patients that achieved an acceptable bony bridge was not significantly different between groups (p=0.16). Jia (2006) reported outcomes on interdental septal heights. Success was defined by the Bergland index Type I and II. Success was achieved significantly more frequently after early secondary bone grafting both for unilateral and bilateral clefts (p=0.049 and p=0.044). Failure of interdental septal heights, defined as Bergland index Type III and IV, was more prevalent after late secondary bone grafting but the differences were not significant.

Miller (2010) and Sindet-Pedersen (1985) reported results on fistulae, but the differences were not significant (Miller: two out of 61 fistulae reported for early bone grafting and three out of 38 reported for in the late bone grafting group; Sindet-Pedersen: no fistulae for early secondary bone grafting before eruption of the canine and various [range 1-11] in other groups). Furthermore, Miller et al (2010) gave a detailed description of the observed complications besides fistulae, like pyogenic granuloma, residual alveolar defect without fistula; hip wound dehiscence; gingival hyperplasia, and fibroma. In addition, Jia (2006) reported one patient with chronic infection of the graft resulting in complete failure in the early bone graft group versus five in the late early bone grafting group. In the early bone graft group 9.8% participants

had complications including fistulae compared to 13.2% in the late secondary bone graft group. Differences were not significant.

None of the studies reported the need for a second graf. Outcomes of interest that were not mentioned in the studies are: orthodontics related to bone graft, physiological shape of the alveolar process, and quality of life measures.

Secondary bone grafting compared to tertiary bone grafting
Trindade-Suedam (2012) reported on septal heights using the Bergland index. Two months after the intervention intermediate and palatal septal heights were significantly better in the secondary bone graft group. After six to twelve months the secondary bone grafting group reported significantly better outcomes for all measured septal heights (buccal, intermediate and palatal) than the group with tertiary bone grafting.

Freihofer et al (1993) found that early secondary bone grafting gave significantly better results than tertiary bone grafting for both unilateral and bilateral clefts for closure of the oronasal communication and achieving at least 50 % of the bone graft height. Dempf (2002) provided descriptive results for bone height, which were slightly better for the secondary bone grafting group than after tertiary bone grafting. For example, 85% of the participants in the secondary group had a bone height score between 50 and 100% versus 68% in the tertiary group. On the other hand, infra-occlusion of the teeth adjacent to the bone gap was more frequently reported after secondary bone grafting (48%)vs. 30% in tertiary group). It is stated that a missing lateral incisor may lead to a vertical growth deficit. Loss of teeth adjacent to the cleft was reported for five patients after tertiary bone grafting compared to none after secondary bone grafting. However, no statistical tests were performed for any of the outcomes. Dempf (2002) detected no functional relevant fistulae for both groups.

Grading the evidence
Grading the evidence started at the level of low evidence because all of the included studies had an observational design. Results were not upgraded for any outcome since no very large magnitude of effect was reported, none of the studies had properly controlled for confounding, and no dose-response effect was observed. Downgrading was, however, necessary as a result of sparse data and limitations of study designs (confounding by indication). The number of patients, and for some outcomes like complications the number of events, were very low. In addition, the study designs had major flaws like inclusion on follow up and drop-out rates above 35%.

Conclusions
Early secondary vs.late secondary bone grafting

Very low GRADE	We found very little proof that in cases of unilateral cleft lip, alveolus and palate, early secondary bone grafting is more effective to facilitate eruption of the canine at the cleft side compared to late secondary bone grafting. *Nishihara, 2014*

Very low	We found very little proof that early secondary bone grafting is more

GRADE	effective to provide adequate alveolar bone height. between the nasal floor and the alveolar crest compared to late secondary bone grafting. *Rawashdeh, 2007; Freihofer, 1993; Sindet-Pedersen, 1985*

Very low GRADE	We found very little proof that early secondary bone grafting has better results to facilitate an acceptable bone bridge compared to late secondary bone grafting. *Nishihara, 2014*

Very low GRADE	We found very little proof that early secondary bone grafting causes fewer fistulas and other complications compared to late secondary bone grafting. *Miller, 2010; Jia, 2006; Sindet-Pedersen, 1985*

Very low GRADE	We found very little proof that early secondary bone grafting has better results on septal heights compared to late secondary bone grafting for uni- and bilateral cleft lip patients. *Jia, 2006*

Very low GRADE	We found very little proof that the success rate of early secondary alveolar bone grafting, in unilateral cases, is better (90%) than in late secondary alveolar bone grafting (SABG) (80%). The success rate of unilateral SABG is better than in bilateral SABG. *Rawashdeh, 2007; Freihofer, 1993*

Early secondary vs.tertiary bone grafting

Very low GRADE	We found very little proof that secondary bone grafting has better results on septal heights compared to tertiary bone grafting, in unilateral cleft and palate patients. *Trindade-Suedam, 2012*

Very low GRADE	We found very little proof that early secondary bone grafting is more effective to facilitate bone volume between the nasal floor and the alveolar crest compared to tertiary bone grafting. *Dempf, 2002; Freihofer, 1993*

Very low GRADE	We found very little proof that early secondary bone grafting causes fewer fistulas and other complications compared to tertiary bone grafting. *Dempf, 2002*

Considerations

Alveolar bone grafting in patients with a unilateral or bilateral cleft lip, alveolus and palate forms a fixed part of the treatment of this group of patients. As far as the timing of this procedure is concerned, the literature describes a preference for the early secondary alveolar bone grafting procedure, in other words before the canine has erupted into the alveolar cleft. This is also the most common time point for this procedure in the Netherlands. There does not appear to be much room for primary and tertiary bone grafting procedures in the Netherlands and - based partly on the consulted literature - these time points for treatment will not be discussed any further. As for tertiary alveolar bone grafting, an exception to this is made in the cases in which an alveolar bone grafting procedure has not been performed in childhood for whatever reason.

Based on the consulted literature, there does not appear to be any hard evidence to support the choice between an early or late secondary alveolar bone grafting procedure. However, it should be noted that in the studied literature, the overall success percentage - i.e. the cumulative result measured over several outcome parameters - was higher for the early secondary alveolar bone grafting procedure. Despite the many variables, this seems to apply mainly to the most important outcome measures, namely eruption of the canine and/or lateral incisor in the transplanted bone into the cleft and the remaining bone height/bone volume that stays in place after the procedure. An important reason stated for this is that the erupting canine has a favourable effect on the construction and maintenance of the transplanted bone. This appears to be an essential factor in preventing reabsorption and in maintaining the constructed bone level during the healing process.

The higher “overall” success percentage for the early secondary alveolar bone grafting procedure applies to both unilateral and bilateral cleft lip, alveolus and palate. However, the literature does reveal that this success percentage is generally lower for a bilateral cleft than for a unilateral cleft. Reasons provided for this include that a bilateral cleft lip, alveolus and palate usually involve a larger defect (and a larger soft tissue deficit), reduced vascularisation and greater scar formation. As a result, it becomes more difficult to achieve an adequate watertight closure over the transplanted bone.
The literature generally does not describe more complications for the other time points of closure compared to the early secondary alveolar closure. However, there is very little evidence to support this.

The timing of alveolar cleft closure should be determined in close consultation with the treating orthodontist. The degree of eruption and the stage of root formation of the canine or lateral incisor on the cleft side play a role in this decision. If the lateral incisor is present, has a normal shape and root formation and is likely to erupt in the cleft, this can be a reason to perform the bone grafting procedure at an earlier stage. A single study recommends performing the bone grafting procedure even before the central and lateral incisors have erupted, in order to improve the retention and gingival condition of these elements and to prevent them from migrating into the cleft. In this context, the patient sometimes also prefers early correction of an aesthetically disturbing rotated central incisor, but this can only take place after the bone grafting procedure. This factor can be taken into consideration when deciding to perform the bone grafting procedure at an earlier time point.

Not much information was found in the consulted literature about the effect of timing on maxillary growth. In a cephalometric study, Semb (1988) studied maxillary growth in patients with a unilateral cleft who underwent alveolar cleft closure before the 12th year of life compared to a group without alveolar cleft closure (historical control group). She found that alveolar cleft closure at the age of 8-9 years had no effect on the anteroposterior and vertical growth of the maxilla. At this age, the anteroposterior and transverse growth of the anterior part of the maxilla is virtually complete, only the vertical growth is not complete yet. The effect of surgical intervention on the growth of the maxilla at this age is therefore very limited.

Recommendations

Preferably close the alveolar cleft by means of an early secondary alveolar bone grafting procedure.

Base the timing for the alveolar bone grafting procedure on the position and the stage of root formation (½ - 2/3) of the canine on the cleft side. The presence of a lateral incisor and the moment of its eruption can bring the timing forward. For certain indications, the position of the central incisor can be of importance.

Decide on the timing of the alveolar bone grafting procedure in close consultation with the treating orthodontist.

Consider tertiary alveolar bone grafting only in cases where no (secondary) alveolar bone grafting procedure was performed or when insufficient bone is present in the alveolar cleft for - for example - an implant at a later age.

Literature

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Module 2: Technique of alveolar bone grafting

Clinical question
Is there a preference for a certain type of bone transplant in the bone grafting procedure in a patient with a unilateral or bilateral cleft lip, alveolar arch (and palate)?

Introduction
Patients with a unilateral or bilateral cleft lip, alveolar arch (and palate) will at some point undergo alveolar cleft closure. It provides a continuous and stable maxillary arch and thereby supports the base of the ala nasi on the cleft side. Persistent oro-nasal communications are closed at this stage. Alveolar cleft closure facilitates canine and/or lateral incisor eruption into the alveolar cleft. Timing and technique of this procedure are important.

Careful surgical tissue handling is an important aspect of alveolar bone grafting, as is the case for all interventions in cleft of the lip and palate surgery. It is essential that the mucoperiosteal flaps that are created are closed in a manner that is as watertight as possible. There is diversity in the choice of bone donor site. In the Netherlands, bone harvested from the anterior iliac crest and mandibular symphysis are often used as grafting material. The autograft is sometimes mixed with a bone substitute. The aim of this clinical question is to determine whether the use of a certain type of bone and/or bone substitute yields better results and/or fewer complications during the bone grafting procedure.

Searching and selecting
To answer the clinical question, a systematic literature analysis was performed based on the following scientific question with accompanying PICO:

- What are the (un)favourable effects of the bone grafting procedure using bone from the iliac crest compared to this procedure performed using chin bone (with or without a bone substitute) in patients with an alveolar cleft?
- **P:** Patients with an alveolar cleft;
- **I:** Bone grafting procedure using iliac crest bone;
- **C:** Bone grafting procedure using chin bone, with or without a bone substitute or a bone grafting procedure using only a bone substitute;
- **O:** Bone volume (bone filling percentage), maxillary height, eruption(disorder) of the canine or lateral incisor, post-operative complications such as persistent oronasal fistula, need to perform revision surgery, shape of the alveolar process, pre/post-operative orthodontics: expansion of dental arch, donor site morbidity, repair of the piriform aperture, pain, quality of life.

Relevant outcome measures
The guideline task force deemed eruption (disorder) of the canine and/or lateral incisor to be a critical measure of outcome for the decision-making process; bone volume (bone filling percentage), maxillary height and post-operative complications are important outcome measures for the decision-making process.

The guideline task force did not define these outcome measures *a priori,* but used the definitions from the studies.

Search and study selection (methods)
A systematic search was performed using the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and March 12, 2014. This search aimed to identify systematic reviews, RCTs, CCTs and observational studies. Detailed search characteristics are summarized in the appendix.

Studies that investigated patients with cleft lip and palate were selected if they compared traditional iliac crest cancellous bone grafting to mandibular bone grafting or autogenous bone with a bone substitute. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: bone filling percentage, maxillary height, dental eruption, or postoperative complications.

The initial search identified 240 references of which 8 were assessed full text. Five studies, all with a non-randomized observational study design, seemed to be relevant but did not present data on the effect size or association for the outcomes of interest. Finally, five studies were included. The evidence tables and risk of bias assessment are added as the appendix.

Summary of the literature
Study characteristics
Two studies compared traditional iliac crest cancellous bone grafting to a resorbable collagen sponge impregnated with rhBMP-2 (InFuse Bone Graft kit (Medtronic, Memphis, Tenn.)) (Alonso, 2010; Canan, 2012). A study by Thuaksuban compared traditional iliac crest cancellous bone grafting to a composite of deproteinized bovine bone (DBB) and autogenous cancellous bone (Thuaksuban, 2010). Two studies compared traditional iliac crest cancellous bone grafting to mandibular bone grafting (Enemark, 2001; Freihofer, 1993).

Alonso (n=16; I:8 vs. C:8) as well as Canan (n=12; I:6 vs. C:6) reported a follow-up of 12 months, Freihofer (n=296; I:123 vs. C:59) of at least 12 months, Thuaksuban (n=27; I:13 vs. C:14) of 24 months, and Enemark (n=57) of 4 years. In all studies the intervention group and the control group were comparable at baseline.

Results
Iliac crest cancellous bone grafting versus mandibular symphyseal bone grafting
Enemark (2001) reported no significant difference in terms of eruption disturbances between the mandibular bone grafting group (31.8%) and the iliac crest bone grafting group (35.1%) ($p > 0.05$). Bone volume measured in 'Marginal Bone Level Scores', however, was significantly superior in the mandibular bone grafting group (1:13 vs. 1:33, $p = 0.029$). The number of complications was scarce, although both groups demonstrated some gingival retraction with a longer crown length at the cleft side central incisor.

Freihofer (1993) found significantly better success rates for mandibular symphyseal bone than for iliac crest bone grafting (92% vs. 46%, $p < 0.05$). Success was defined as obtaining no oronasal communication and with at least 50 % of the bone graft height.

Iliac crest cancellous bone grafting versus autogenous bone with a bone substitute or a solitary bone substitute without autogenous bone.

There was no difference in bone filling percentage after 12 months measured by Alonso (2010) and Canan (2012). Alonso reported a significant difference regarding maxillary height between the groups. The maxillary height in the bone-graft substitute group lagged behind compared to the group with iliac crest bone graft after 12 months (mean 10.2 mm vs. 13.9 mm, $p = 0.001$). By contrast, Canan (2012) reported no difference on maxillary height. In both studies, there was no difference in bone healing (postoperative defect volume) between the groups after 12 months (Alonso and Canan et al). Alonso reported undisturbed dental eruption in both groups. No further details were described.

Thuaksuban found no statistically significant difference in average bone graft densities and heights between both groups at each time interval (Thuaksuban, 2010).

Grading the evidence

Grading the evidence regarding mandibular bone grafting started at the level of low evidence because all of the included studies had an observational design. Results were not upgraded for any outcome since no very large magnitude of effect was reported, none of the studies had properly controlled for confounding, and no dose-response effect was observed. Downgrading was, however, necessary as a result of sparse data and limitations of study designs (confounding by indication). The number of patients, and for some outcomes like complications, the number of events were very low.

Conclusions

Very low GRADE	We found very little proof that mandibular symphyseal bone grafting with a bone subsitute is more likely to result in a clinically relevant difference regarding bone volumefilling percentage, maxillary height, and bone healing as compared to Iliac crest cancellous bone grafting. The overall outcome of iliac crest cancellous bone and mandibular symphysis bone to restore the alveolar cleft defects are comparable. *Enemark, 2001; Freihofer, 1993; Alonso, 2010; Canan, 2012; Thuaksuban, 2010*

Very low GRADE	We found very little proof that bone grafting with rhBMP2 on a resorbable collagen sponge is more likely to result in better dental eruption as compared to Iliac crest cancellous bone grafting. *Alonso, 2010; Canan, 2012*

Very low GRADE	We found very little proof that bone grafting with a bone substitute is more likely to result in better dental eruption as compared to Iliac crest cancellous bone grafting.

	Alonso, 2010; Canan, 2012; Freihofer,1993

Very Low GRADE	We found very little proof that adding a bone substitute to an autogenous bone graft (mandibular symphysis) is more likely to give a better result in overall clinical outcome than using an autogenous bone graft alone. *Thuaksuban, 2010*

Considerations

Alveolar cleft bone grafting with autologous bone is still the gold standard for the bone grafting procedure. Bone from either the iliac crest or the chin is used for this purpose. Bone from the iliac crest is mesenchymal in origin and ossifies through a cartilaginous phase (enchondral ossification). Bone from the chin is ectomesenchymal in origin and ossifies without this cartilaginous phase. No evidence was found in the literature for the hypothesis used by some that chin bone therefore yields better results. As bone from the iliac crest and the chin are by far the most commonly used, other donor sites such as the calvarium, tibia and rib have not been discussed in this guideline.

Based on the consulted literature, we can state that the iliac crest and chin bone yield comparable results. The guideline task force therefore concluded that both donor sites can be used. However, there is a high degree of heterogeneity in the formulated outcome measures, which makes proper comparison difficult. The important outcome measures - bone height and bone volume - are best measured using a (cone beam) CT scan. This is a fairly new method and is therefore not widely used yet. This method of measurement was used in only two (Alonso, 2010; Canan, 2012) of the five studies. In the other three studies, these parameters were measured with the aid of conventional X-rays, which only provide a two dimensional image of the transplanted region.

In practice, the volume of the alveolar cleft appears to be a guiding factor in the choice of bone transplant. In general, a unilateral cleft can be repaired using chin bone, but for a larger volume of the alveolar cleft - as is the case in a bilateral cleft - the chin bone is often not sufficient (unless vomer bone is also used following an osteotomy of the premaxilla).

A chin bone transplant results in only intra-oral scars and does not have the co-morbidity that is sometimes associated with the harvesting of bone from the iliac crest. Disadvantages of using chin bone are potential damage to the permanent lower anterior teeth and neuropraxia of the mental nerve. As previously described, the amount of bone that is available can also be insufficient in case of a large volume of the alveolar cleft. This can be the case particularly with early timing of the procedure, when the permanent canines in the mandible are not fully erupted. This limits the bone volume that can be harvested. Mixing the harvested material with a bone substitute can offer a solution. The advantage of using the iliac crest as the donor site is that there is always enough bone available. Depending on the setting, it can also be harvested simultaneously, which can result in a reduction of operating time. No studies were found that reliably studied the cost-effectiveness of bone harvested from the iliac crest versus bone harvested from the chin, with or without a bone substitute.

There is a role for the use of bone substitutes that aim to increase the volume of the autologous bone transplant that is used. Current literature describes good results primarily with the use of calcium phosphate matrices. At the moment, the complete replacement of a bone transplant by rhBMP2 for the filling of the alveolar bone defect in an alveolar cleft is not recommended due to the harmful side effects and the suboptimal dose-release curve (expert opinion N. G. Janssen based on Article by Woo, 2012 JOMS; "Adverse events reported after the use of recombinant human bone morphogenetic protein."). However, ongoing research into other bone substitutes looks promising for the future.

Recommendations

Reconstruct the alveolar cleft using bone harvested from the iliac crest or the chin (if needed supplemented by a bone substitute).

If a larger volume is required, use bone from the iliac crest, or opt for bone from the chin supplemented by a bone substitute.

Based on the literature, it is not possible to make a recommendation for the choice of the bone substitute to be used.

The use of only a bone substitute for the reconstruction of an alveolar cleft, in other words without an autologous bone transplant, should only be performed in a research context and is as yet not suitable for use in general practice.

Literature

Alonso N, Tanikawa DY, Freitas Rda S, Canan L Jr, Ozawa TO, et al. Evaluation of maxillary alveolar reconstruction using a resorbable collagen sponge with recombinant human bone morphogenetic protein-2 in cleft lip and palate patients. Tissue Eng Part C Methods. 2010 Oct;16(5):1183-9. doi: 10.1089/ten.TEC.2009.0824

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Freihofer HP, Borstlap WA, Kuijpers-Jagtman AM, Voorsmit RA, van Damme PA, Heidbuchel KL, et al. Timing and transplant materials for closure of alveolar clefts. A clinical comparison of 296 cases. J CRANIO-MAXILLO-FAC SURG 1993 Jun;21(4):143-8.

Thuaksuban N, Nuntanaranont T, Pripatnanont P. A comparison of autogenous bone graft combined with deproteinized bovine bone and autogenous bone graft alone for treatment of alveolar cleft. Int J Oral Maxillofac Surg. 2010 Dec;39(12):1175-80. doi: 10.1016/j.ijom.2010.07.008. Epub 2010 Sep

Woo EJ. Adverse events reported after the use of recombinant human bone morphogenetic protein 2. J Oral Maxillofac Surg. 2012 Apr;70(4):765-7. doi: 10.1016/j.joms.2011.09.008. Epub 2011 Dec 16.

Chapter 9 Orthodontic treatment in patients with clefts of the lip and palate

Module 1. Naso-alveolar moulding (NAM)

Clinical question
Is there an indication for naso-alveolar moulding (NAM) in patients with a complete unilateral or bilateral cleft lip, alveolus and palate?

Introduction
Neonatal Infant Orthopaedics (IO) aims to improve the position of the maxillary segments using an intra-oral appliance in patients with a complete unilateral or bilateral cleft lip, alveolus and palate (UCLP/BCLP). In addition, many other goals of this therapy have been mentioned in the literature (Hosseini, 2017). In the Netherlands, a 'landmark' randomised controlled trial (RCT) was performed (DUTCHCLEFT (2001)) to examine the effects of IO versus no IO with a passive palatal plate in children with a UCLP up to 12 years of age. The study revealed that IO has no added value in the long term (Kuijpers-Jagtman, 2013). Following publication of this research, virtually all centres in the Netherlands stopped using this therapy for children with a UCLP, whilst it is still used for patients with a BCLP. The technique of naso-alveolar mo(u)lding (NAM) emerged at the same time, in which nasal stents were added to the palatal plate to achieve an improved shape of the nose, after which surgical closure of the lip is performed, either alone or in combination with periosteoplasty of the cleft alveolus (Maull, 1999). This treatment is hardly used in the Netherlands, but globally there is a heated discussion about the usefulness of NAM.

Searching and selecting
In order to answer the clinical question, a systematic literature analysis was performed based on the following scientific question:

> What are the effects of NAM, compared to no NAM or NAM compared to neonatal infant orthopaedics without nasal stents, in patients with a complete unilateral or bilateral cleft?

P: patients with a complete unilateral or bilateral cleft lip, alveolus and palate;
I: naso-alveolar mo(u)lding ;
C: no naso-alveolar mo(u)lding or infant orthopaedics without nasal stents;
O: shape and symmetry of the nose; psychosocial wellbeing of the parents; aesthetic result; cost-effectiveness; facilitation of the surgical procedure; shape of the upper dental arch; frequency of crossbite, maxillofacial growth.

Relevant outcome measures
The guideline task force deemed the shape and functioning of the nose and the aesthetic result to be critical outcome measures for the decision-making process; facilitation of the lip surgery, psychosocial wellbeing of the parents and cost-effectiveness were deemed important outcome measures for the decision-making process. The guideline task force did not define these outcome measures *a priori*, but

used the definitions from the studies. The guideline task force did not define any clinically (patient) relevant differences.

Searching and selecting (Method)
A systematic search was performed in the databases of Medline (through OVID) and Embase (though Embase.com) between 1993 and August 11th, 2017. This search aimed to identify published systematic reviews, RCTs and controlled clinical trials (CCTs). The search strategy is described in the Appendix

Studies that investigated the effectiveness of NAM compared to no NAM and no IO in patients with a complete unilateral or bilateral cleft were selected. The initial search identified 479 references of which 134 were assessed full text. After assessment of full text 132 studies were excluded and 2 studies included. Reasons for exclusion are described in the exclusion table.

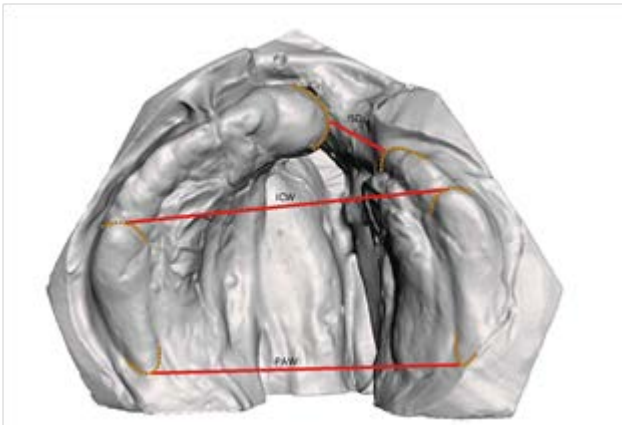
Summary of the literature
Description of studies
A total of 2 studies are included in this literature summary (Liang, 2018; Shetty, 2017).

Liang (2018) is a study that compares the effect of NAM (n=42) versus no NAM (n=42) on long-term nasal shape and symmetry in patients with complete non-syndromic UCLP. The allocation of treatment was based on time period of investigation. All patients that entered the hospital in 2001 had no NAM. All patients that entered the hospital between 2008 and 2010 received NAM. The treatment started between 24 to 61 days (mean age 33 days). The duration of the NAM ranged from 36 to 104 days (mean 72 days). After that, primary cheiloplasty was performed without nasal cartilage dissection at a mean age of 113 days in the NAM group. In the no-NAM group the same surgical procedure was followed by the same surgeon at a mean age of 109 days. A score for nasal shape and symmetry was based on full-face and submental photographs taken 4 to 5 years postoperatively. A panel of 10 professionals from different medical disciplines rated full face frontal pictures for the position of the alar base, and symmetry of the nasal dome and nasolabial fold. On submental oblique facial photographs, the panel rated symmetry of the nasal dome and nostrils, length of the columella, and shape of the nostril sill and tip of the nose. A score ranging from 1-5 per picture was calculated (1= poor; 2= fair; 3= average; 4= good; and 5= excellent). The score of the two pictures was combined into a total score (2 to 10) per patient. The professionals were blinded for the type of treatment. The procedure resulted in a total score between 20 to 100 points per patient.

Shetty (2017) is a study investigating the long-term effect of NAM (n=60) versus no NAM (n=60) on the growth of the maxillary arch in patients with UCLP at different ages. The randomization of participants to the study versus control group was not described in the article. The intervention group was divided into three subgroups (I: NAM initiated within 1 month, II: between 1 and 6 months, III: between 6 and 12 months). NAM was started at 11 days (range 1 to 28) in subgroup I, 94 days (range 33 to 180) in subgroup II and 235 days (range 180 to 365) in subgroup III. Patients with UCLP in subgroup I were treated

with NAM until 6 months of age and in subgroup II and III for a minimum of 3 months. The control group was also divided into three groups (I: underwent operation at 6 months of age, II: between 6 and 9 months of age, III: between 9 and 15 months of age). Cheiloplasty was performed at the same time in the case and control group. Palatoplasty was performed in both groups at 18 months.

Figure 2.1



Modified from Shetty (2017) (courtesy Robin Bruggink, Radboudumc). To quantify maxillary arch dimensions 3 distances were measured: intersegment distance (ISD, compares to alveolar cleft width), intercanine width (ICW) and posterior arch width (PAW) at first visit (T1), before cheiloplasty (T2) and at 6 years (T3)

Results

Nasal shape and symmetry

The reliability coefficient was α= 0.925, indicating measurement consistency among the medical professionals. The mean score ± SD was 66.62 ± 14.25 and 66.31 ± 15.08 in the NAM and no NAM group respectively. The difference between the groups was not statistically different (F= 0.009, P= 0.923) (Liang, 2018).

Evidential value of the literature

Grading the evidence started at a level of high evidence, because the used data was derived from a RCT. Downgrading with three levels was, however, necessary as there were limitations in study design (no adequate randomisation, no allocation concealment, no blinding of care providers and patients), there was indirect evidence (participants with a specific ethnicity) and imprecision (small sample size).

Psychosocial wellbeing of the parents

Differences in psychosocial wellbeing between parents of both groups were not assessed in the included study.

Evidential value of the literature

Grading the evidence was not possible, because no articles were found investigating differences in psychosocial wellbeing between parents of both groups.

Esthetic outcome

Differences in esthetic outcomes between both groups were not assessed in the included studies.

Evidential value of the literature

Grading the evidence was not possible, because no articles were found investigating differences in esthetic outcome between both groups.

Cost effectiveness

Differences in cost effectiveness between both groups were not assessed in the included studies.

Evidential value of the literature

Grading the evidence was not possible, because no articles were found investigating differences in cost effectiveness between parents of both groups.

Facilitation of surgery

Differences in facilitation of surgery between both groups were not assessed in the included studies.

Evidential value of the literature

Grading the evidence was not possible, because no articles were found investigating differences in facilitation of surgery between both groups.

Shape of upper arch

The distance ISD was not significantly different between the NAM and the control groups at T1 and T3, but was significantly smaller in the NAM-groups at T2 (Mean difference (95% CI) I: -11.45 (-12.54, -10.37); II: -8.00 (-9.26, -6.74); III: -6.80 (-8.10, -5.51). The ICW was not significantly different between the NAM and control groups at T1 and T2, but was significantly different at T3 (Mean difference (95% CI) I: 3.30 (2.56, 4.04); II: 2.15 (1.31, 2.99); III: 1.15 (0.18, 2.12)). The PAW was not significantly different between the study and control group at T1, T2 and T3 (Shetty, 2017).

The change in mean ISD between T1 and T2 and T2 and T3 was significantly different in the study group versus the control group in all subgroups. The change in mean ICW between T1 and T2, T2 and T3, and T1 and T3 was also significantly different in the study group versus the control group in all subgroups (except between T1 and T2 in subgroup I). No statistical differences were found in mean PAW between T1 and T2, T2 and T3, and T1 and T3 in the study versus control group in all subgroups (except between T2 and T3 in subgroup III) (Shetty, 2017).

Evidential value of the literature

Grading the evidence started at a level of high evidence, because the used data was derived from a RCT. Downgrading with three levels was, however, necessary as there were limitations in study design (no adequate randomisation and no allocation concealment), there was indirect evidence (participants with a specific ethnicity) and imprecision (small sample size).

Cross bite

Differences in cross bite between both groups were not assessed in the included studies.

Evidential value of the literature

Grading the evidence was not possible, because no articles were found investigating differences in cross bite between both groups.

Maxillofacial growth

Differences in maxillofacial growth between both groups were not assessed in the included studies.

Evidential value of the literature

Grading the evidence was not possible, because no articles were found investigating differences in cross bite between both groups.

Conclusions

Very low GRADE	We found very low quality evidence that NAM, compared to no NAM, is associated with no differences in nasal shape and symmetry of patients with a complete unilateral cleft lip and palate. *Sources (Liang, 2018)*

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of NAM, compared to no NAM, on psychosocial wellbeing of parents of patients with a complete unilateral or bilateral cleft lip and palate.

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of NAM, compared to no NAM, on esthetic outcome of patients with a complete unilateral or bilateral cleft lip and palate.

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of NAM, compared to no NAM, on cost effectiveness of patients with a complete unilateral or bilateral cleft lip and palate.

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of NAM, compared to no NAM, on facilitation of surgery of patients with a complete unilateral or bilateral cleft lip and palate.

Very low GRADE	We found very low quality evidence that NAM, compared to no NAM, is associated with no difference in maxillary arch dimensions of patients with a complete unilateral cleft lip and palate. *Sources (Shetty, 2017)*

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of NAM, compared to no NAM, on cross bite of patients with a complete unilateral or bilateral cleft lip and palate.

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of NAM, compared to no NAM, on maxillofacial growth of patients with a complete unilateral or bilateral cleft lip and palate.

Considerations

Even though NAM has formed part of the multi-disciplinary treatment of babies with clefts of the lip and palate in centres worldwide for more than 20 years, very little research of good quality is available about this therapy. The guideline task force identified two recent studies (Liang, 2018; Shetty, 2017) in which the shape of the nose (Liang, 2016) and the shape of the upper dental arch were examined after NAM (Shetty, 2017). Both studies are of a very poor methodological quality. Other possible favourable or unfavourable effects of NAM have not been reported (yet) in the literature in studies of a high quality. It is therefore not possible to provide evidence-based recommendations for the use of NAM based on the current literature.

The guideline task force therefore consulted the Special Interest Group Orthodontics (SIG orthodontics) of the Dutch Association for Cleft Lip and Palate and Craniofacial Anomalies (February 2018). This association unites all orthodontists in the Netherlands who regularly treat children with clefts of the lip and palate.

The respondents are all knowledgeable about NAM, but are aware that there is no evidence to support this therapy so far. None of the respondents use NAM. The cleft orthodontists are very reticent due to the lack of scientific proof and the costs of the treatment and even more so due to the increase in 'burden of care' for the parents, whilst there is no proven effectiveness. They emphasise that good clinical research is urgently required.

The question that formed the focal point of this part of the guideline, 'Is there an indication for NAM in patients with a complete unilateral or bilateral cleft lip, alveolar arch and palate?', can neither be confirmed nor denied given the current state of affairs. In addition, it is important to take into consideration that NAM is labour-intensive for the parents and orthodontist due to the frequent treatment sessions required for this treatment and the costs of the total treatment increase as a result, whilst the effectiveness has not been proven. On the other hand, there have been no reports to date of any negative effects of NAM on the development of the maxillary arch, the shape of the nose and the aesthetic results in the literature.

A search of some international clinical trial registers (see below) revealed that there are currently no ongoing trials that could be expected to provide an answer. Equal experience in both interventions is required to perform randomised controlled research in which NAM is compared to another intervention or non-intervention. The recently published results of the Scandcleft trial emphasised this once more: the difference in experience of the surgeons for the procedures in the arms of the trial influenced the results of this trial (Rautio, 2017; Shaw, 2017). Therefore, the guideline task force recommends using NAM in preparation for a trial.

Considering the number of parameters that need to be answered, the guideline task force suggests being reticent about the use of NAM in babies with a unilateral or bilateral cleft lip, alveolar arch and palate and to perform further randomised clinical research before more robust recommendations can be made about the indication for NAM.

Recommendation

Be reticent about the use of NAM in babies with a complete unilateral or bilateral cleft lip, alveolar arch and palate and only apply NAM in preparation of or in the context of a clinical trial.

Literature

Hosseini HR, Kaklamanos EG, Athanasiou AE. Treatment outcomes of pre-surgical infant orthopedics in patients with non-syndromic cleft lip and/or palate: A systematic review and meta-analysis of randomized controlled trials. PLoS One. 2017;12(7):e0181768. doi: 10.1371/journal.pone.0181768. eCollection 2017. PubMed PMID: 28742129; PubMed Central PMCID: PMC5524403.

Kuijpers-Jagtman AM, Prahl C. History of neonatal orthopedics: past to present. In: Cleft Lip and Palate. Diagnosis and Management. Ed. Berkowitz, S. Heidelberg New York Dordrecht London: Springer-Verlag. 2013:455-472.

Liang Z, Yao J, Chen PK, et al. Effect of Presurgical Nasoalveolar Molding on Nasal Symmetry in Unilateral Complete Cleft Lip/Palate Patients After Primary Cheiloplasty Without Concomitant Nasal Cartilage Dissection: Early Childhood Evaluation. Cleft Palate Craniofac J. 2018;55(7):935-940. doi: 10.1597/14-296. PubMed PMID: 28085515.

Maull DJ, Grayson BH, Cutting CB, et al. Long-term effects of nasoalveolar molding on three-dimensional nasal shape in unilateral clefts. Cleft Palate Craniofac J. 1999;36(5):391-7. PubMed PMID: 10499400.

Rautio J, Andersen M, Bolund S, et al. Scandcleft randomised trials of primary surgery for unilateral cleft lip and palate: 2. Surgical results. J Plast Surg Hand Surg. 2017;51(1):14-20. doi: 10.1080/2000656X.2016.1254646. PubMed PMID: 28218552.

Shaw W, Semb G. The Scandcleft randomised trials of primary surgery for unilateral cleft lip and palate: 11. What next? J Plast Surg Hand Surg. 2017;51(1):88-93. doi: 10.1080/2000656X.2016.1254644. PubMed PMID: 28218554.

Shetty V, Agrawal RK, Sailer HF. Long-term effect of presurgical nasoalveolar molding on growth of maxillary arch in unilateral cleft lip and palate: randomized controlled trial. Int J Oral Maxillofac Surg. 2017;46(8):977-987. doi: 10.1016/j.ijom.2017.03.006. PubMed PMID: 28416097.

Module 2: Maxillary protraction

Clinical question
When should maxillary protraction be applied to the maxilla in children with clefts of the lip and palate?

Sub-questions:
- Which considerations play a role in the decision to apply maxillary protraction in children with a cleft lip and alveolus, cleft lip, alveolus and palate or cleft palate only and what is the most optimal time to do so?
- Is there a preference for a certain technique of maxillary protraction?

Introduction
In patients with a cleft lip, alveolus and palate the growth of the maxilla can become disrupted in three dimensions. A disrupted ventral (forward) growth can result in underdevelopment of the maxilla in the sagittal plane, which is often clearly visible in the face and gives the patient a characteristic “cleft” face. This often becomes manifest at an early age. Such an underdevelopment of the maxilla can be corrected at the end of the growth period by performing a maxillary osteotomy or surgical distraction.

Another option is to adjust the maxillary growth from an early age and thereby possibly avoid the need for an osteotomy at a later age, or to reduce the sagittal discrepancy that needs to be bridged surgically. A technique was introduced in the 1980s, in which extra-oral traction is applied to the maxilla to stimulate the growth of the sutures around the maxilla. An essential part of this treatment strategy is that it is started when the deciduous teeth are still present. Later on, therapies were developed that can also be applied whilst the permanent teeth are erupting and that use a combination of maxillary expansion and/or skeletal anchorage. It is important to know at what age maxillary protraction is most effective in terms of a stable result at the end of the growth phase of the face and which technique is preferable.

Searching and selecting
To answer the clinical question, a systematic literature analysis was performed based on the following scientific question and accompanying PICO:

- Will maxillary protraction reduce midfacial deficiency as compared to no treatment in cleft lip and palate patients?

- **P:** Cleft lip and palate patients;
- **I:** Maxillary protraction;
- **C:** No treatment;
- **O:** Primary outcomes: reduction of midfacial deficiency, overjet, ANB angle, Wits appraisal, facial aesthetics. Secondary outcomes: adverse effects, self-esteem.

Relevant outcome measures

The guideline task force deemed a reduction in midfacial deficiency and an increase in the overjet to be critical outcome measures for the decision-making process. The guideline task force deemed facial aesthetics, side effects of the treatment and quality of life to be important outcome measures for the decision-making process.

The guideline task force did not define these outcome measures *a priori*, but used the variables and definitions from the studies.

Search and study selection (methods)
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and September 24th, 2014. This search aimed to identify systematic reviews, randomized controlled trials (RCTs), CCTs, and observational studies.

Studies included were systematic reviews, RCTs, controlled trials and observational studies that described at least one of the primary outcomes (reduction of midfacial deficiency, overjet, ANB angle, Wits appraisal) in patients with cleft lip and palate who underwent maxillary protraction. It was essential that the long-term effects of the maxillary protraction (after maturity, defined as 18 years of age) were described in the study, ergo that a sufficiently lengthy follow-up was performed.

The initial search identified 371 references of which 48 were assessed full text. Forty-six studies seemed to be relevant, but after examination of the full text did not answer the research question adequately or did not present data on the effect size or association for the outcomes of interest with the required follow-up time. Finally, two retrospective observational studies were included.

Summary of the literature
Study characteristics
Two retrospective observational studies were included. Borzabadi-Farahani (2014) assessed the dentoskeletal effect of late maxillary protraction (MP) in patients with unilateral cleft lip and palate versus a control group of untreated unilateral cleft lip and palate patients. The study group was comprised of 18 patients (Asian, Hispanic, Caucasian, and African-American background), and the control group of 17 patients. Lip repair was performed at 3 months of age using the Millard technique and the palate was closed with greater palatine flaps at 10-12 months. The Alt-RAMEC approach (Liou and Tsai, 2005) was used to loosen the circummaxillary sutures prior to application of maxillary protraction. Maxillary expansion and compression rate were set at 1 mm per day. This protocol was followed by fulltime wear of Class III elastics and night-time wear of a reverse pull headgear. Lateral cephalograms were taken at the age of 13 to 14 years (T1) and also at 17-18 years (T2).

The study reports a statistically significant change across time between the MP-group and the control group for 10 cephalometric variables (values mean diff in MP group between T2-T1):
SNA (°): 1.95 (95% CI: 0.75 – 3.15); A ⊥Na Perp (mm): 1.82 (95% CI: 0.86 – 2.77); CoA (mm): 2.92 (95% CI: 1.53 – 4.31); ANB(°): 3.13 (95% CI: 2.02 – 4.24); Wits (mm): 7.82 (5.01 – 10.54); Mx-Md Diff (mm): 0.62 (95% CI: -1.58 – 2.83); Occl Plane-SN(°): -3.98

(95% CI: -5.99 - -1.98); overjet (mm) 8.82 (95% CI: 5.90 – 11.74); FMIA (°): 4.05 (95% CI: -0.05 – 8.15); and IMPA (°): -5.77 (95% CI: -9.74 - -1.80). Late maxillary protraction created a slight open bite (0.66mm). Trends for overeruption of mandibular incisors and an increased lower face height (p=0.07 for both) were noted in the study group. Figure 1 and 2 copied from the study demonstrate the cephalometric landmarks and main cephalometric planes and measurements used in this study and elucidate the abbreviations used in the text above.

The results showed that Alt-RAMEC followed by late maxillary protraction in unilateral cleft lip and palate had a combined skeletal and dental effect (protraction of maxilla, improvement of the skeletal jaw relationship and dental compensations like counterclockwise rotation of the occlusal plane, retroclination of mandibular incisors, open bite tendency) in patients with UCLP.

Susami (2014) described the short- and long- term effects of maxillary protraction (MP) in mixed dentition patients with unilateral cleft lip and palate. In this study 11 Japanese patients were treated with maxillary protraction and followed until the completion of growth. The lip had been repaired at 3 to 6 months of age using the modified Millard technique and the palate was closed at 12 to 24 months using a pushback method in all cases. Mean age at the start of treatment was 8y10m, the mean duration of maxillary protraction was 3y7m. The mean age at the end of the observation period was 18y0m (mean length of follow-up 9y2m). The intra-oral appliance was a lingual arch with buccal extension arms and a facial mask was applied during night-time (force 150-200 gF per side during 8-10 hrs). Full fixed appliance treatment was performed after MP in all patients. Lateral cephalograms were taken before and after MP and after completion of growth.

The authors report a large variation in the effects of MP. Eventually, 5 out of 11 patients treated with MP required orthognathic surgery. The overjet improved to within normal limits in the six cases that did not require orthognathic surgery, but a large negative overjet was found in the remaining 5 cases immediately before orthognathic surgery. On average, the overbite had decreased after MP treatment, although the decrease was not significant.

Table 2 shows the average changes in cephalometric measurements.

Table 2. Average changes in cephalometric measurements

Parameter	*Start of MP Mean (SD)*	*End of MP Mean (SD)*	*After Growth Mean (SD)*
A-PV (mm)	60.2 (3.1)	62.2 (3.6)	62.1 (4.4)
A-AV (mm)	-5.6 (2.2)	-5.6 (1.7)	-7.9 (2.0)
SNA (°)	76.6 (2.6)	76.5 (2.6)	73.9 (2.5)
Max. L (mm)	79.1 (3.5)	83.2 (4.0)	84.1 (4.8)
Pog-AV (mm)	-10.4 (6.6)	-10.4 (8.4)	-11.3 (9.7)
SNB (°)	77.2 (4.0)	76.8 (4.0)	75.7 (4.4)
Mand. L (mm)	108.7 (6.2)	118.4 (9.0)	125.9 (10.3)
FH-MP (°)	30.9 (5.8)	31.9 (6.3)	32.6 (7.0)
ANB (°)	-0.5 (2.9)	-0.3 (3.7)	-1.9 (3.3)
Max.-mand. diff. (mm)	29.6 (3.9)	35.3 (7.4)	41.8 (7.0)
Wits value (mm)	-7.8 (3.2)	-6.4 (5.4)	-6.8 (5.8)
U6-AV (mm)	-37.7 (3.5)	-34.4 (4.1)	-33.5 (4.0)
U1-FH (°)	97.0 (9.3)	110.1 (8.7)	109.8 (6.9)
Overjet (mm)	-6.2 (3.0)	-1.9 (5.6)	-2.2 (6.5)

Overbite (mm)	4.2 (2.8)	2.5 (2.3)	1.8 (1.6)

The Frankfurt plane (FH) served as the horizontal reference line, and two lines perpendicular to FH were used as the vertical reference lines.
PV = posterior vertical reference line through sella;
AV = anterior vertical reference line through nasion;
Values of linear measurements are positive in the anterior direction. MP = maxillary protraction; A-PV = point A – posterior vertical reference line distance; A-AV = point A-anterior vertical reference line distance; Max L = maxillary length; Pog AV = pogonion – anterior vertical reference line distance; Mand. L = mandibular length; FH-MP = Frankfurt – mandibular plane angle; Max. – mand. diff. = difference between maxillary and mandibular length; Wits = distance between points A and B projected on the occlusal plane; U6-AV = maxillary molar – anterior vertical reference line distance; U1-FH = upper incisor – Frankfurt horizontal plane angle.

Grading the evidence

The quality of evidence was graded as very low, due to the retrospective observational nature of the study (low evidence), the small sample size in both studies, and the mixed ethnic background of the sample in the Borzabadi-Farahani study (2014). GRADE states that observational studies are graded as low quality of evidence by outset. Due to imprecision (small sample size with no underlying power calculation), the quality of evidence was further downgraded by one level, from low to very low.

Conclusions

Very low GRADE	There is a very low level of evidence that loosening of the circummaxillary sutures (Alt-RAMEC approach) followed by maxillary protraction as a late treatment (at the age of 13-14 years) for unilateral cleft lip and palate patients produces a combination of skeletal changes (protraction of the maxilla, improvement of the jaw relationship) and dental compensations (counterclockwise rotation of the occlusal plane, retroclination of mandibular incisors) and is also associated with some unwanted tooth movements (open bite tendency, mandibular incisors retroclination). *Borzabadi-Farahani, 2014*

Very low GRADE	It is unclear what the effects are of maxillary protraction as an early treatment (on average 8 years old) for unilateral cleft lip and palate patients on maxillary growth. *Susami, 2014*

Considerations

The literature describes various methods for maxillary protraction of the maxilla in patients with clefts of the lip and palate. However, there is only a very limited amount of literature with a very low level of evidential value that describes the long-term results of maxillary protraction, in which patients were monitored until facial growth was complete. Therefore, the recommendation in this guideline is primarily based on expert opinion and partly on literature describing adverse effects on the mandible in children without clefts of the lip and palate.

In the treatment of underdevelopment of the maxilla, the patient wears elastics on both sides that are attached from an extra-oral face mask to an intra-oral orthodontic device that is anchored in the dentition. In this form of maxillary protraction, the forces are effectively transferred via the periodontal ligament of the teeth to the maxillary bone and the sutures surrounding the maxilla. As a result, a part of the jaw relationship correction is dento-alveolar in origin and not skeletal. A meta-analysis of children with an underdevelopment of the maxilla without clefts of the lip and palate, in which three randomised controlled trials were included, reveals that - in addition to a forward-moving effect on the maxilla - backward displacement of the mandible with a "clockwise" rotation of the mandibular plane takes place, along with a "counterclockwise" rotation of the palatal plane (Cordasco, 2014). These effects result in an extension of the lower half of the face. A mesial displacement of the first molars in the maxilla has also been described, along with protrusion of the upper incisors and retrusion of the lower incisors (Kim, 1999; MacDonald, 1999; Jäger, 2001). There is no reason to assume that the effects on the mandible and the lower half of the face would be any different in children with clefts of the lip and palate. Both the previously mentioned systematic review by Cordasco, 2014, and the Cochrane review by Watkinson, 2013, involving children without clefts of the lip and palate, also concluded that it was not possible to decide about the effectiveness of the facial orthopaedic treatment of underdevelopment of the maxilla in the long term. The same picture emerges from the literature research performed for this guideline with regard to children with clefts of the lip and palate.

After the literature study for this guideline was completed, a systematic review was published by Foersch (2015) that discusses maxillary protraction in Class III patients without clefts of the lip and palate, in combination with expansion or expansion/compression of the maxilla according to an Alt-RAMEC protocol as proposed by Liou and Tsai (2005). The aim of the expansion prior to maxillary protraction is to open the sutures surrounding the maxilla. The results show that maxillary protraction in combination with expansion does not result in a markedly greater effect on ventral growth of the maxilla than protraction alone. However, alternating expansion and compression (Alt-RAMEC) did result in greater ventral displacement of the maxilla. It is not yet known to what extent this also applies to patients with clefts of the lip and palate.

The aim of maxillary protraction is to influence the growth of the maxilla at a skeletal level whilst causing as few dental adverse effects as possible. A new possibility for this is the use of skeletal anchorage in the maxilla in the form of bone anchors or bone screws. The introduction of skeletal anchorage by means of bone anchors made it possible to apply forward-moving traction forces directly from the face mask to the bone of the

maxilla. De Clerck (2009) introduced a method in which it is no longer necessary to wear an external face mask. In this treatment method, the forces are applied entirely intra-orally via elastics that must be worn 24 hours a day between the bone anchors in the mandible and the maxilla. The technique is called “bone anchored maxillary protraction” (BAMP). The bone anchors are attached on both sides to the zygomaticoalveolar crest in the maxilla and buccally to the alveolar process in the mandible between the lateral incisor and the cuspid tooth. Case series studies with BAMP in children without clefts of the lip and palate show a favourable but very variable effect on the maxilla of an average of 3.7 mm forward displacement with minimal dental effects (Baccetti, 2004; Nguyen, 2011). Modification of the mandibular fossa was observed, resulting in a more backward position of the mandible (De Clerck, 2012). However, long-term results for BAMP are not available yet. In a recent overview of the results for BAMP (2015), De Clerck states with regard to the use of BAMP for orofacial clefts that a positive effect can be expected (for which, incidentally, he provides no evidence), but that it is not yet clear to what extent BAMP is able to negate the effect of scar tissue formation on the growth.

Various centres all over the world are currently performing studies involving children with clefts of the lip and palate, but as yet it is not possible to draw any conclusion about the effect of BAMP on this group.

The guideline task force is of the opinion that - according to the current state of scientific progress - maxillary protraction using a face mask on a dentally anchored device should not be used on patients with clefts of the lip and palate. In the long term, maxillary protraction on a dentally anchored device probably does not yield the envisaged result and the result of surgery on the maxilla is probably superior.

Exceptions to the general advice not to apply maxillary protraction using a face mask on a dentally anchored device include those cases in which the patient and/or the parents do not want orthogrnatic surgery. In the case of slight underdevelopment of the maxilla, one can consider applying active maxillary protraction to the maxilla via a dentally anchored device at a young age and for a period of no more than 12 to 18 months. The table below lists a number of favourable and unfavourable factors based on expert opinion, which can be used as a guideline.

Favourable factors	Unfavourable factors
Patients aged between 5 and 9 years	Patient > 12 years
Mild skeletal defect ANB < -1^0 with SNB angle normal for age	Severe skeletal defect ANB > -1^0 with SNB angle enlarged for age
Minimal aesthetic abnormalities of the face	Abnormal aesthetics of the face
Convergent growth pattern with low anterior facial height	Divergent growth pattern with normal / high anterior facial height
AP displacement of the mandible in habitual occlusion (negative overjet)	No AP shift of the mandible
Symmetrical condylar growth	Asymmetrical condylar growth
No family history of hyperplasia of the mandible	Family history of mandibular hyperplasia
Good cooperation in the orthodontic	Good cooperation doubtful

treatment is expected	

In such borderline cases, maxillary protraction on a dentally anchored device can be considered, because this treatment could potentially prevent the need for surgical treatment. In that case, the patient and parents should be thoroughly informed about the treatment and the uncertainty about the result in the long term.

Recommendations

In general, never apply maxillary protraction using a face mask on a dentally anchored orthodontic device in children with clefts of the lip and palate with deficient forward growth of the maxilla.

Consider maxillary protraction with a face mask on a dentally anchored orthodontic device in the case of:

1) slight underdevelopment of the maxilla, or;
2) if the patient and/or parents do not want surgical treatment, or;
3) if the patient has a number of favourable characteristics. The following can serve as a guideline:
   - patient aged between five and nine years;
   - mild skeletal defect ANB < -1^0 with SNB angle normal for age;
   - minimal aesthetic abnormalities of the face;
   - convergent growth pattern with low anterior face height;
   - AP displacement of the mandible in habitual occlusion (negative overjet);
   - symmetrical condylar growth;
   - no family history of hyperplasia of the mandible;
   - good cooperation in the orthodontic treatment is expected.

If maxillary protraction with a face mask on a dentally anchored orthodontic device is applied:

Inform the patient and parents that the effect can be limited and that it will only become clear at the end of the growth period whether an osteotomy of the maxilla will be necessary after all.

Literature

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Module 3: Retention

Clinical question
Which retention device is the most effective in the long term for children with clefts of the lip and palate (alveolus and palate) with regard to retention of the tooth position that has been achieved and the arch form of the maxilla?

Sub-question:
- Which retention duration is necessary to maintain the treatment result?

Introduction
Upon completion of any orthodontic treatment, whether this is a patient with or without clefts of the lip and palate, the shape of the dental arch and the position of the teeth need to be maintained using a removable or fixed retention device. Without retention, the teeth have a tendency to return partially or completely to their original position. Orthodontic retention can consist of fixed wires behind the lower and upper front teeth, removable retention devices or a combination of both. The retention device can remain in position for life (permanent retention) or for a limited period.

The functional circumstances differ in patients with clefts of the lip and palate compared to patients without clefts of the lip and palate. They have scar tissue in the lip and on the palate. The nasal passage may also be disrupted, resulting in habitual mouth breathing and a lower position of the tongue in the oral cavity. In addition, there is often severe rotation of anterior teeth prior to treatment and certain teeth may be absent. All these factors affect the long-term results of the treatment.

It is important to know which retention strategy in patients who have undergone surgery for clefts of the lip and palate offers the most stable final result in the long term with regard to position of the teeth, arch form and occlusion. This applies both to the type of retention and the duration of the retention. In addition, it is also important to note which type of retention is the most acceptable to the patient and what the possible detrimental effects are.

Searching and selecting
In order to answer the clinical question, a systematic literature analysis was performed based on the following scientific question and accompanying PICO:

- Will maxillary protraction reduce midfacial deficiency as compared to no treatment in cleft lip and palate patients?

- **P:** Cleft lip and palate patients who have finished orthodontic treatment;
- **I:** Orthodontic retention procedure A;
- **C:** Orthodontic retention procedure B;
- **O:** Maintaining/stabilising teeth in corrected positions following orthodontic treatment or prevent relapse = Little's index, GOSLON Yardstick, cross bite score f.e. Huddart score, maxillary arch shape and arch width, duration of retention.

Relevant outcome measures
The guideline task force deemed the measures for correct tooth position and jaw relationship (Little's index, GOSLON Yardstick, cross bite score f.e. Huddart score, maxillary arch shape, arch width) to be critical outcome measures for the decision-making process. The guideline task force deemed the duration of retention to be an important outcome measure for the decision-making process.

The guideline task force did not define these outcome measures a priori, but used the variables and definitions from the studies.

Search and study selection (methods)
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and September 24th, 2014. This search aimed to identify systematic reviews, randomized controlled trials (RCTs), CCTs, and observational studies.

Studies included were systematic reviews, RCTs, controlled trials and observational studies that described at least one of the primary outcomes (Little's index, GOSLON Yardstick, cross bite score f.e. Huddart score, maxillary arch shape, arch width or duration of retention) in patients with cleft lip and palate who underwent retention. It was essential that the long term effects of retention (after maturity, defined as 18 years of age) were described in the study, ergo that a sufficiently lengthy follow-up was performed.

The initial search identified 178 references of which 24 were assessed full text. Twenty three studies seemed to be relevant, but after examination of the full text did not answer the research question adequately, or did not present data on the effect size or association for the outcomes of interest with the required follow-up time. Finally, one prospective observational study was included.

Summary of the literature
Description of included study
One study was included in the literature summary, the prospective observational study of Marcussen, 2004. The purpose of this study was to evaluate the occlusion and maxillary dental arch dimensions in adults with repaired complete unilateral cleft lip and palate and to investigate patterns of change in early adulthood.

A total of 39 patients, all adults, were included in this study. These patients had undergone their primary surgery in the Cleft Centre of Linköping (Sweden) consisting of lip closure according to the Millard technique (at 3 months of age) and palatal closure according to the Wardill-Kilner technique (at 18 months of age). All patients had received orthodontic treatment with fixed appliances by the cleft centre orthodontists or elsewhere. The patients were then divided into three groups according to the type of retention in the upper arch: 1) no retention (n=15), 2) retention with a bonded twisted retainer (n=13), 3) an onlay or fixed bridge (n=11). Occlusion was evaluated according to a scoring system developed by Huddart and Bodenham. Dental casts were taken at

baseline (defined as 19 years of age) and at end of follow-up. The maxillary arch dimensions were measured digitally using a video imaging system with a magnification of 3x. Patients were followed for a mean of 5.6 years (range 0.9 – 9.6 years).

Results

Marcusson, 2004 reported that the occlusal score and the maxillary arch dimensions were reduced in all of the three groups, but there was no difference between the three groups, as shown below in Table 1.

Table 1. Difference (in mm) and P-values for maxillary arch dimensions between baseline and end of follow up for three different retention procedures

Measurement	No retention (n=15)		Bonded retainer (n=13)		Onlay/fixed bridge (n=11)		p-values between groups	Total sample (n=39)		
	Mean	SD	Mean	SD	Mean	SD		Mean	SD	p-value
Maxillary canine width	-0.7	0.9	-0.6	0.6	-0.5	0.8	>0.05	-0.6	0.8	<0.001
Maxillary second premolar width	-1.6	1.4	-1.7	1.6	-1.7	1.4	>0.05	-1.7	1.4	<0.001
Maxillary first molar width	-1.7	1.6	-1.1	1.3	-1.4	1.3	>0.05	-1.4	1.4	<0.001
Maxillary sagittal length	-1.0	0.9	-0.6	0.8	-0.6	0.9	>0.05	-0.8	0.9	<0.001
Arch length cleft side	-1.5	1.3	-0.7	0.9	-0.9	0.7	>0.05	-1.1	1.1	<0.001
Arch length non-cleft side	-1.1	1.4	-1.0	1.2	-1.1	0.9	>0.05	-1.0	1.2	<0.001
Overjet	-0.2	0.6	-0.4	0.7	-0.2	1.2	>0.05	-0.3	0.8	<0.05
Overbite	-0.3	1.1	0.0	0.8	0.0	0.7	>0.05	-0.1	0.9	>0.05

Regarding the entire sample of 39 patients: there was a significant deterioration in the total cross bite score during the follow-up period and this was larger on the cleft than on the non-cleft side. There were no significant differences in the anterior scores. The transversal and sagittal maxillary arch dimensions decreased significantly during the follow-up interval, also as demonstrated in Table 1, irrespective of the type of retention.

Grading the evidence

GRADE states that observational studies are graded as low quality of evidence by outset. Due to imprecision (small sample size with no underlying power calculation), the quality of evidence was further downgraded by one level, from low to very low.

Conclusions

Very low GRADE	There is evidence of very low quality that the maxillary arch dimensions are similar in unilateral cleft lip and palate patients, whether they undergo no retention of the upper arch or retention with a bonded twisted retainer or an onlay/fixed bridge. *Marcusson, 2004*

Considerations

Two factors are important in determining the choice of retention following completed orthodontic treatment in a patient with clefts of the lip and palate. Firstly, the position

of the teeth needs to be retained. The retention policy for this does not differ from the policy for a patient without clefts of the lip and palate. The second aspect that needs to be taken into consideration is the tendency of the transverse dimensions of the upper dental arch to relapse. This applies primarily to patients who have undergone palatal surgery, in other words patients who have undergone surgery for a cleft lip, alveolus and palate and to a lesser extent in patients who have undergone surgery for a cleft palate only.

It is known from animal experiments that the presence of scar tissue on the palate contributes to disrupted growth of the maxilla , as is often seen in patients with clefts of the lip and palate (Wijdeveld, 1991; Von den Hoff, 2013; Semb and Shaw, 2013; Li, 2015). In contrast, the surgical closure of the lip has only a very limited detrimental effect on the growth. Matured palatal scar tissue also differs from tissue that has not undergone surgery: the scar tissue is less well vascularised, less cell-rich, contains no elastic fibres and the orientation of collageneous fibres is in the transverse direction. The scar tissue is also anchored to the palatal bone, whilst this is much less likely in tissue that has not undergone surgery. Furthermore, the collageneous fibres in the scar tissue are partly continuous with the collageneous fibres of the periodontal ligament (Van de Water et al, 2013; Von den Hoff et al, 2013; Li et al, 2015). As a result, the palatal scar tissue is probably jointly responsible for the high tendency towards relapse of the transverse dimensions of the upper dental arch. The only study (Marcusson, 2004) that we were able to include in our literature research does indeed show that the upper dental arch narrows over time, irrespective of the retention method that is used. However, this study had a very low score for the quality of the scientific evidence that was found.

As the systematic literature research into retention after orthodontic treatment of orofacial cleft patients did not yield any scientific evidence for the procedures that should be followed, the recommendations are based on expert opinion. In addition to retention of the position of the teeth, it is also recommended to reduce the tendency towards transverse relapse of the upper dental arch through use of permanent retention during the night in the form of a removable retention device.

Recommendations

Use the same form of retention of the position of the teeth as for a patient without clefts of the lip and palate.

In addition, for a patient with a cleft lip, alveolar arch and palate, use a removable orthodontic retention device for the retention of the width of the upper dental arch that is worn at night for the rest of the patient's life.

Check the retention device at least once every two years.

Literature

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Module 4: Le Fort I osteotomy versus distraction osteogenesis

Clinical question
What are the considerations when opting for forward displacement of the maxilla by means of a classic Le Fort I osteotomy or distraction osteogenesis in patients with clefts of the lip and palate?

Introduction
Patients with a cleft lip, alveolus and palate or an isolated cleft palate often have growth retardation (hypoplasia) of the maxilla in three dimensions. The underlying cause is an intrinsic growth deficiency, in combination with an effect on growth due to surgical interventions to close the lip and particularly the palate at a young age. For correction using ventral traction by means of orthodontic devices, please refer to the chapter 'Orthodontic treatment of patients with clefts of the lip and palate - Ventral traction'. If necessary, the growth retardation can be corrected at the end of the growth period by means of a combined surgical-orthodontic treatment. Prior to the surgical correction, the upper and lower dental arches are aligned orthodontically, after which the sagittal skeletal discrepancy and any vertical and transverse discrepancy are corrected by means of an osteotomy of the maxilla, either alone or in combination with an osteotomy of the mandible and chin.

In cleft patients this procedure is delayed until the patient has stopped growing and the classic Le Fort I osteotomy (LF1) only takes place from the age of 17 or 18 years. In patients without a cleft, the treatment is often performed at an earlier stage - even if the patient has not stopped growing yet - particularly in the case of mandibular hypoplasia and a horizontal growth pattern.

Surgeons usually opt for an LF1 to move the maxilla in a ventral direction, either alone or in combination with a sagittal ramus osteotomy of the mandibule with dorsal displacement. If the patient also exhibits a transverse and/or vertical discrepancy, the LF1 can be performed in multiple segments or a SARME (Surgically Assisted Rapid Maxillary Expansion) can be an option. This module will not discuss this option in any further detail. However, distraction osteogenesis (DOG) of the maxilla is certainly an option, particularly in the case of a large sagittal discrepancy that cannot be resolved with an LF1. If desired, this procedure can be combined with a BSSO. This module will not discuss this option in any further detail.

In this guideline module, the guideline task force has attempted to formulate an answer to the clinical question in which situation a LF1 osteotomy is preferable and when DOG is a good option.

Searching and selecting
To answer the clinical question, a systematic literature analysis was performed based on the following scientific question:

What is the effect of a classic Le Fort I osteotomy (LF1) - compared to distraction osteogenesis (DOG) - on speech development, relapse, revision surgery, chewing function, malocclusion and postoperative position and relation of the bone and soft tissues in patients with clefts of the lip and palate?

P: Patients with a cleft lip, alveolus and palate or an isolated cleft palate;
I: Classic Le Fort I osteotomy (LF1);
C: Distraction osteogenesis of the maxilla (DOG);
O: Speech (for example velopharyngeal insufficiency/rhinolalia aperta), relapse, revisional surgery (for example speech improvement surgeries), chewing function, malocclusion, postoperative relation of bone and soft tissues and patient reported outcomes (PROs)

Relevant outcome measures
The guideline task force deemed speech (for example velo-pharyngeal dysfunction/rhinolalia aperta), relapse, revision surgery (for example pharyngoplasty), chewing function and malocclusion to be critical outcome measures for the decision-making process, and stability and aesthetics to be important outcome measures for the decision-making process. The guideline task force did not define these outcome measures *in advance*, but used the definitions from the studies. The guideline task force did not define any clinically (patient) relevant differences.

Searching & selecting (method)
A systematic Cochrane review was used to elaborate the research question. The topic of that systematic review is comparable with the research question (Kloukos, 2016).

Additionally, a systematic search was performed, with relevant search terms, in the databases of Medline (though OVID), and Embase (though Embase.com) between 1948 and May 2017. The search aimed to check the sensitivity and specificity of the search performed for the Cochrane systematic review, and to identify systematic reviews, randomized controlled trials (RCTs) and observational studies published after the last search date as reported in the Cochrane systematic review. The search strategy is described in the Appendix.

Studies which investigated the effectiveness of LF1, compared to the DOG, in patients with a cleft lip and palate were selected. The initial search identified 421 references, which indicated that the search of the systematic review was sensitive and specific. Four studies, published after the publication date of the systematic review, were identified. All these studies were excluded after reading title and abstract. Reasons for exclusion are described in the exclusion table.

Summary of the literature
Description of studies
One study, a systematic review of Kloukos (2016), was included in this literature summary. Kloukos (2016) aimed to investigate the short- and 5 years effects of maxillary distraction osteogenesis (DOG) compared to Le-Fort-I osteotomy (LF1), in patients with a complete unilateral cleft lip and palate, or a complete bilateral cleft lip and palate (involving the alveolar process). Primary outcome measures were: 1) changes in

midfacial and/or transversal soft and hard tissue (assessed by superimposing lateral cephalometric radiography and/or photographic archives, when applicable. Transversal maxillary changes were assessed with anteroposterior cephalometric radiography or digital cast models of the occlusion); 2) relapse and/or change after treatment (assessed with lateral cephalographs taken at different postoperative times) and 3) perceptual speech assessment (id est articulation, resonance (hypernasality and hyponasality) and nasal emission using f.e. video, conducted by a professional speech-language therapist.) Secondary outcome measures were: 1) instrumental assessment of velopharyngeal function (nasoendoscopy or videonasopharyngoscopy or videofluoroscopy); 2) patient-reported outcomes (assessment of self-esteem and psychological adjustment by validated and internationally accepted questionnaires) and 3) adverse effects of clinical morbidities of the surgical procedure (for example mucosal infection, sinusitis, transection of vessels) (Kloukos, 2016).

In the systematic review RCTs investigating the short- and long-term effects of LF1 versus DOG in non-syndromic cleft patients aged 15 years and older were included. Five databases were searched until February 2016 (Kloukos, 2016). Initial 416 studies were included, but 400 studies were excluded based on title and/or abstract analysis. Sixteen articles were evaluated on full-text, ten studies were eliminated, six remained (Cheung, 2006a; Chanchareonsook, 2007; Chua,2010a; Chua,2010b; Chua ,2012a; Chua, 2012b). The six articles were all based on one randomized controlled trial performed between 2002 and 2008 at the University of Hong Kong. Not all the publications reported all the outcomes of all the participants (Kloukos, 2016).

The six publications describe the characteristics of 47 participants, which needed maxillary advancement of 4 mm to 10 mm (Kloukos, 2016). The included patients underwent a LF1 or DOG and were between 13 and 45 years of age. Studies about participants with a syndromic, atypical, and/or unclear type of cleft and palate were excluded. The study has several methodological limitations: a small sample size, and a high risk of several types of bias (selection, performance, detection, attrition, reporting and probable other types of bias) (Kloukos, 2016).

Both treatments produce significant soft tissue improvements (Kloukos, 2016). DOG tended to give more stable long-term results. Speech and velopharyngeal status was comparable in both groups. DOG seems to reduce the self-esteem of the participants, until the distractors were removed, at three months postoperatively, but two years after surgery this surgical procedure improves self-esteem (Kloukos, 2016).

Results

Speech and velopharyngeal function

Two publications were included in the systematic review which assessed the effect of LF1 versus DOG on speech and velopharyngeal function. Data from 22 out of 47 participants were available (Chanchareonsook, 2007; Chua, 2010b). Only the most recent paper with the longest follow-up time was used in the analysis, because data of the two studies overlapped (Chua, 2010b). The mean advancement in both the LF1 and the DOG-group was 6.5mm. No statistical significant difference, between LF1 versus DOG, was found in hypernasality (RR 9.0, 95% CI (0.54, 149.5)), nasal emission (RR 0.33, 95% CI (0.015, 7.39)), and velopharyngeal function (RR 0.78, 95% (CI 0.40, 1.53)) at 17 months postoperatively (Chua, 2010b).

Evidential value of the literature
Grading the evidence started at a level of high evidence, because the used data was derived from a RCT. Downgrading with four levels was, however, necessary as there were limitations in study design (for example selection bias, attrition bias), there was indirect evidence (for example narrow range of participants with a specific ethnicity and specific disease characteristics used) and imprecision (for example sample size calculation was only performed for the outcome skeletal relapse).

Skeletal relapse
Two publications were included in the systematic review which examined relapse of the maxilla. One article examined short-term relapse (one year postoperatively) in 29 participants, another article assessed long-term relapse (five years postoperatively) in 47 participants. Long-term (five years postoperative) relapse is not only determined by relapse, but might also be influenced by skeletal growth. Therefore, the guideline task force decided to describe long-term relapse as change after treatment. The maxillary relapse and change after treatment was examined using series of lateral cephalograms. Data of the two studies overlapped, therefore only the study of Chua (2010a), which investigated the long-term effects was used. In the study of Chua (2010a) 47 participants were included, 25 participants underwent LF1 and 22 participants DOG. Long-term data were available of only 16 participants. In the patients, which underwent a LF1, the A-point (subspinale) and P-point (a microscrew placed at the mesial root of the upper first molar) showed horizontal relapse with 2.53 mm and 2.45 mm, respectively five years postoperatively (Chua, 2010a). In the DOG-group the A-point and P-point moved anterior with 2.27 mm and 2.51 mm respectively five years postoperatively (mean difference A- point: -4.8 mm, 95% (CI -9.19, -0.41)). Moreover, it was mentioned in the included systematic review that five years after the surgical intervention, 3 of the 25 participants in the LF1-group, and 1 of the 22 participants in the DOG-group, changed into a Class III occlusion, despite orthodontic intervention and surgical repositioning (Kloukos, 2016).

Evidential value of the literature
Grading the evidence started at a level of high evidence, because the used data was derived from a RCT. Downgrading with four levels was, however, necessary as there were limitations in study design (for example selection bias, attrition bias), there was indirect evidence (for example narrow range of participants with a specific ethnicity and specific disease characteristics used) and imprecision (for example wide confidence interval).

Revisional or corrective surgery
Differences in revisional surgery (for example pharyngoplasty), between participants in the LF1-group and the DOG-group, were not assessed in the included systematic review.

Evidential value of the literature
Grading the evidence was not possible, because no articles were found investigating differences in revisional surgery, between participants in the LF1-group and the DOG-group.

Chewing function

Differences in chewing function, between participants in the LF1-group and the DOG-group, were not assessed in the included systematic review.

Evidential value of the literature

Grading the evidence was not possible, because no articles were found, investigating differences in chewing function, between participants in the LF1-group and the DOG-group.

Malocclusion

Differences in the prevalence of malocclusion, between participants in the LF1-group versus the DOG-group, were not assessed in the included systematic review.

Evidential value of the literature

Grading the evidence was not possible, because no articles were found, investigating differences in occlusion, between participants in the LF1-group and the DOG-group.

Alterations in soft and hard tissues

One article was included in the systematic review which investigated alterations in soft and hard tissues, including 39 participants (Chua, 2012b). The alterations were measured through the change in position of various cephalometric landmarks horizontally (x) and vertically (y). The LF1-group, compared to the DOG-group, indicated less maxillary advancement, described as the advancement of Subspinale A-point: (MDs) of -5.63 mm (P= 0.003) six months postoperatively, -5.27 mm (P= 0.005) one year after the operation and -4.40 mm (95% CI -8.56, -0.24) two years postoperatively. The LF1-group, compared to the DOG-group, indicated non-significant horizontal changes in the soft tissues such as pronasale (MD -0.94 mm, P= 0.74), subnasale (MD 1.53 mm, P= 0.33) and stomion superius (MD -4.20 mm, P= 0.12). The LF1-group, compared to the DOG-group, indicated statistical significant changes in labrale superius after two years of follow-up (MD 3.42 mm, P=0.023). Changes tended to be greater in the distraction-osteogenesis group, but no firm evidence indicated soft tissue differences between the two groups (Chua, 2012b).

Evidential value of the literature

Grading the evidence started at a level of high evidence, because the used data was derived from a RCT. Downgrading with four levels was, however, necessary as there were limitations in study design (for example selection bias, attrition bias), there was indirect evidence (for example narrow range of participants with a specific ethnicity and specific disease characteristics used) and imprecision (for example sample size calculation was only performed for one outcome measure).

Patient reported outcomes (PROs)

Patient reported outcome (PROs) were measured until 2 years after surgery (Chua, 2012a). There was no difference between the LF1-group and DOG-group in terms of Social Avoidance and Distress Scale (SADS) at any time point. To measure self-esteem the Cultural-Free Self-Esteem Inventory (CFSEI) was used. There was also no difference between the groups in general self-esteem after 12 and 24 months, however patients who underwent DOG had a significant lower social self-esteem in the first three months postoperatively (P= 0.023). After 6 months there was no significant difference in self-

esteem between the groups (P=0.896). Satisfaction with life was measured with the Satisfaction With Life-Scale (SWLS). After two years postoperatively, patients in the LF1-group were less satisfied with life, compared to patients in the DOG-group (MD -2.95, 95%CI -5.76, -0.14, P= 0.001) (Chua, 2012a).

Evidential value of the literature
Grading the evidence started at a level of high evidence, because the used data was derived from a RCT. Downgrading with four levels was, however, necessary as there were limitations in study design (for example selection bias, attrition bias), there was indirect evidence (for example narrow range of participants with a specific ethnicity and specific disease characteristics used) and imprecision (for example sample size calculation was only performed for one outcome measure).

Conclusions

Very low GRADE	We found very low quality evidence that le Fort-I osteotomy, compared to distraction osteogenesis, is not associated with differences in speech, nasal emission, and velopharyngeal function in patients with a complete unilateral cleft lip and palate, or a complete bilateral cleft lip and palate (involving the alveolar process). *Sources (Chua, 2010b)*

Very low GRADE	We found very low quality evidence that the classical le Fort-I osteotomy, compared to distraction osteogenesis, is associated with more skeletal relapse and a lower skeletal stability in patients with a complete unilateral cleft lip and palate, or a complete bilateral cleft lip and palate (involving the alveolar process). *Sources (Chua, 2010a)*

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of classical le Fort-I osteotomy, compared to distraction osteogenesis, on type and amount of revisional or corrective surgeries in patients with a cleft lip and palate .

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of classical le Fort-I osteotomy, compared to distraction osteogenesis, on chewing function in patients with a cleft lip and palate.

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of classical le Fort-I osteotomy, compared to distraction osteogenesis, on malocclusion in patients with a cleft lip and palate.

Very low GRADE	We found very low quality evidence that the classical le Fort-I osteotomy, compared to distraction osteogenesis, is associated with anteroposterior postoperative differences in cephalometric values for maxillofacial morphology in patients with a complete unilateral cleft lip and palate, or a complete bilateral cleft lip and palate (involving the alveolar process). *Sources (Chua, 2012b)*

Very low GRADE	We found very low quality evidence that the classical le Fort-I osteotomy, compared to distraction osteogenesis, is associated with no differences in patient reported outcome (PROs) in patients with a complete unilateral cleft lip and palate, or a complete bilateral cleft lip and palate (involving the alveolar process). *Sources (Chua, 2012a)*

Considerations

The decision to opt for a combined orthodontic-surgical course of treatment in cleft patients hardly differs from that of non-cleft patients and there is usually consensus about this decision. The indication for an orthognathic treatment is a sagittal (and sometimes transverse) dental and skeletal discrepancy between the maxilla, mandible and the other parts of the face to such an extent that this can no longer be resolved by orthodontic treatment alone and/or patients experience functional, aesthetic and/or psychosocial problems caused by this discrepancy.

This module about osteotomies in cleft patients examined which considerations play a role in the choice between an LF1 or a DOG of the maxilla. In concrete terms, cleft patients usually have a large, inverted sagittal overbite and accompanying hypoplasia of the maxilla, sometimes accompanied by a transverse discrepancy. The aim of the treatment is to correct the skeletal discrepancy, improve the aesthetics of the face, achieve proper occlusion and articulation and to increase the patient's quality of life. From an aesthetic perspective, the correction of the maxillary and in many cases midfacial hypoplasia, which are so characteristic for cleft patients, is essential.

The most important question for the guideline task force was which surgical technique allows the aforementioned goals to be achieved in the best and most predictable manner: a LF1 - either alone or in combination with an osteotomy of the mandible and/or chin - or a DOG of the maxilla. One significant disadvantage of moving the maxilla forward is a possible deterioration in speech as a result of increased velopharyngeal insufficiency. Therefore, the guideline task force also wanted to know whether it would be possible to predict when this problem will occur and whether the used surgical technique has any influence.

Although it seems obvious that a larger forward displacement of the maxilla would be associated with a higher risk of post-operative deterioration in speech, no tangible evidence of this was found in the literature that was consulted. Also important in this regard is the quality of the speech prior to the osteotomy. In patients with pre-existing

velopharyngeal insufficiency, ventral displacement of the maxilla may have a negative effect at an earlier stage on this insufficiency, than if this were not the case. However, a predictive value in size and number is not available. As any deterioration in speech would be a significant disadvantage of forward displacement of the maxilla, we deemed it important to look at whether velopharyngeal insufficiency occurs after forward displacement of the maxilla in cleft patients. None of the studies that we included provide an answer to this question. Research not included in this study refers to more significant speech deterioration in the event of pre-operative 'borderline' or evident velopharyngeal insufficiency (Witzel, 1995; Janulewicz, 2004). Another study correlates the degree of anterior displacement of the maxilla to the risk of post-operative velopharyngeal insufficiency (VPI), where patients with extreme pre-operative maxillary hypoplasia in the DOG group exhibit less VPI than LF1 patients (Kumar, 2006).

When looking at speech as a measure of outcome in the included studies, no significant differences were found between LF1 and DOG at the level of hypernasality, nasal air loss and velopharyngeal insufficiency. A possible explanation for this could be that the distance across which the maxilla needs to be moved in the ventral direction is the same, whether an LF1 or a DOG is performed. The most important difference is that this is performed in one time in the case of a conventional LF1 and over a period of 2 to 3 weeks in the case of a DOG.

The following critical measure of outcome that was examined is which of the 2 surgical interventions yields the most stable end result, in other words: which procedure is least likely to result in a relapse. We can examine 3 factors here: dentition (occlusion), bone and soft tissues. As far as the soft tissues are concerned, the systematic review by Kloukos (2016) states that both procedures have a positive effect on the soft tissues and in particular on the upper lip, but that the differences between the procedures are not statistically significant. The studies used 2 points on lateral cephalometric radiographs to measure the relapse at a skeletal level: The sub-spinal A point and at a micro screw inserted at the level of the mesial radix of the first molar in the maxilla. Both the short-term (1 year) and the long-term results (5 years) reveal that an LFI osteotomy exhibits a relapse in a posterior and cranial direction. In the DOG group, the maxilla moves in an anterior and caudal direction post-operatively. The authors postulated that the gradual movement of the maxilla in the DOG procedure is the most important factor contributing to the improved stability. The fact that the maxilla moves forward and down during the post-operative phase after a DOG is attributed to the use of elastics that pull the maxilla in this direction. All measurements were performed on lateral cephalometric radiographs and not on CTs or CBCTs. As far as occlusion as a measure of outcome for stability is concerned, 3 of the 25 patients in the LF1 group and 1 of the 22 patients in the DOG group ended up with a Class III malocclusion again after the procedure. Due to this small difference in numbers, it is only possible to state that both techniques usually result in good final occlusion. A factor that is worth mentioning, but not implemented often in the Netherlands, is that none of the reviewed studies reported the use of an autologous bone graft (rib or iliac crest) performed at the same time as the classic Le Fort 1 osteotomy in order to bridge the large bone gap and achieve improved ossification with less relapse.

The literature also does not report any differences between an LF1 and a DOG in the final ability to chew, being an important objective of an orthognathic treatment.

As an orthognathic treatment and forward movement of the maxilla aims to improve the sometimes stigmatising profile of a patient with clefts of the lip and palate, we also wanted to include aesthetics as an outcome. The Cochrane review describes aesthetics based on the analysis of X-ray skull profile images. However, according to the guideline task force aesthetic changes cannot be measured adequately with this medium.

The Cochrane review by Kloukos (2016) is based on a study group of 47 patients described in 6 articles. The small group of patients combined with the many methodological shortcomings in the research resulted in a high 'overall bias' risk and the quality of the evidence overall is therefore low. Therefore, it is not possible to provide an unambiguous answer to our questions based on the review. Based on the literature consulted, we are therefore unable to issue a recommendation about when to opt for an LF1 and when to opt for a DOG. However, we did feel that it was necessary to express a view on this in the recommendations listed below based on 'expert opinion'. We substantiated this expert opinion by presenting the question and the policy about when to opt for an LF1 and when to opt for a DOG to the maxillofacial surgeons of the larger cleft teams in the Netherlands. As no significant differences were found between the LF1 and the DOG for virtually all the outcome measures, it seems appropriate to use the DOG only when the distance that needs to be bridged in a ventral direction cannot be achieved using an LF1 alone and a simultaneous setback of the mandible is undesirable for whatever reason. The maximum distance that the maxilla can be moved in a ventral direction in non-cleft patients is approximately 10 to 12 mm. This distance is usually less in patients with a cleft, due to the presence of scar tissue on the palate as a result of closure of the soft and hard palates.

When the ventral displacement of the maxilla that needs to be achieved with a LF1 or DOG is so large that it does not seem feasible, it is also possible to opt for a combination with a setback of the mandible. The disadvantages of this include the risk of neuropraxia of the inferior alveolar nerve and potential dislocation or exacerbation of obstructive airway problems. Of course this procedure needs to fit in the profile plan for the patient.

Disadvantages of DOG in general are the higher costs of the distractor itself and the fact that a second procedure is required to remove the distractor. Patients also usually experience more problems with the distractor as a result of post-operative pain and wound infections. It is also difficult to determine the correct vector for the direction of the distraction (Baas; 2015).

The immediate post-operative follow-up treatment, both surgical (for example the use of inter-maxillary fixation) and orthodontic treatment, has not been described in great detail in the literature. However, it is the opinion of the guideline task force that the post-operative treatment protocol is an important factor to achieve a good end result.

Of course it is important to discuss the considerations that determine the final choice for a LF1 or a DOG in detail with the patient and his/her parents and to provide a detailed explanation.

Recommendation

Consider a classic Le Fort 1 - either alone or in combination with a setback osteotomy of the mandible - in cleft patients with a sagittal discrepancy between the upper and lower jaws that is so large that it can no longer be resolved by orthodontic treatment alone. Consider a distraction osteogenesis only in the case of large sagittal discrepancies. Both treatments have specific advantages and disadvantages, which can determine the choice per individual patient and per surgeon.

Literature

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Chapter 10 Rhinoplasty in patients with clefts of the lip and palate

Module: Rhinoplasty

Clinical question
What are the indications for performing rhinoplasty at a young age in children with a cleft lip (+/-alveolar arch and palate)?

Introduction

In case of a cleft lip, the nose is always affected to a greater or lesser extent due to embryological development. On the affected side, the nostril is pulled in a lateral direction, making the tip of the nose less prominent with a shift of the columella to the non-affected side. In case of a bilateral cleft lip, the condition results in a shortened columella. Functional problems can also occur in the nasal passage as a result of deviation of the nasal septum. Modifications to the nose are already performed during lip closure and secondary corrections can be performed at a later stage. Early correction results in earlier correction of the defect, but can cause growth abnormalities of the nose. The risk of growth abnormalities applies primarily if surgery is performed on the septum at an early age, because the anterior septum contains an important growth centre. It is therefore important to know which treatment strategy yields the best (final) result.

Searching and selecting

In order to answer the clinical question, a systematic literature analysis was performed based on the following PICO:

- **P:** Orofacial cleft with at least a cleft lip;
- **I:** Rhinoplasty (both primary and secondary) at age < 18 years;
- **C:** Rhinoplasty (both primary and secondary) at age > 18 years;
- **O:** Shape of nose, functioning of nasal passage.

Relevant outcome measures
The guideline task force deemed the shape of the nose and the functioning of the nasal passage to be critical outcome measures for the decision-making process.

Search and selection (methods)
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and March 12, 2014. This search was aimed to identify systematic reviews, RCTs, CCTs, and observational studies. Detailed search characteristics are shown in the “Onderbouwing”.

Studies that investigated patients with cleft lip and palate were selected if they compared rhinoplasty performed in patients below the age of 18 years with rhinoplasty performed in patients older than 18 years. It was essential that the long term effects of the rhinopolasty (after maturity, defined as 18 years) were described in the study. Data

on effect sizes or primary data had to be available for at least one of the outcomes of interest: cosmetic appeal of nose shape and functional nasal passage.
The initial search identified 369 references of which 14 were assessed on full text. Twelve studies, all with a non-randomized observational study design, seemed to be relevant but did not present data on the effect size or association for the outcomes of interest with the required follow-up time. Finally, two studies were included, although they did not answer the research question directly. No evidence tables and risk of bias assessments could be performed of these observational studies without a control group, although due to their design they were deemed automatically as very low quality of evidence.

Summary of the literature

Study characterics

No studies were identified during the literature search that answered the research question directly. However, two studies were found that had an indirect relation to the research question. McComb 1995 is an observational study that describes the long term results (18 years) of a primary rhinoplasty during cleft lip correction surgery (n=10) versus another (not further described) type of rhinoplasty (n=20) and healthy controls (n=23). Facial photographs of the study subjects were examined using a software programme, and the degree of facial symmetry was determined. The following features were studied: in the anteroposterioir view: vertical sloping of the alar and the lower lip asymmetry; in the inferior (basal) view: the overall nasal outline, the upper nasal perimeter and the nostrils. Also the total amount of symmetry in all these features was determined.

McComb (2009) describes a case-series of 10 patients that are being evaluated 18 years after an open-tip rhinoplasty, performed simultaneously with a cleft lip correction surgery. One patient was lost to follow-up at the age of 14 years, thus these results are shown up to that age.

Results

McComb (1995) describes that the healthy controls had a significantly more symmetrical face compared to the cleft palate patients. There was no significant difference in facial symmetry between the cleft palate patients who underwent a primary cleft nose correction compared to those that underwent a different type of rhinoplasty. Furthermore the facial symmetry of the cleft lip patients was compared at the age of 10 and 18 years, and no significant difference was found.

McComb (2009) reports in a case-series of 10 patients who underwent an open tip primary rhinoplasty during cleft palate surgery, that the nasal development of these patients is overall satisfactory. There is no interference with growth and the operative scar is barely visible.

Grading the evidence

It is not possible to grade this evidence, since the research question cannot be answered directly with the available literature.

Conclusions
Not applicable

Considerations
It is important for us to realise that many publications about rhinoplasty at a young age in children with clefts of the lip and palate only describe what the author did to the nose during the procedure, without an adequate comparison and without adequate follow-up.[1] Various publications indicate that a primary rhinoplasty can result in an improvement of the shape, but the follow-up is often tooshort. Several publications indicate that secondary rhinoplasty is often required at a later stage.[2] A limited amount of comparative research has been performed, unfortunately without follow-up to age 18 but only for several months to years.[3] It is regularly claimed that an external rhinoplasty and/or correction of the septum can be performed at a young age, but there is often no evidence to support this and the follow-up is often not long enough.[4]

There are also publications that state that early nasal surgery can result in growth retardation of the septum and impaired forward growth of the nose. It is unlikely that catch-up growth will take place (Kobus, 1978; Krupp, 1990; McComb, 1990; Roberts-Harry, 1996; Rullo, 2009; Takato, 1990, Wray, 1976). Several publications indicate that an improvement in the shape of the nose can be achieved with secondary nasal surgery, but a difference compared to the non-cleft population remains (Meazzini, 2010; Okawachi, 2011). The nostril is usually moved during lip closure and the columella is modified, but a true rhinoplasty with modification of the nasal bone, the lower and upper lateral cartilage and the entire nasal septum is usually not performed (Ahuja, 2001; Kim, 2004). Naso-alveolar moulding is thought to simplify primary closure of the lip and nose, but there is no comparative research (with versus without naso-alveolar moulding) that evaluates the effect on the nose (Van der Heijden, 2013).
It is good to bear in mind that the aveolar bone grafting procedure has an effect on the nose, as does a LeFort 1 osteotomy (Agarwal, 2012; Heliovaara, 2001; Takato, 1994; Wu, 2013). It is therefore recommended to perform the definitive rhinoplasty only after stabilisation of the LeFort osteotomy and after completion of any course of orthognathic treatment. (Wu, 2010; expert opinion).

The guideline task force concludes that the possible disadvantages of early nasal surgery mentioned in the literature (growth retardation, more complicated definitive surgery in adulthood due to scar formation) are not compensated by proven benefits. There is a lack of evidence that the shape of the nose after early rhinoplasty becomes normal or so much better that it yields positive effects with regard to the patient's psychosocial wellbeing. There are therefore no psychosocial arguments to justify early rhinoplasty.

The guideline task force concludes that if nasal passage abnormalities occur at a young age, a concha reduction can be considered to improve the functional symptoms (Bhandarkar 2010).

If the patient or his parents state a desire for early nasal surgery, then this request should be given serious consideration. It is important to discuss that early nasal surgery does not - according to the literature - result in a normal shape of the nose and that further surgery is often required in adulthood. There is also no evidence to suggest that early nasal surgery relieves any psychological objections. We recommend involving a psychologist or behavioural expert in the decision-making process to evaluate the desire for improvement of the appearance. Psychosocial treatment can also be started if necessary. Also do not forget to mention the disadvantages of surgery, such as the risk of scar formation and the risk that the result will not be permanent.

Recommendations

During primary lip closure, pay attention to the primary correction of the nostril and the position of the caudal septum and columella of the nose.

Preferably delay secondary surgery of the nose for clefts of the lip and palate until growth of the mid-face has been completed and any orthognathic surgery has been completed, in order to limit the total number of procedures.

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Chapter 11 Psychosocial guidance for patients with clefts of the lip and palate

Module: Psychosocial guidance

Clinical question
What is the effectiveness of psychosocial guidance as part of a multi-disciplinary team approach for children with clefts of the lip and palate and their parents?

- At which moments during the development of the child can psychosocial guidance best take place?

Introduction

Parents of a child with a congenital abnormality, such as clefts of the lip and palate, have various reasons to be concerned about their child's future. Experience has taught us that these concerns usually develop immediately after the orofacial cleft is diagnosed (during the prenatal stage or later) and may be present at various moments in the child's development. Clinical practice reveals that parents can experience acceptance problems, grief and concerns about issues such as their child's social acceptance in the future. The course of the guidance offered to parents (and child) with regard to the psychosocial wellbeing and raising the child is complex and covers various phases in the development of the child from baby to (young) adult. Although much of the primary treatment is medical/surgical in nature, the ultimate goal of the entire treatment by a cleft team is to achieve psychosocial wellbeing of the child with clefts of the lip and palate and his or her family. It is therefore desirable to create an inventory about whether and when parents and child could benefit from psychosocial support and - if so - at which moments in the development of the child this can best take place.

Searching and selecting

In order to answer the clinical question, a systematic literature analysis was performed based on scientific queries with the following PICOs:

- What is the effectiveness of psychosocial guidance as part of a multi-disciplinary team approach for children with clefts of the lip and palate and their parents?

- **P:** Patients with clefts of the lip and palate and the parents of these patients
- **I:** Psychosocial guidance
- **C:** -
- **O:** Sufficient knowledge about psychosocial aspects of orofacial cleft, psychosocial wellbeing of child and parents, quality of life, psychosocial development.

- What type of psychosocial problems in development can occur in children with clefts of the lip and palate and when do these problems present themselves?

- **P:** Patients with clefts of the lip and palate and the parents of these patients
- **I:** -
- **C:** -
- **O:** Sufficient knowledge about psychosocial development of children with clefts of the lip and palate, development, intelligence and behaviour.

Relevant outcome measures
The guideline task force deemed quality of life of the child, adequate psychosocial development, intelligence, presence of behavioural disorders and psychosocial wellbeing of child and parents to be critical outcome measures for the decision-making process.

The guideline task force deemed the knowledge about psychosocial development to be an important measure of outcome for the decision-making process.

Search and selection (methods)
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and October 21st, 2014 for PICO 1 and between 2000 and March 9th 2015 . This search was aimed to identify systematic reviews, RCTs and observational studies.

For PICO 1 studies were selected if they investigated the effectiveness of psychological interventions on the psychosocial development of children with cleft lip and/or palate and/or their parents. Children were identified as younger than 18 years of age. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: quality of life (of children with clefts of the lip and palate and/or their parents), psychological/psychosocial development (of children with cleft palate and/or their parents), intelligence, behavioral disorders and knowledge of psychosocial development. For PICO 1: the initial search identified 213 references of which 12 were assessed on full text. After assessment of full text 11 studies were excluded and 1 study was included.

For PICO 2 studies were selected if they investigated the psychosocial development of children with cleft lip and/or palate and/or their parents. Children were identified as younger than 18 years of age. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: quality of life (of children with clefts of the lip and palate and/or their parents), psychological/psychosocial development (of children with clefts of the lip and palate and/or their parents), intelligence, behavioral disorders and knowledge of psychosocial development.

For PICO 2: the initial search identified 376 references of which 34 were assessed on full text. After assessment of full text 9 studies were excluded and 25 studies were included. Regarding the psychosocial development, a GRADE or EBRO assessment of the evidence could not be provided, since the research question was not prognostic, diagnostic or intervention-based by nature. Hence, no evidence tables were provided for the studies included in this part of the literature summary.

Summary of the literature

Description of studies

Psychosocial interventions

One study, a systematic review, was included in this literature summary. Norman, 2014 aimed to assess the effectiveness of different psychological interventions for children and adults with cleft lip and/or palate and their parents. Six databases (including Medline and Embase) were searched until June 2013. Studies were included if at least 90% of participants had cleft lip/palate (or parents of children with cleft lip/palate), unless results were reported separately for patients with cleft lip and/or palate or raw data were available upon request from authors. A total of 7 studies were included in this review.

Psychosocial development

For this literature summary the conclusions of systematic review by Hunt, 2005_1 was considered as a fundament. The conclusions from the review were supplemented by the 24 studies published after the systematic literature search of this review was performed (December 2003). No GRADE-assessment was performed of these studies and no literature conclusions were formulated, since the study designs was not suitable for this. However, the studies are described narratively in the paragraphs below.

Hunt, 2005 is a systematic review examining the psychosocial impact of cleft lip and palate among children and adults. The following specific research questions were assessed: 1) are children and adults with cleft lip and palate at increased risk of impaired psychosocial functioning? 2) What, if any, type of psychosocial impairment do children and adults with cleft lip and palate develop? 3) Is there a relationship between cleft types and the prevalence and severity of psychosocial impairment? 4) Are children with cleft lip and palate more vulnerable to psychosocial problems at particular stages of development? In this review a systematic search was performed up to December 2003 and found 64 papers that met the inclusion criteria, that were prospective, retrospective or cross-sectional in nature. Only 30 of the included studies had a control group.

Baker, 2008 is a cross-sectional study that examined the role of parent's coping strategies and social support in the family impact of cleft lip and palate and levels of adjustment. A total of 103 parents of children and young adults with cleft lip and palate (age 0 – 18 years) participated in this study, by filling out a Coping Response Inventory, the Interpersonal Support Evaluation List – Short Form, the Stress-related Growth Scale, the Family Impact Scale and the General Health Questionnaire.

Berger, 2009 is a cross-sectional study exploring the nature of psychosocial adjustment in young people with a cleft and their parents. A total of 145 participants aged 11 – 16 years and their families were included in this study. Participants completed measures of psychological adjustment, coping, social experiences and satisfaction with appearance, cleft-related factors and demographic information.

Brand, 2008 is a cross-sectional assessed psychological functioning and interactional competencies and sleep patterns in children with cleft lip and palate. A total of 32 children with cleft lip and palate and 34 controls aged 6-16 years old were included in this study. For psychosocial assessment the Strength and Difficulties Questionnaire and a

questionnaire on interactional competencies was used. For sleep assessment a sleep log was completed for seven consecutive nights.

Collett, 2012 is a cross-sectional study that aimed to determine whether psychosocial functioning in children with orofacial clefts and their parents differs from unaffected controls. A total of 93 participants with orofacial clefts and 124 controls aged 5-9 years were included in this study. Psychosocial functioning was measured by the Child Behaviour Checklist, the PedsQL 4.0, the Social Competence Scale and the Parenting Stress Inventory.

Demir, 2011 is a cross-sectional study aiming to determine whether children with non-syndromic cleft lip and palate are more likely to be diagnosed with psychiatric disorders and whether cleft-related factors are related to psychopathology. A total of 20 children aged 6-16 years with cleft lip and palate were included in this study together with 40 controls without cleft lip and palate. Children were assessed by psychiatric interviews and by the Child Depression Inventory, State-trait Anxiety Inventory for Children, Piers-Harris Children Self-Concept Scale, Schedule for Affective Disorders and Schizophrenia for School-aged Children – Present and Lifetime version, Ankara Articulation Test, Wechsler Intelligence Scale for Children, Beck Anxiety Inventory and Beck Depression Inventory.

Feragen, 2009 is a cross-sectional study that assessed self-reported social experience in children with a cleft lip and/or palate. A total of 268 10-year old children were included in this study, also their parents were requested to participate. The Child Experience Questionnaire, Personal Inventory for Children and Satisfaction with Appearance Scales were used to study cognitive, emotional and psychosocial functioning.

Feragen, 2010_1 is a cross-sectional study that investigated associations between perceived peer harassment and satisfaction with appearance in children with a cleft lip and/or palate. A total of 661 children with a cleft (non-visible in 227 patients) aged 10-16 years were included in this study. Peer harassment was measured by the Child Experience Questionnaire. Satisfaction with appearance was measured with the Satisfaction with Appearance Scales.

Feragen, 2010_2 is a cross-sectional study that investigates the role of friendships and social acceptance in adolescents with a cleft. A total of 196 adolescents with a visible cleft, 93 with a non-visible cleft and 1832 controls with no cleft were included in this study. The adolescents aged 16 years filled out the Hopkins Symptom Checklist for depressive symptoms and the Self-Perception Profile for Adolescents.

Feragen, 2014 is a cross-sectional study that explores psychological functioning in adolescents with a cleft aged 16 years. A total of 857 adolescents with a cleft (non-visible in 284 participants) and 1832 healthy controls were included in this study. Cognitive, emotional, behavioral, appearance-related and psychosocial adjustment was assessed by the Hopkins Symptom Checklist, the Harter Self-Perception Scale for adolescents, the Child Experience Questionnaire and Satisfaction with Appearance Scale.

Hentges, 2011 reports a follow-up of the population of Murray, 2007, when the children are aged 7 years. Again, cognitive development of children with delayed lip closure

(n=49), early lip closure (n=44) and healthy controls (n=77) were assessed in terms of Intelligent Quotient, language and school development.

Hoek, 2009 is a cross-sectional study that examined the social-emotional health of children with a cleft performed in the Netherlands. In total 80 children with a cleft, aged 9-12 years were included in this study. The participants, as well as their parents and teachers filled in questionnaires about their social-emotional health: the “Strength hand Difficulties Questionnaire”, the “Child Behavior checklist” (parents) and the “Teacher’s Report form” (teachers).

Hunt, 2006 is a cross sectional study that aimed to determine the psychosocial effects of cleft lip and/or palate among children and young adults, and compare those effects to a control group without cleft lip and/or palate. A total of 160 children / young adults aged 8-21 years were included in this study, together with 113 controls. Psychological functioning was assessed using validated psychological questionnaires. Happiness with facial appearance was rated using the visual analogue scale. Social functioning, including experience with teasing/bullying was assessed using a semi-structured interview.

Hunt, 2007 is a cross-sectional study that aimed 1) to determine the opinion of parents regarding the psychosocial functioning of their child with cleft lip and palate, 2) to identify predictors of psychosocial functioning, 3) to determine the level of agreement between children with cleft lip and palate and their parents. A total of 129 parents of children with cleft lip and palate and 96 parents of healthy controls were included in this study. Children were aged 8-18 (mean 12) years. Parents completed the Child Behavioural checklist, were interviewed and gave their opinion of the child’s self-esteem, anxiety, happiness and problems caused by facial appearance using visual analogue scales.

Hutchinson, 2011 is a systematic review and meta-analysis that examined the cross-cultural psychosocial impact of cleft lip and/or palate in non-Anglo populations. A total of 4 studies containing 2276 adolescents and adults with cleft lip and palate were included in this review. The studies were performed in China, Hong-Kong, Taiwan and Norway. Effect sizes were estimated using Cohen’s d and confidence intervals.

Kramer, 2009 is a cross-sectional study that studied the quality of life and social functioning in schoolchildren with a cleft and their families. A total of 170 children with cleft lip and palate and their families were included in this study. Both child and family were requested to fill in the Impact on Family Scale Questionnaire. The results were compared with age-matched average scores of unaffected children from a control group of 132 families.

Murray, 2007 is an observational study in which the effect of early versus late cleft lip repair are studied on infant development and mother-infant interactions. A total of 94 infants with cleft lip, and 96 control infants were examined. Early lip closure (<1 month) was performed in 48 infants and late lip closure (3-4 months) in 55 infants. Cognitive development, behavioural problems and attachment were assessed at 2, 6 and 12 months.

Murray, 2010 is an observational study that studies the effect of cleft lip on socio-emotional functioning in school-aged children. A total of 93 children with cleft lip (with and without cleft palate) and 77 controls were included in this study at the age of 18 months, and followed for 7 years. Socio-emotional functioning of children was assessed using teacher and maternal reports, observations of social interactions, and child social representations.

Petrackova, 2015 is a observational study that compares the effects of early versus late exposure to anesthesia on intelligence quotient and psychosocial development in children who were operated for cleft lip. In 15 patient early lip closure, in the first 8 days of life, was performed. In 17 patients late repair, at 3-10 months, was performed. Intelligence quotient and psychosocial development were compared at the age of 3-7 years.

Roberts, 2012 is a systematic review that examined the cognitive functioning of children and adults with cleft lip and palate or cleft lip or cleft palate only. A total of 29 papers was included in this review, containing data from 1 546 persons with a cleft and 279 805 controls. The included studies showed large heterogeneity (age of study population, length of follow-up, measurement of outcome variables). Cohen's d effect sizes were calculated to compare the difference between the cognitive performance of the cleft and control groups for the 10 broad cognitive domains. Effect sizes were weighed by inverse variances (corrected for sample size per study). Due to the large heterogeneity of the included studies, the results of these weighed effect sizes should be interpreted with caution.

Silfer, 2003 is a cross-sectional study in which the social interaction patterns of children with and without clefts were studied. A total of 34 children with oral clefts aged 8-15 years were matched to 34 non-cleft controls (match for sex, age and socioeconomic status). Participants were videotaped while interacting with a peer confederate. The cleft- and control groups were compared on social behaviour.

Speltz, 2000 is a prospective longitudinal study that examines cognitive and psychomotor development in patients with a cleft. A total of 29 patients with cleft lip and palate, 28 with cleft palate only, and 69 healthy controls were included in this study. Infants were administered the Bayley Scales of Infant Development at the age of 3, 12 and 24 months.

Swanenburg de Veye, 2002 is a cross-sectional study which studies the association between associated congenital malformations and the mental and psychomotor development of children with clefts. A total of 148 children with cleft lip (n=56), cleft palate (n=32) or both (n=62) were included. The children's level of development was determined by means of the Dutch version of the Bayley Scales of Infant Development.

Wehby, 2012 is a longitudinal database study (it is not mentioned whether the data collection was prospective or retrospective) that examines behavioural health in children aged 2-12 with oral clefts. A population-based sample of 104 children with oral clefts in the United States of America is used for this purpose. Behaviour was evaluated using the Child Behavior Checklist or the Pediatric Behaviour Scale 30, depending on age compared with normative samples.

Wehby, 2014 is a longitudinal database study (it is not mentioned whether the data collection was prospective or retrospective) that compares the academic achievement of children with oral clefts to their classmates in a population-based study in the United States of America. The sample included 588 children with clefts (3744 child-grade observations) and 1874 classmates without clefts (13159 child-grade observations). Differences were assessed at different ages/levels of education (elementary, middle and high school). Academic achievement was assessed by using standardized tests of academic progress developed by the Iowa testing programs.

Results

Psychosocial interventions

Norman, 2014 concludes that out of the 7 included studies only 2 were randomized controlled trials (RCTs) and included for full data analysis (one of which failed to meet the full inclusion criteria). Both of these RCTs were performed in adults (some with clefts), and therefore, not relevant to answering our research question. The five remaining studies were observational and included only in a narrative synthesis, because data were available for people or parents of those with cleft lip and/or palate only. Two studies (Maddern, 2006; n=29 and Kapp-Simon, 2005, n=20) were performed in children (some with clefts) and one in parents of children with cleft palate (Pelchat, 2004, n=76).

Maddern, 2006 described the effect of cognitive behavioural training (CBT) in children with any form of disfigurement aged 5-16 years. A total of 4 sessions was administered by a clinical psychologist or assistant psychologist (duration of sessions not stated). Patients were followed for 6 months after the intervention. At 6 months follow-up children reported a reduction in the frequency of teasing and in the degree of distress it caused both in the classroom and in the playground. Parents reported reductions in their children's' somatising behaviour and levels of anxiety.

Kapp-Simon, 2005 described the effect of social skills training (SST) in children with craniofacial conditions aged 12-14 years. A total of 12 sessions lasting 90 minutes were administered. Children on the waiting list for the SST served as controls. Both target and peer-controlled total communication improved across time with adolescents receiving social skills intervention showing significantly more improvement than those adolescents not receiving direct social skills interventions. Adolescents receiving treatment participated in significantly more target initiated conversations lasting at least three interchanges and showed a trend toward a greater frequency of target initiations and positive responses to peer initiations. Peers were more likely to respond to treatment subject initiations after intervention. Fewer treatment subjects used nondirected communication, whereas control subjects continued to use nondirected communication at a slightly increased frequency.

Pelchat, 2004 describes a family intervention program (a form of CBT) in parents of newborn children with cleft lip and/or palate and Down syndrome. The intervention consisted out of 6-8 sessions administered by a nurse (duration of session not stated). Parents reported to be significantly satisfied about the intervention program. Parents of children with cleft lip and/or palate were significantly more satisfied than the children of parents with Down’s syndrome.

Pooling and meta-analysis of data was not possible due to heterogeneity of the included studies. This review found no evidence to support any specific intervention.

Psychosocial development

Hunt, 2005 summarizes that the majority of adults and children with cleft lip and palate do not appear to experience major psychosocial problems. Berger, 2009; Collett, 2012; Hoek, 2009 and Feragen, 2014 concur with these findings. It has to be noted, though, that literature has tended to report the psychosocial functioning of cleft lip and palate children in a general way. This has often disguised specific problems that these children have in relation to adjustment, behavioural problems, self-concept, self-esteem, self-confidence, body image, satisfaction with facial appearance, satisfaction with speech, social life, anxiety, depression and learning problems. Children with cleft lip and palate has been described as more external in locus of control and significantly more felt dependent than non-cleft controls. Children with cleft lip and palate also tend to have higher levels of hostility, negative self-worth, a negative outlook and greater dependence compared with the general population. Furthermore, children with cleft lip and palate tend to see their parents as having more negative feelings and worrying more, and adolescents express a lower degree of perceived parental acceptance than controls. Feragen, 2009 reports that psychosocial resilience is associated with adequate emotional functioning, high satisfaction with appearance and a lower frequency of reported teasing.

Self-concept appears to be good among children with cleft lip and palate, in some cases even better than in the control group. This concurs with the findings of Kramer, 2009, who reports that children with cleft lip and palate have a better quality of life than the control group. But when present, limitations in quality of life in children with cleft lip and palate mostly affected the social role. However, when specific components of self-concept are examined, some problems emerge. Children with cleft lip and palate may have lower personal and social self-concept scores compared to non-cleft controls.

Self-esteem is considered to be generally good among children with cleft lip and palate, although it has been linked to the child's opinion about facial appearance. Children who are more accepting their cleft tend to have a higher self-esteem, and the more physically attractive persons rates themselves, the higher that person's self-esteem tends to be. Children, adolescents and adults have reported that their self-confidence has been affected by having a cleft lip and palate. Hunt, 2007 reports that self-esteem is lower in children with clefts compared to healthy controls. Regarding timing of cleft lip surgery, Petrackova, 2015 reports that children with early cleft-lip surgery (<8 days) have a better self-esteem than those with late (3-10 months) lip surgery.

Regarding body-image, although most children seem relatively satisfied, some features (nose and teeth) are considered less satisfactory and may result in problems with body image. There is conflicting evidence about satisfaction with facial appearance, 3 studies report that cleft lip and palate patients are generally pleased with their facial appearance, while 5 studies report that many cleft lip and palate patients express dissatisfaction. Silfer, 2003 also reports that children with clefts and their parents report greater dissatisfaction with facial appearance. A visible scar appears to be of most concern. Likewise, Feragen, 2014 reports that cleft visibility was a risk factor for

dissatisfaction with appearance, while Feragen, 2010_1 states that cleft visibility was not associated with appearance dissatisfaction, although this relation is strongly mediated by experiences of peer harassment. Feragen, 2010_2 adds that subjective dissatisfaction with facial appearance is related to depressive symptoms. Hunt, 2006 and Hunt, 2007 report that happiness with appearance is lower in children with clefts compared to healthy controls, and that this happiness is related to how visible the scar is and whether the child has been teased. Satisfaction with facial appearance has been linked to the incidence of behavioural problems, this finding is also reported in Wehby, 2012.

Regarding behavioural problems, there are contrasting reports in children with cleft lip and palate. On one hand, 2 studies reported that children with cleft lip and palate have higher than average levels of internalizing behaviour (that is a risk factor for developing anxiety problems). On the other hand, 2 studies reported that children with cleft lip and palate are less aggressive than controls and do not exhibit any signs of delinquency.

Patients with cleft lip and palate appear to be more socially affected as a result of having a cleft (as reported by professionals who care for cleft lip and palate patients and self-reports by adults with cleft lip and palate). Several studies performed in the 1970's have shown that young people with cleft lip and palate are more likely to drop out at school and less likely to belong to a club or society. Also, a larger proportion of adolescents with cleft lip and palate indicate no aspiration for further education, when compared to controls (also study from 1974).

Wehby, 2012 reports that most children with oral clefts had similar behavioural health outcomes as unaffected children, except for increased risk of inattention / hyperactivity at the age 6-12 years. In contrast, Brand, 2008 reports that there was no difference in conduct problems or hyperactivity between children with cleft lip and palate and non-cleft controls aged 6 – 16 years. Hoek, 2009 also reports that there is less deviant behavior in children with clefts compared to controls with no clefts. Hunt, 2006 and Hunt, 2007 however report that more behavioural problems were reported in children with cleft lip and palate, when compared to healthy controls. Factors associated with behavioural problems were visibility of a scar and having being teased.

No studies regarding anxiety and depression in children with cleft lip and palate were reported, but in adults cleft lip and palate patients had a higher prevalence of anxiety and depression when compared to controls as assessed by Hunt, 2005. Also, dissatisfaction with facial appearance was found to be a predictor of depression, both among cleft lip and palate patients and controls, this finding is also confirmed in Feragen, 2010_2 and Demir, 2011. Murray, 2010 supplements that children with clefts aged 1.5 – 9 years had raised rates of teacher-reported social problems, and anxious and withdrawn-depressed behaviour. Hoek, 2009 also concludes that there is more depressive behaviour as reported by parents in children with clefts aged 9-12 years. Demir, 2011 supplements that social anxiety and major depressive disorder were more prevalent among children with cleft lip and palate than among controls without cleft lip and palate in children aged 6-16 years. However, Feragen 2010_2 reports that boys with a cleft report less depressive symptoms than their peers with no cleft, while overall there was no difference in depressive symptoms between 16-year olds with and without a cleft. Both Hunt, 2006 and Hunt, 2007 supplement that more anxiety was reported in children with cleft lip and palate when compared to healthy controls. Teasing was

greater among participants who had cleft lip and/or palate and was a predictor of anxiety.

Regarding mother-child attachment, no differences were found between children with cleft lip and palate and controls in the studies described by Hunt, 2005. Likewise, Murray, 2007 reports no significant difference in attachment between cleft lip infants and their mothers versus controls at 18 months. However, some differences (less secure attachment for cleft infants) at 2 months of age are reported.

Regarding development, babies with cleft lip and palate at 5 months of age were found at risk of delayed development. However, at 36 months of age this difference seems to dissipate, except in the area of expressive language. A study from 2000, using both longitudinal and cross-sectional data, found that the difference in mental developmental scores decreased significantly as infants with cleft lip and palate increased in age. Specific learning problems have been described in two studies in children with cleft lip and palate with one study reporting that 1 in every 4 children with a cleft repeated a grade at school. The results of Wehby, 2014 concur with these conclusions: children with oral clefts had lower scores than their classmates across all domains of school levels. Furthermore, children with clefts were approximately one-half grade behind their classmates and had higher rates of academic underachievement. The Dutch study by Hoek, 2009 also reports that 1 in 3 children with a cleft had a learning problem. Timing of lip closure (and accompanying anesthesia) does not seem to influence the intelligence quotient or psychosocial development in patients with cleft lip, as reported by Petrackova, 2015. However, Murray, 2007 reports that late lip closure (3-4 months of age) is associated with worse scores on the Bayley Scales of Mental Development, when compared to neonatal lip closure. Hentges, 2011 supplements that the same infants as in Murray, 2007, at the age of 7 years, score lower on IQ, language and school achievements, compared to healthy controls, particularly those with late repair. Murray, 2010 and Silfer, 2003 also report that social interaction patterns of children with clefts are less developed than those of children without clefts. Also, in adults and adolescents with cleft lip and palate the level of psychosocial development is lower than in individuals without cleft lip and palate in a non-Anglosaxon population, as shown by the meta-analysis Hutchinson, 2011.

The type of cleft and its severity appears to have little influence on the individual's overall psychosocial functioning. No significant association has been found between cleft type and the incidence of behavioural problems, self-esteem, mental and motor development or psychosocial functioning in general. However, a few differences between cleft types have been found in relation to self-concept, satisfaction with facial appearance, depression, attachment, learning problems and interpersonal relationships. In accordance with the findings of Hunt, 2005, Roberts 2012 reports that the cleft patients score lower than controls on the following cognitive domains: academic, attention / executive function, sensorimotor function, language and general cognition. However, cleft patients score similar to controls on the cognitive domains: visuospatial, memory (both delayed recall and immediate recall), motor skills and processing speed. Regarding differences in learning problems in relation to cleft type, Wehby, 2014 mentions that children with cleft lip and palate and cleft palate (but not children with cleft lip only) were more likely to use special education services. Swanenburg de Veye, 2002 reports that children with an isolated cleft palate showed the highest percentage

of minor malformations that are minor, yet possibly worry some, while children with an isolated cleft lip showed the least. The children with associated congenital malformations appeared to be most disadvantaged with respect to their development. On the other hand Speltz, 2000 reports (in a slightly smaller sample) that the mental and psychomotor developmental scores of the cleft lip and palate group and the cleft palate only group were lower than those of the control group, but did not differ from one another.

Hunt, 2005 concludes that overall a few differences between cleft types have been found in relations esteem, satisfaction with facial appearance, depression, attachment, learning problems and interpersonal relationships. With a few exceptions, the age of the individuals with cleft lip and palate does not appear to influence the occurrence or severity of psychosocial problems. However, the included studies lack uniformity and consistency required to adequately summarize the psychosocial problems resulting from cleft lip and palate.

Age and psychosocial problems

Hunt, 2005 concludes that overall the age of an individual with cleft lip and palate does not appear to influence the occurrence or severity of psychosocial problems. However, there are a few nuances to this conclusion. Increasing conduct problems have been reported as the child grows older. In relation to speech, parents and children with cleft lip and palate have reported increased satisfaction as the child grows older. While individuals of all ages have reported dissatisfaction with their facial appearance, one study did find that younger children and adolescents (age 10-15 years) were less satisfied with their appearance than subjects aged 20 years. Satisfaction with appearance in females has been found to decrease with age among those with inter-oral defects only.

Baker, 2008 concludes that for parents, having a younger child with cleft lip and palate is associated with a greater impact on the family than having an older child with cleft lip and palate.

Hutchinson, 2011 reports that adolescents are significantly less impacted by psychosocial issues than adults, in non-Anglosaxon populations.

Speltz, 2000 reports that in infants aged 3-24 months there is no difference in changes of psychomotor or mental developmental index across time, when compared to healthy controls.

Wehby, 2012 finds that there is a significant difference ($p<0.05$) in inattention/ hyperactivity risk between children with oral clefts aged 2-5 years (4.4%) and aged 6-12 years (20.3%).

Wehby, 2014 supplements the conclusion of Hunt, 2005 that there were no consistent patterns of changes in educational achievements across school levels (elementary-, middle- and high school).

Grading the evidence

Regarding the psychosocial development, a GRADE or EBRO assessment of the evidence could not be provided, since the research question was not prognostic, diagnostic or intervention-based by nature. Hence, no evidence tables were provided for the studies included in this part of the literature summary.

Regarding the psychosocial interventions, a GRADE or EBRO assessment of the evidence could not be provided, since there was insufficient evidence to support any psychosocial intervention.

Conclusions

No assessment	Currently there is insufficient evidence to support any specific psychosocial intervention for individuals with cleft lip and/or palate and their parents. *Norman, 2014*

No assessment	The age of an individual with cleft lip and palate does not appear to influence the occurrence or severity of psychosocial problems. *Hunt, 2005*

Considerations

Diagnosis of psychosocial problems

Despite the fact that parents in the focus group indicated that they feel a need for psychosocial support for themselves and their child, no evidence was found in the literature for specific psychosocial problems in children with an isolated orofacial cleft, when the entire group was compared to children without clefts of the lip and palate (Hunt, 2005; Feragen, 2007; Hoek, 2009). Within the total group of children with an isolated orofacial cleft there are certainly children with psychosocial problems, but there seem to be no specific child characteristics (such as type of cleft, gender, age, dissatisfaction about appearance, self-image, cognitive development) that are directly related to the psychosocial wellbeing of the child. We know that within the group of children with an isolated orofacial cleft some children develop psychosocial problems, but it is not possible to predict in advance which children will be do so. (Hunt, 2007; Feragen, 2009; Feragen, 2014).

It should be noted here that the studies varied greatly in research methodology, size of the group, age of the study population, study resources used and the psychological constructs that were measured. More specifically, the article by Hunt, (2005) notes that there is a tendency in the literature towards describing “psychosocial functioning” in general. Possibly, specific problems that these children may experience (such as acceptance, behaviour, learning difficulties, self-image, satisfaction about appearance, bullying) are masked. Consequently, the results of the studies cannot be generalised well and cannot be compared properly.

The clinical experience shows that parents of a child with clefts of the lip and palate often experience different emotions and reactions, which can result in feeling

overwhelmed. Feelings of disappointment about the abnormality are often hard to handle. As parents you are supposed to be happy about your baby. You cannot reject your child or be angry with it (for example, because you feel aggrieved). In addition, the way family, friends and others react to the abnormality can vary greatly and can sometimes also be confusing.

The literature reveals that the consequences of having a child with a congenital defect such as clefts of the lip and palate are greater on a family when the child is young and there are additional medical problems (Baker et al, 2008). In addition, family variables can affect the psychosocial development of the child. This includes demographic variables (such as socio-economic status). The parenting skills (Murray et al, 2010), the level of parental stress (Endriga et al, 2003) and the mother-child interaction (Colett et al, 2009, Speltz et al, 2000) are listed as risk variables for the development of socio-economic problems, reading problems, language problems and lower cognitive capacity in children with clefts of the lip and palate.

There is no scientific research available regarding any increased risk of psychosocial problems due to the presence of clefts of the lip and palate in children. No child factors have therefore been identified, based on which you can predict which children are at increased risk of developing psychosocial problems. Several individual parent factors (such as acceptance, disappointment, grief) do turn out to contribute.

As children with clefts of the lip and palate are examined and treated in a multi-disciplinary cleft team and parents in the focus group have indicated that they would like to see integration of all diagnostic tests and treatment, it is desirable to routinely include the psychosocial diagnostic tests and treatment related to the orofacial cleft in the care of clefts of the lip and palate. A commonly used tool for early detection of psychosocial problems in children and/or parents is a screening at set times to check for aspects that could be affecting children with clefts of the lip and palate and/or parents of children with clefts of the lip and palate, such as socio-emotional development, fear of medical procedures, problems relating to appearance and acceptance. Specifically due to the fact that it is not possible to predict in advance whether child factors and family/parent factors have a protective or inhibitory effect on psychosocial development, the recommendation is to have a low threshold for screening of all children with clefts of the lip and palate. Considering the nature of the screening (for a complex mix of protective and inhibitory child and family/parent factors), this task is reserved for a behavioural expert with post-academic training (clinical psychologist or special education generalist). More specifically, the recommendation is to examine within this screening the following aspects of psychosocial development with regard to the child factors and the family/parent factors.

Diagnostic child factors

Wellbeing

The literature reveals that there are indications that the feeling of wellbeing of some children with clefts of the lip and palate is less than that of their peers. This can be expressed in emotional problems, behavioural problems and interaction problems, including problems in friendships and perceived bullying (Hunt, 2004). It is desirable to have a consultation with children on a regular basis and pay attention to their perceived wellbeing. As the literature reveals that parents can have a different perception of

wellbeing and any psychosocial problems than the child itself, it is important that the parents are also asked about this on a regular basis. This can take place from an early age. It is advisable to ask specifically whether the child is being bullied (Hunt, 2007), whether it has adequate social skills or has problems related to self-esteem (Feragen et al, 2009).

In addition to the consultation with the child and the parents, we recommend using a validated instrument to gain insight into any possible psychosocial problem that the child may experience. Both the international literature and the psychodiagnostic process use the SDQ (Strength and Difficulties Questionnaire, adapted for the Netherlands by Treffers et al, 2000) as a measuring instrument to determine psychosocial problems. The SDQ is an internationally validated screening list for children aged 3-17 years old. This questionnaire can be completed by the parents, teachers and the child (from age 11 years onwards). The list screens for emotional factors, behavioural problems, hyperactivity/attention deficit, problems with peers and prosocial behaviour. The results of this questionnaire can be used to determine whether further investigation is indicated. The questionnaire takes 5 to 10 minutes to complete. The advice from the guideline task force is to include this instrument as a standard part of the examination protocol for cleft teams, because (in addition to the consultation) this is a validated instrument used to make an inventory of psychosocial problems. When all cleft teams use the same instrument, it also becomes possible to use it for broad scientific research. Standard completion and analysis of this screening instrument in addition to the consultation will take about 10 minutes for the behavioural expert.

If the screening of the child and/or parents indicates that psychosocial problems that may be related to the orofacial cleft or medical treatment are present, further psychological examination within the cleft team is indicated. Concerning young children in particular, observation during playing can form an important part of this more extensive diagnostic testing (Murray et al, 2010).

Intelligence / cognition / learning

There is some evidence to suggest that some children with an isolated orofacial cleft can develop learning problems, in particular reading and language problems (Hoek et al, 2009; Roberts, 2012; Wehby, 2014). Despite the fact that international literature suggests that intensive diagnostic testing should be performed within the cleft teams, the guideline task force sees no need for this within the Dutch education system. The Dutch education system has sound diagnostic tests for learning problems. However, it is advisable to be informed about school performance during the consultation. In case of educational problems not tested in the regular education structure, further investigation is indicated. In case the multi-disciplinary cleft team has any doubts about the child's general development (for example, below average language comprehension) diagnostic investigation is indicated as well. These diagnostic tests can often take place within the regular education structures, except when a relationship between the education problems and the orofacial cleft is expected and the specific knowledge of the cleft team is required. For example, in children with clefts of the lip and palate and multiple congenital abnormalities. The literature demonstrates lower scores on development tests for this group (Swanenburg de Veye, 2003). For this reason, it is important to monitor the development of this group of children thoughtfully and schedule repeat examinations by the cleft teams.

Diagnostic family/parent factors

In addition to child factors, the literature also describes family/parent factors that need to be identified. The interaction between parents and child is an important factor. Some children with clefts of the lip and palate have an impaired parent-child interaction. These children are at increased risk of unfavourable development. (Hentges, 2011). Based partly on clinical experiences from parents from the focus group, the guideline task force deems it important to include factors such as parental stress, parenting skills and the acceptance of the cleft (including a possible mourning process of not having a "perfect" child) in the consultations. Clinical practice shows that these variables can affect the parenting and thereby the psychosocial development of children with clefts of the lip and palate.

With regard to the family/parent variables, the guideline task force recommends using a validated instrument for screening in addition to conversations. The Family Questionnaire (*Gezinsvragenlijst* or GVL, van der Ploeg & Scholte, 2008) is a suitable questionnaire for identifying family factors. The GVL is a questionnaire that provides insight into the quality of family and parenting conditions in children aged 4-18 years. The questionnaire can be completed by the parents or educators of the child. The list screens for responsiveness (parenting relationship), communication, organisation, partner relationship and social network. The questionnaire takes 30 minutes to complete. The advice from the guideline task force is to include this instrument as a standard part of the examination protocol for cleft teams, because (in addition to conversations) this is a validated instrument used to create an inventory of family factors. When all cleft teams use the same instrument, it also becomes possible to use it for scientific research. Standard completion and detailed interpretation of this screening instrument in addition to the consultation will take about 15 minutes for the behavioural expert.

If the screening reveals that there are signs of influencing family/parent factors, then further diagnostic testing by the cleft team is indicated. Within this diagnostic process, in addition to the request for assistance by the parents and child, the use of video recordings of the interaction is desirable, as is observation during playing in which the interaction between parent and child can also be observed (Collett and Speltz, 2006).

In summary, the advice to cleft teams is to screen the children with clefts of the lip and palate for both child factors and family/parent factors, by means of consultations and standardised instruments. In a consultation with parents and/or child, particular attention should be paid to problems associated with the orofacial cleft and its medical treatment. Based on the literature, no defined ages were found at which this screening should take place. However, several suggestions are provided, for example with regard to important transition moments. Based on the information from the literature, clinical experience and experiences of parents in the focus group, we recommend the following screening moments, during which the parents will sometimes be seen alone and sometimes with the child.

Basic diagnostic tests (screening) for psychosocial problems

First weeks after birth

Informant:	parents
Subjects:	all family factors
Form:	consultation
Between the ages of 2 and 3 years	
Informant:	parents and child
Subjects:	psychosocial child factors and family factors
Form:	consultation with parents and observation of child, in interaction with parents
*5 years**	
Informant:	parents
Subjects:	psychosocial child factors and family factors
Form:	consultation and completion of GVL and SDQ
*10 to 11 years***	
Informant:	parents and child
Subjects:	psychosocial child factors and family factors
Form:	consultation with parents, consultation with child and completion of GVL and SDQ, consultation with parents, consultation with child
17 years	
Informant:	child
Subjects:	child factors and discussion of possible genetic factors of the orofacial cleft
Form:	consultation

*** in the year before the child starts group 3 (first year of primary school)**
**** Group 7/8 (final years) of primary school**

These basic diagnostic tests for the detection of psychosocial problems take an average of 5 hours per child per treatment pathway and should be performed under the final responsibility of a behavioural expert with post-academic training. Any additional diagnostic tests that are required have not been included in this calculation.

Treatment of psychosocial problems
The literature provides advice about possible effective treatments or treatment goals. For children, the recommendations include starting social skills training if necessary (Collett and Speltz, 2006), cognitive behavioural therapy (Norman, 2014) or therapy to learn alternative coping strategies (Baker et al, 2008). For parents, the recommendations include possible treatment aimed at grief and acceptance, learning coping strategies (Endriga et al, 2003), discussing fears and concerns that the parents may have for their child and the future (Pelchat et al, 2004).

Based on clinical experience and recommendations from parents in the focus group, the guideline task force concluded that treatment of parents and child by specialised care providers is very desirable. The aforementioned treatment methods are performed in the Netherlands by therapists with varying backgrounds. Depending on the complexity of the psychosocial problems and the parents' request for help, this can take place within the cleft team (by a social worker, clinical psychologist or a special education generalist), or in the environment where the child lives, with possible supervision from the cleft team. In addition to treatment, contact with people who have experienced similar situations can be helpful. Therefore, it is desirable to inform patients at an early stage about the existing patient organisations (such as BOSK) and the options that they offer for online and offline contact with other parents and children.

If the diagnostic tests reveal that complex psychosocial problems exist, then treatment by - or under the final responsibility of - a behavioural expert with post-academic training is indicated. Simple psychosocial problems can be treated by a therapist with training at the higher professional (non-university) level.

Summary and conclusions

Based on the scientific literature, we cannot conclude with certainty which children with clefts of the lip and palate do have an increased risk of psychosocial problems (and what type of problems specifically); in addition, it has also not been proven whether psychosocial guidance would be helpful in this regard.

Due to a lack of scientific evidence, no unambiguous conclusion can be drawn about any increased risk of psychosocial problems due to the presence of clefts of the lip and palate in children. The scientific literature also does not provide enough information to make any statements regarding the effectiveness of psychosocial guidance on the psychosocial development of children with clefts of the lip and palate.

Despite the lack of thorough scientific research, the guideline task force has concluded - based on its own experience from clinical practice and the feedback from patients during the focus group meeting - that there is a need amongst parents for psychosocial guidance for both themselves and their child. The opinion of the guideline task force is that psychosocial guidance should form a standard part of good quality care for children with clefts of the lip and palate and that it is useful to screen parents and children for this. The opinion of the guideline task force is also that screening moments should take place at birth and at important transition moments in the life of a child with clefts of the lip and palate: at the age of two to three years (before starting school), 5 years (before start of the learning process), 10 to 11 years (before transition to secondary education), 17 years (before transition to tertiary education). During this contact, screening should be performed for child factors (wellbeing, possible learning problems and acceptance problems) and family/parent factors (acceptance problems, grief and parenting style). The guideline task force recommends that the same validated instrument should be used for this screening. Based on the results of the screening, the parents and child should be offered further diagnostic tests and treatment. In order to offer such screening, a cleft team must have access to a behavioural expert with post-academic training (clinical psychologist or special education generalist) and a social worker for less complex problems.

Recommendations

Screen the child with clefts of the lip and palate and the parents for psychosocial problems after birth, at the age of 2 to 3 years, 5 years, 10 to 11 years and 17 years.

During this contact, screening should be performed for child factors (wellbeing, possible learning problems, fear of medical procedures and acceptance problems) and family/parent factors (acceptance problems, grief and parenting style).

In addition to consultations, all cleft teams should use the same validated instrument (SDQ, GVL, conversation with parent and/or child).

Based on the results of the screening, offer the parents and child further diagnostic tests or treatment if necessary.

Appoint a behavioural expert with post-academic training (clinical psychologist or special education generalist) and a social worker for less complex problems in each cleft team for the diagnosis of psychosocial problems of the child and family and for the treatment of complex psychosocial problems.

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Chapter 12 Organisation of care in the Netherlands

Introduction

Since the 1960s, the care of patients with clefts of the lip and palate in the Netherlands has been provided in multi-disciplinary cleft teams based on British and Scandinavian examples. It was thought that the quality of care will improve as a result of a structural multi-disciplinary approach according to a set treatment protocol and work agreements wihin a team. Over the years, the number of cleft teams in the Netherlands has decreased from 23 (Prahl-Andersen, 1983) to 11 (NVSCA registration 1 January 2016). Since 1985, all Dutch teams have been member of the Dutch Association for Cleft Palate and Craniofacial Anomalies (NVSCA). This association aims to ensure optimal care for patients born with clefts of the lip and palate or other craniofacial anomalies within the Netherlands and the Flemish part of Belgium. In order to achieve this, the NVSCA has set up a registration for patients with clefts of the lip and palate and/or craniofacial anomalies. The NVSCA registration has been validated for clefts of the lip and palate, with and without additional congenital defects (Rozendaal, 2010; 2012a; 2012b) and generates important epidemiological data (Luijsterburg and Vermeij-Keers, 2011; Luijsterburg, 2014). More information is available online via www.schisis.nl.

The aim of this chapter is to establish criteria for good clinical practice for cleft teams in the Netherlands, including criteria for the multi-disciplinary composition of cleft teams, qualifications for team members and the responsibility of cleft teams regarding quality control and documentation of long-term outcomes. Where possible, these criteria are based on scientific data and takes into consideration the existing standards in the Netherlands and abroad.

National organisation of care

During the period 2000-2005, the board of the NVSCA actively aimed to improve the quality and consistency of care of patients with clefts of the lip and palate in the Netherlands by implementing so-called Special Interest Groups (SIGs). These are groups of healthcare providers with the same specialisation, who are active in the treatment of patients with clefts of the lip and palate and who meet in order to learn from each other, discuss their treatment methods and results, formulate quality requirements, etc. This initiative has resulted in the guideline task forces for speech therapy and orthodontics, but has so far not expanded to other disciplines.

In 2012, the NVSCA published a second edition of the strategic outline for the period 2012-2016 (www.schisis.nl/nvsca/leden/welkom). This memorandum discusses efforts to further improve the quality of care for patients born with clefts of the lip and palate and/or craniofacial anomalies. In the memorandum the NVSCA proposes to introduce a cycle of quality audits for the Dutch cleft teams together with a quality registration.

The memorandum of the NVSCA states that a minimum number of new, unoperated patients/(un)operated adopted children with clefts of the lip and palate must be treated per team per year in order to guarantee the quality of a team. In line with the recommendations by the Dutch Healthcare Inspection about working towards concentration of highly complex, but low frequency care in the Netherlands in general, the NVSCA recommends that each cleft team should treat at least 20 new, unoperated

patients/(un)operated adopted children with clefts of the lip and palate in order to guarantee the quality of care. The guideline task force agrees with this standpoint and therefore has not made any (deviating) recommendations in this guideline.

Regional and local organisation of care

The cleft teams in the Netherlands are expected to implement this guideline at a regional/local level. The guideline task force is of the opinion that a number of minimum accessory conditions must be met in order to guarantee the quality and consistency of care within a cleft team. Although the United States does not have organised care for patients with clefts of the lip and palate at a national level, the "American Cleft Palate-Craniofacial Association" (ACPA) has put a great deal of thought into the criteria that the care offered by cleft and craniofacial teams must meet. The recommendations made by the guideline task force in this chapter with regard to the various aspects of the organisation of care are partly based on the most recent edition of the ACPA Parameters for Evaluation and Treatment of Patients with Cleft Lip/Palate or Other Craniofacial Anomalies (2009), the ACPA Standards for Approval of Cleft Palate and Craniofacial Teams (revised version, June 2015) and - to a lesser extent - the information from the NHS standard contract for cleft lip and/or palate services (NHS, 2013). Information from the aforementioned sources was combined with data from the strategic outline of the NVSCA (2012) and the Guideline "Counselling after Prenatal Diagnosis of clefts of the lip and palate" (NVPC, 2011) (for the last two documents, refer to: www.schisis.nl).

Multi-disciplinary composition and functioning of a cleft team

During the invitational conference held with regard to this guideline, various parties indicated that they would like to see the guideline task force draft a number of requirements for both the composition of a cleft team and the tasks and responsibilities of the members of a cleft team. The guideline task force describes the - in their opinion – optimal composition of a cleft team below. The starting point here is that a cleft team with this composition should be able to offer the care described in the guideline at an optimum level. The guideline task force expects the Dutch cleft teams to examine their own composition critically and use this proposed team composition as a reference framework. It should be noted here that some tasks within a cleft team can be performed by various disciplines.

Optimum composition of a cleft team

For optimum prenatal and postnatal care of (future) parents of and children with clefts of the lip and palate, the guideline task force is of the opinion that a cleft team should have access to the professionals described below. Taking into consideration efficiency and cost management, it is not necessary for all cleft team members to be present at every consultation. This depends on the patient's age and stage in the treatment pathway. In order to guarantee the continuity of care and to act as each other's "sparring partner", it is vital that a number of disciplines should have <u>at least two specialists</u> - each with recent experience in the treatment of patients with clefts of the lip and palate - available per cleft team (refer below). Recommendations with regard to the consultation moments for the clinical geneticist, psychologist or NVO special education generalist and paediatric dentist have been included in the relevant chapters.

A cleft team should consist of:

At least two specialists from each of the following disciplines

- Ear, Nose and Throat specialist
- Speech therapist
- Oral and maxillofacial surgeon
- Orthodontist
- Plastic surgeon

At least one specialist from each of the following disciplines

- Clinical psychologist
- (Paediatric) dentist
- Social worker or nurse specialised in cleft consultations

The following healthcare professionals <u>with focus on orofacial clefts</u> should be available for consultations, preferably in the same healthcare facility:

- Anaesthesiologist with paediatric registration
- Audiologist
- Gynaecologist and/or sonographer or ultrasound technician
- Clinical Geneticist
- Paediatrician
- (Paediatric) neurologist
- (Paediatric) psychiatrist
- (Paediatric) radiologist
- Maxillofacial prosthetist
- Oral hygienist
- Ophthalmologist
- Nurse

Competencies of team members

The quality of the care provided is of the utmost importance for patients, parents and professionals. It is therefore essential that all members of the team are skilled in the care of patients with clefts of the lip and palate. However, this chapter does not discuss the "scope" of the activities of the individual (para)medical specialist within the team. The requirements regarding training and experience for (medical) specialists within the cleft team are determined by the respective scientific associations and their registration committees. These requirements are regularly updated. Each cleft team must therefore ensure that the team members not only have the necessary and up-to-date qualifications and registrations within their countries, but also that they are members of the NVSCA or similar organisation (if existant in the country where the cleft team is located) and actively participate in (inter)national SIGs related to their discipline. This applies in particular to the first two of the aforementioned groups: Ear, Nose and Throat specialist, speech therapist, oral and maxillofacial surgeon, orthodontist, plastic surgeon, clinical psychologist or NVO special education generalist, (paediatric) dentist and social worker or nurse specialised in cleft consultations.

In addition, team members must have regular and recent experience in the treatment of patients with clefts of the lip and palate. This last point was mentioned specifically by patients and parents during the focus group meeting that was held with regard to this

guideline. Patients and parents deem the experience of team members – particularly the surgeons – more important than a minimum number of treated patients per year. Experience is defined as acquiring knowledge via fellowships, attending conferences, watching/shadowing colleagues etc. in the relevant area of expertise in cleft centres in the Netherlands or elsewhere in the world.

Responsibilities and functioning of the team

The main task of the multi-disciplinary cleft team is to deliver integrated care to the individual patient, to guarantee the quality of the treatment and to provide longitudinal follow-up. In general, it can be stated that every patient that is seen by the team is expected to receive an effective and multi-disciplinary treatment plan aimed at creating the conditions that will ideally allow the child with clefts of the lip and palate to grow up to become an adult without cleft stigmata. This is defined as a person with a face in which the cleft is hardly noticeable, with good hearing and speech, with functional and aesthetically acceptable dentition and a harmonious social-psychological development in combination with the efficient use of time and resources, both for the patient and his/her parents and the care facility.

In order to achieve the aforementioned goal, cleft teams must adhere to the following specific starting points (in random order):

Team functioning

- The team has a coordinator, who facilitates the proper functioning and efficiency of the team and helps patients and families in the coordination of their care and helps them understand and implement the treatment plans.
- The team conducts regular (multi-disciplinary) consultations (at least once a month) in the physical presence of the patient (and parents).
- The team offers prenatal care and counselling, as set out in the Guideline "Counselling after Prenatal Diagnosis of clefts of the lip and palate" available at the website www.richtlijnendatabase.nl (in Dutch).
- The team is responsible for the development and maintenance of an evidence-based treatment protocol and accompanying care pathway for children with clefts of the lip and palate for the centre in question, from the prenatal stage to the end of the treatment at age 18-22, jointly based on this guideline and the Dutch Guideline "Counselling after Prenatal Diagnosis of clefts of the lip and palate".
- The team maintains systematic contacts with the primary care professionals (such as GP and dentist), not only of the individual patient, but also with the primary care professionals from the catchment area in general. If desired/indicated, the team will invite primary care professionals to attend team meetings.
- The team keeps a record of each patient, including a history, diagnosis, examinations, treatment plans, surgical reports and supporting documentation such as medical photographs, X-rays, dental models, speech recordings, audiograms.
- The team ensures that other professional healthcare providers, healthcare insurance companies, teaching staff and the general public are aware of and have an understanding of the concerns and needs of patients who are born with clefts of the lip and palate and their family.

- The team has regular contacts with the relevant patients' and parents' association and vice versa.

Communication with and partnership of the patients and those around them

- The team specifically involves the patient / parents as a partner in the treatment process and the decision-making process surrounding the treatment.
- The team has a fixed point of contact, or has appointed one or more team members to establish the initial contact with the patient and parents and to speak to other healthcare providers/referring physicians.
- The team is responsible for adequate communication about the contents of the evidence-based treatment protocol and accompanying care pathway to the patient and those around him.
- The team communicates to the patient, parents and referring specialists about which specialisms within the team are responsible for certain (surgical) procedures during the treatment pathway.
- Guided by the evidence-based treatment protocol, the team is responsible for drafting a longitudinal treatment plan for each patient, individualised according to growth and development, treatment outcomes, burden of illness for the patient and those around him and progress in medical-technical possibilities.
- Deviations from the treatment protocol for an individual patient must be described and clarified in the patient file and explained to the patient.
- In consultation with the patient and those around him, all decisions regarding the treatment are weighed against the expected outcomes/results and related factors, such as growth of the face, hearing, speech, dentition and psychosocial consequences / impact for the patient and those around him.
- The team/the care facility offers the option to view the electronic patient file and/or otherwise communicates the findings, the treatment plan/treatment recommendation and other recommendations - including up-to-date information about who has the end responsibility for a particular (part) of the treatment - with every patient and his/her family in written or digital form, as well as in face-to-face contact with the patient.
- The team provides information about the (results of) the ongoing treatment to the patient and those around him and ensures that they understand this information.
- The team ensures that both parents are well-informed, with team members taking into consideration that individual parents may have different concerns.
- The team shows understanding and flexibility in providing care to patients and their families who do not speak Dutch, are from a different culture or who have a different ethnic background. Where necessary, the coordinator will arrange for adequate interpretation of both the verbal and written communication.
- The team will assist the patient and family in switching to another cleft team if they move to a different region or country.
- The team offers coaching/guidance to adolescents and their families with regard to the completion of (active) treatment and provides information about services that are available to adults born with clefts of the lip and palate.
- A cleft team must be able to provide the required care from birth through to the age at which the patient is fully grown, in such a manner that the entire treatment pathway can be completed, even if the patient is older than 18 years.

- Upon completion of the treatment for clefts of the lip and palate (between the ages of 18 and 22 years), the team will communicate to the patient where he or she can seek help in future for any late problems or consequences of his or her cleft. Every team should state clearly whether the team has a central point of contact (cleft team coordinator) for adult patients. If this is not the case, then the cleft team should indicate that care is provided via the individual medical specialties. The guideline task force would prefer to see the cleft teams remain accessible for the late consequences of clefts of the lip and palate in adults.
- The team aims to ensure that adults born with clefts of the lip and palate should have access to the latest developments in diagnosis and treatment. This also implies that contact details of (former) patients should be kept up-to-date.

Facilities for the cleft team

- The team has an administrative location with a secretarial office and/or coordinator, including clear contact details (telephone number and website), which is accessible 24 hours per day.
- The team has a physical location in which it can hold team consultations and individual consultations with the patient/parents and for the storage of non-digital patient data.
- The team/the facility has adequate diagnostic facilities, including at least the option to take casts from the initial unoperated cleft, extra-oral and intra-oral photography, 3D photogrammetry, nasal endoscopy, the ability to perform computed nasometry, the ability to produce audiograms, the ability to create audio and video recordings of the speech, (three-dimensional) X-ray diagnostics, including the option to perform pharyngograms and prenatal (ultrasound) diagnostics.
- The team/the facility has adequate surgical facilities and accompanying peri-operative care.
- The team is located in a hospital with a paediatric department and preferably in a hospital with a Paediatric Centre, so that the surgical treatment of children of all ages with clefts of the lip and palate is possible.
- The team/the facility has access to at least one anaesthesiologist (preferably more) who meets the requirements for surgeries involving children younger than 2 years of age, as described in the Dutch guideline on anaesthesiology for children (updated in 2018).

Quality assurance

- The team participates in the central (anonymous) Dutch registration by the NVSCA for unoperated new patients and new (un)operated adopted children born with clefts of the lip and palate (or similar registrations in other countries).
- The team treats at least 20 new unoperated patients per year, in accordance with the recommendation by the NVSCA and to be assessed over a period of 5 years, as already mentioned above under the heading “competencies”.
- The team systematically evaluates the quality of the patient care provided by the team, with participation of all team members (internal audit).
- The team/the facility conducts periodic research into the satisfaction of patients and parents about the treatment by the team.

- The team uses external audits by colleagues to evaluate the quality of care provided by the team and participates in the cycle of quality visitations of cleft teams in the Netherlands, as organised by the NVSCA.
- The team organises meetings - held at least 2x per year – to register and discuss complications regarding the treatment of clefts of the lip and palate in a systematic way, which should be attented by all team members.
- The team drafts an annual report, that is sent to the other cleft teams in NL and to the NVSCA. The annual report at least includes a list of team members with their specialisation, the number of new unoperated patients and patients that have already been treated elsewhere that were registered for treatment, the number of surgeries/procedures that were performed, the treatment protocol used by the team, a summary of the complication registration, the results of patient-related outcomes and finally, the outcomes of scientific research and presentations by members of the cleft team about cleft-related topics.

Ongoing training and refresher courses

- The team ensures that all members of the cleft team are members of the NVSCA (or similar oragnisation in other countries).
- The team stimulates a pro-active approach by all team members regarding ongoing training and refresher courses in the field of orofacial clefts and stimulates and facilitates participation by team members in such training. The guideline task force is of the opinion that members of a cleft team should follow at least 8 hours of (refresher) training per year, which are specifically related to care for patients with clefts of the lip and palate.
- The team aims to offer early diagnosis of clefts of the lip and palate in (newborn) children by ensuring adequate training in the recognition of children with clefts of the lip and palate for hospital staff, midwives and neonatologists involved, but also for primary care practitioners and child health centres.
- The team aims to offer adequate training and information to hospital staff and primary care practitioners in the critical aspects of the primary care and treatment of a (newborn) child with clefts of the lip and palate , including feeding.

Quality measurement of orofacial cleft care: documentation and data registration

There is (as yet) no uniform or validated method to measure the quality of care for patients with clefts of the lip and palate and the outcomes thereof. By the year 2000, the Eurocleft project had reached a consensus in Europe about a standard documentation set for orofacial clefts (Shaw, 2001). A number of teams in the Netherlands largely follow this schedule. Recently, these recommendations were also adopted in the USA and Canada upon completion of the Americleft project (ACPA, 2013). It was noted here that this schedule will be modified in the future. The guideline task force has therefore opted for a pragmatic approach and recommends that the Eurocleft documentation schedule (refer to Shaw, 2001 for this) should be followed for the time being, whilst awaiting further developments regarding PROMs.

Recently, the International Consortium for Health Outcome Measurement (ICHOM) developed new outcome measures for orofacial clefts.[5] The Dutch translation of one of the patient questionnaires (the Cleft Q - patient) is currently being validated. These types of instruments will make it possible, at least in theory, to compare the outcomes with other centres anywhere else in the world.
Considering these developments, it is currently impossible for the guideline task force to provide a detailed guideline for minimal data registration. In anticipation of a structural quality registration, the guideline task force recommends that each team should use a uniform approach to documenting certain information, both upon registration of the patient with the team and also at set time points during and at the end of the treatment (age 22 years). The data collected at registration should be stored for a minimum of 22 years and should be available during the final evaluation. For the time being, the guideline task force therefore recommends use of the Eurocleft documentation schedule.

The guideline task force is of the opinion that it is desirable for cleft teams to participate in ICHOM or similar systematic approaches for PROMs and that participation in PROMs should form a part of the checklist for the future quality visitation to be performed by the NVSCA.

Recent developments in the centralisation of orofacial cleft care in the United Kingdom

The treatment of a child with clefts of the lip and palate is complex and takes a long time. Considering the large variability in the types of clefts of the lip and palate - i.e. sub-phenotypes - the treatment is never routine and never standard. Furthermore, the number of children born in the Netherlands with this abnormality - including adopted children - is relatively low (n=350-400 per year in a population of 17 million). Twenty years ago, the United Kingdom (UK) realised - based on the results from the EUROCLEFT study and later the CSAG study (Clinical Standards Advisory Group) - that decentralised and low-frequency care was associated with sub-optimal treatment results (Shaw et al, 1992; Bearn et al, 2001). This resulted in a strong concentration of care in England, with the number of centres being reduced from 57 to 11 in a population of 64 million (Persson et al, 2015).

Fifteen years after this centralisation, the results of treatment of clefts of the lip and palate were studied once more in the Cleft Care UK study (CCUK), in a comparable set-up to the previous CSAG study (Persson et al, 2015). The results of the CCUK study were published recently (Ness et al, 2015). In summary, the results reveal that orofacial cleft treatment has changed over the past 15 years. There is reduced variability in the surgical techniques that are used, hearing aids are used more frequently and tympanostomy tubes are inserted less frequently (Smallridge et al, 2015). The centralised care setting that is currently in place in the UK has resulted in a significant improvement in the relation between maxilla and mandibula (Al-Ghatam et al, 2015), the speech (Sell et al, 2015) and also – albeit less convincing – the aesthetic result (Al-Ghatam et al, 2015),

[5] International Consortium for Health Outcome Measurement. Cleft lip & palate data collection guide. Version 3.1 Revised: October 16th, 2015.

whilst the prevalence of caries and hearing loss remains unchanged (Smallridge et al, 2015). In the CCUK study, fewer parents indicated that their child suffers from low self-esteem compared to the previous CSAG study. However, the satisfaction of the parents about the treatment remains persistently high (Waylen et al, 2015). These results demonstrate that centralisation of care does indeed appear to contribute to an improved quality of orofacial cleft care in the United Kingdom.

Quality audits

The guideline task force is of the opinion that the system of quality audits and quality registration envisaged by the NVSCA could contribute to further improvement of the quality and consistency of the care provided by cleft teams in the Netherlands. This chapter can serve as a potential guideline for such quality audits.

The guideline task force advises the NVSCA to follow the American system for "approval" of teams - as formulated by ACPA - during a visitation (ACPA Standards for Approval of Cleft Palate and Craniofacial Teams, 2015 edition). The ACPA defines 6 components that are deemed essential for the quality of care offered by the team to patients with clefts of the lip and palate, regardless of the type of cleft or craniofacial abnormality. These components can be tested during a visitation. This concerns the following items:

1. Composition of the team
2. Team management and responsibilities
3. Communication with patient, family and referring specialists
4. Capabilities for treating patients from ethnic minorities and adoption
5. Ensuring psychosocial care for patients and parents
6. Evaluation and documentation of outcomes/results of the treatment

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Chapter 13 Dentistry for patients with clefts of the lip and palate

Module: Dentistry

Clinical question
What is the role of the dentist with an affinity for paediatric dentistry in the cleft team and the general dentist in the dental care of children with clefts of the lip and palate?

Introduction
Healthy teeth are important, because they have an impact on general health. Various studies have demonstrated that bacterial infections in the mouth are linked to diseases such as diabetes and cardiovascular disease (Garci, 2000; Li, 2000; Otomo-Corgel, 2012). Caries in children has even been associated with growth retardation (Acs, 1992, Acs, 1998; Elise, 1990; Sheiham, 2006), although there is no irrefutable evidence of this relationship (van Gemert-Schriks, 2011).

However, health is not merely expressed in physical parameters, it is also a sense of wellbeing. The latter is best described as the quality of life and in this regard the literature does report very clearly: the quality of life of children is negatively affected by oral diseases such as caries and gingivitis. Pain, sleepless nights, school absenteeism and poor intake of food have been mentioned (Low, 1999; Versloot, 2006).

Therefore, good oral health is deemed important for everyone and in the case of oral diseases prevention remains better than cure.

As described in the guideline “Oral Care for Youngsters”, early diagnosis and prevention are considered the core elements of oral care today. Of course the dentist and the dental hygienist play a vital role in this. It is not really that prevention needs to improve or increase, it just needs to be offered in a different manner. Education and preventative measures need to be offered in a “tailor-made” fashion (Ekstrand, 2005; Evans, 2009; Hausen, 2007). The oral care provider will firstly need to determine the individual (caries) risk of the patient, before selecting the correct approach to prevent and/or treat caries (or other oral diseases).

Children with clefts of the lip and palate may have an increased risk of developing caries and gum disease. However, the pathogenesis of both oral diseases does not differ from that of children without clefts of the lip and palate. Good oral hygiene and a sensible eating pattern/diet are undeniably very important for children in general and children with clefts of the lip and palate in particular.

This chapter will discuss what the frameworks - both organisational and content-wise - should look like for dental care of children with clefts of the lip and palate in the Netherlands.

Searching and selecting
A systematic literature search was not performed for this chapter, because the query about the organisation of dental care for children with clefts of the lip and palate cannot be summarised in a search question. Therefore, the guideline task force opted for a consensus method.

Summary of the literature
N/A.

Conclusions
Not applicable.

Considerations
Children with clefts of the lip and palate often have poorer oral hygiene, more gingivitis (Perdikogiammi, 2009; Parapanisiou, 2009) and more caries (Hewson, 2001; Cheng, 2007; Wells, 2013; Antonarakis, 2013) than children without clefts of the lip and palate. The pathogenesis of the aforementioned oral diseases is the same for children with and without clefts of the lip and palate. However, it has been reported that children with clefts of the lip and palate are more likely to suffer from dental anomalies, such as agenesis and hypodontia, impactions, abnormal shape of dental elements and enamel hypoplasias (Costa, 2012; Cheng, 2007; Burke and Shaw, 1992; Bacher,1991; Jamalian, 2015; Bartzela, 2013). Abnormal occlusion and articulation can also be present. In addition to these congenital abnormalities, the increased risk can also be explained by the fact that children with clefts of the lip and palate often have different eating habits and/or that children and their parents/carers experience specific problems when caring for the teeth: fear of brushing the area around the orofacial cleft, hard to reach surfaces due to abnormal shape/position of teeth, practical problems with swallowing, acceptance problems, etc. The recommendation is that parents and children should be given more adequate information and guidance about oral hygiene and eating habits (Wells, 2013; Antonarakis, 2013). The recently published results of the Cleft Care UK study (CCUK) reveal an average DMFT[6] of 2.3, with 48% of the children being free of caries and 44.7% with untreated caries. The oral hygiene was generally good and 96% of the children were registered with a dentist (Smallridge, 2015). However, the literature is not conclusive on this point. Just as many articles described finding no differences in oral health between children with and without clefts of the lip and palate (Wong, 1998; Lucas, 2000; Lages, 2004; Hasslöf, 2007).

The literature repeatedly states that dental care is vitally important for children with a cleft lip, alveolar arch and/or palate (Madahar, 2013; Sandler, 2014). However, there is little to no relevant literature about how dental care for children with clefts of the lip and palate should be organised. A lot has been written about the increased risk that

[6] DMFT: Decayed, Missing, Filled, Tooth, deciduous teeth. The sum of the elements affected by caries lesions in the deciduous teeth is expressed as the DMFT index. The number of deciduous elements (tooth, t) with a cavity (decayed, d), with one or more fillings (filled, f) and deciduous elements that have been lost to caries (missing, m) are added together.

children with clefts of the lip and palate have of developing caries and/or gingivitis (Antonarakis, 2013; Cheng, 2007; Dalhof, 1989; Hewson, 2001; Parapanisiou, 2009; Perdikogiammi, 2009; Sundell, 2015; Wells, 2013). The abnormal eruption order, tooth position and tooth shape promote the colonisation by facultative pathogenic micro-organisms in the oral cavity and make maintaining good oral hygiene a challenge.

The oral care provider must assume responsibility for this and will need to take into consideration previously mentioned factors when providing education and instruction. The education will need to be offered in a sufficiently individualised ("tailor-made") manner in order to be effective in the prevention of oral diseases (Cheng, 2007).

Another point of attention in the dental care of children with clefts of the lip and palate is developing a good bond of trust between the oral care provider and the children and their parents/carers. Children with clefts of the lip and palate receive a lot of medical attention and interventions in the oral region from an early age. This can result in an increased risk of developing a medically-related fear, including fear of the dentist or the dental setting. Frequent, relatively low-stimulus exposure may be effective at preventing or reducing this fear in children (Waaijen, 2001).

In theory, every general dentist should be able to provide adequate dental care (both preventative and curative) for children with clefts of the lip and palate. However, in the Netherlands, children are usually only seen by the general dentist from the age of about 2 years. Often even later, around the 4th or 5th year of life. This is too late to achieve any real preventative effect of primary education and information. An early dental consultation is therefore essential for children with an increased risk. However, not all oral care practices and/or oral care practitioners are geared to treating such young children. Furthermore, the current reimbursement system does not offer a lot of room to cover the costs of these purely preventative/informative consultations.

Part of the oral care for children with clefts of the lip and palate should preferably be performed within the framework of the cleft team. This primarily involves the very first consultation, an estimate of the risk profile, the setting of the primary diagnosis and the offering of primary preventative education and information and arranging follow-up if necessary. Taking into consideration the specific health burden of patients with clefts of the lip and palate, it is desirable to have this preventative care performed by a dentist with a specific affinity for this area of dentistry.

The guideline task force therefore proposes including a preferably specialised dentist - a so-called paediatric dentist - in the cleft team. This is a dentist who has completed a post-initial master´s degree programme in paediatric dentistry. A dentist without this certified specialisation, but with the necessary affinity with children, could also fulfil this task.

The dentist in the cleft team can then perform the primary diagnosis, perform a risk assessment and create a short-term and long-term oral care plan. The latter will of course take place in consultation/agreement with the other disciplines in the cleft team and in consultation with the general dentist, so that treatments are aligned properly and treatment choices can be made in consultation. An initial consultation with the dentist from the cleft team should preferably take place around the time that the first

deciduous elements erupt (six to twelve months). This consultation is primarily informative in nature.

In consultation with the parents/carers and - if applicable - the child, the practical implementation of the oral care plan can take place in the practice of the general dentist or in the practice of the paediatric dentist of the cleft team. If the patient does not have a general dentist, then the dentist or orthodontist from the cleft team can mediate in the process of finding a suitable general dentist. The dentist in the cleft team therefore plays a type of "directing role" in the implementation of the individual oral care plan that has been drafted for the patient in question. The dentist from the cleft team should preferably see the patient at certain set times. Furthermore, the dentist from the cleft team will need to be available at all times for consultations from patients and general dentists to answer questions about oral health, tooth development, specific dental treatments, calamities or other matters.

The division of roles between the dentist and orthodontist of the cleft team and the general dentist must be clear to all involved in order to guarantee good dental monitoring of the child with clefts of the lip and palate. The general dentist will always be informed by the cleft team about the progress of the treatment in general and the oral care plan in particular. Conversely, a general dentist must contact the cleft team when treating a child with clefts of the lip and palate in his practice and must consult with the cleft team when this is deemed necessary.

Early diagnosis and prevention form the cornerstones of dental care in children with clefts of the lip and palate, as described in the introduction. Children with clefts of the lip and palate and their parents/carers will require "tailor-made" guidance from the cleft team in collaboration with a dentist, oral hygienist and possibly a prevention assistant. Visits to the general dentist can be spaced six months apart, but may need to be scheduled more frequently if indicated for individual patients. Based on Eurocleft, the guideline task force recommends imaging to take place form the age of 5 or 6 years.

Here we would like to refer to the guideline "Oral Care for Youngsters".

The primary care dentist is advised to contact the cleft team when treating a child with clefts of the lip and palate in his practice and must offer opportunities for consultation with the cleft team when this is deemed necessary. Children with clefts of the lip and palate have an increased risk of developing caries and gum disease.

Recommendations

For the cleft team

Include a (paediatric) dentist with an affinity for paediatric dentistry in the cleft team.

An initial consultation with the dentist from the cleft team should take place as soon as the first deciduous elements have erupted (six to twelve months).

Within the cleft team, check the teeth of children with clefts of the lip and palate at the age of 5 years, including the use of X-ray imaging. This should take place in addition to the periodic monitoring by the general dentist.

Inform the primary care dentist about the treatment pathway implemented by the cleft team and discuss who will provide the dental care.

For the general dentist

Contact the cleft team when treating a child with clefts of the lip and palate in your practice and offer opportunities for consultation with the cleft team when you deem this necessary.

Check the teeth of children with clefts of the lip and palate at least every 6 months.

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Appendix 1 Implementation of the guideline and indicators

Implementation plan

This plan was drafted to promote the implementation of the guideline "Treatment of Patients with clefts of the lip and palate". In the process of drafting this plan, an inventory was created of the recommendations for which a significant change to the current healthcare practice would be required.

Method

The guideline task force evaluated the recommendations based on the following points:

- by when the recommendation should be implemented everywhere;
- the expected impact of implementation of the recommendation on the healthcare costs;
- accessory conditions for implementation of the recommendation;
- possible barriers that could hamper implementation of the recommendation;
- possible actions that could promote the implementation of the recommendation;
- party responsible for the actions that need to be undertaken.

The aforementioned points were considered for each recommendation. However, it is impossible to answer each point for each recommendation. It is possible to distinguish between "strongly formulated recommendations" and "weakly formulated recommendations". In the first case, the guideline task force makes a clear statement about something that definitely should or definitely should not be done. In the second case, the recommendation is less certain (for example "Consider ...") and therefore leaves more room for alternative options. In general, the aforementioned points are worked out in more detail for the "strongly formulated recommendations" than for the "weakly formulated recommendations".

Implementation deadlines

"Strongly formulated recommendations" need to be implemented as soon as possible. For most of the "strongly formulated recommendations" this means that they need to be implemented immediately during the next year and that everyone should comply with these recommendations within one year after the authorisation date. Many recommendations already form part of the current practice and therefore should pose few implementation problems, if any.

However, an implementation deadline of 2 years should be maintained for the following recommendations, which means that everyone should comply with these recommendations by the end of 2018. These recommendations relate to the referral of patients with clefts of the lip and palate to the Medical Genetics department of a University Medical Centre and recommendations for which some teams/institutions will need to appoint new professionals within their team, as may be the case for the recommendations regarding psychosocial support and dentistry.

Patients with a cleft lip (with or without a cleft alveolar arch), a cleft lip-alveolar arch and

palate or a cleft palateshould preferably be referred to the Medical Genetics department of a University Medical Centre before the first surgery.

Screen the child with clefts of the lip and palate and his/her parents for psychosocial problems: after birth, at the age of 2-3 years, 5 years, 10-11 years and 17 years.

Within the cleft team, appoint a behavioural expert with post-graduate training (clinical psychologist or special education generalist and a social worker, for the less complex problems) for the diagnosis of psychosocial problems of the child and family and for the treatment of complex psychosocial problems.

Include a (paediatric) dentist in the cleft team, specialised in paediatric dentistry.

The implementation of PROMs should be viewed as a long-term project. Investigation into the validity of previously developed PROMs for orofacial cleft only started recently and cannot be used as a widely applicable instrument yet. The guideline task force is definitely in favour of the validation and implementation of PROMs, but it is not realistic to create a tight schedule for the implementation at this stage. The guideline task force is of the opinion that PROMs for orofacial cleft need to be implemented gradually over the next 5 years, so that - with revision of the current guideline in 5 years - PROMs can be included as a routine recommendation in the revised guideline.
As described in the chapter “Organisation of care”, the guideline task force is in favour of setting up a quality visitation cycle of the cleft teams, for which the NVSCA has already taken the lead. The guideline task force recommends that all teams in the Netherlands should have been visited once by the time that this guideline is revised in 5 years. Practically, this equates to approximately 2 visits per year for the NVSCA over the next 5 years, which the guideline task force deems feasible.

Indicators
Indicators are measurable elements of healthcare that give an indication about the degree of quality of the care provided. An indicator acts as a signal: it is not a direct measure of quality, but points to a certain aspect of performance and can form an indication to perform further investigation. A useful way of categorising indicators is by dividing them into structural, process and outcome indicators.
Structural indicators provide information about the (organisational) accessory conditions within which the care is provided. An example of a structural indicator is “The presence of a stroke unit”. Process indicators provide information about the procedures that need to be performed within a care process in order to deliver quality. The characteristic of process indicators is that they can be influenced directly: they measure how (often) something is done. An example of a process indicator is “The percentage of patients with diabetes that undergoes an ophthalmological examination annually”. Outcome indicators provide information about the outcomes of care processes measured at patient level. Outcome indicators are dependent on many factors and are therefore often hard to trace back to direct patient care. An example of an outcome indicator is “The percentage of patients with severe pain 36 hours after a surgical procedure”.

Indicators can provide important information within a department, institution or association about (the outcomes of) healthcare processes or about - for example -

customer satisfaction (internal use of indicators). Whilst developing the draft guideline, the guideline task force also considered the development of internal quality indicators in order to monitor and improve the implementation of the guideline in practice. More information about the method for indicator development can be obtained from the Knowledge Institute of Medical Specialists.

However, the guideline task force decided not to develop new indicators with the current guideline. The guideline task force recommends that the involved scientific associations should develop outcome indicators several years from now, once the quality registration by the NVSCA and PROMs — based on, for example, ICHOM — are fully operational. In order to achieve this, the cleft teams should first be given the time to work towards a uniform method, as described in the chapter “Organisation of care and the implementation of PROMs”.

Appendix 2 Knowledge gaps

During the development of the Guideline on Treatment of Patients with clefts of the lip and palate, we searched systematically for research findings that could be useful in answering the clinical questions. Although a part (or sub-section) of the clinical questions were answered using the results from these search actions, many were not. The use of evidence-based guideline development methods made it clear to us that there are still gaps in the available knowledge in the field of orofacial clefts. This is due in part to the fact that the studies included too few patients and in part to the fact that different sub-phenotypes of orofacial cleft were included in the study to obtain sufficient power. Unfortunately, both of these factors result in a lack of evidence. The guideline task force is therefore of the opinion that (further) study is desirable, in order to provide a clearer answer in future to questions from the practical setting. For this reason, the guideline task force has marked the most important knowledge gaps and has indicated per chapter which areas further research should focus on.

Genetic diagnostics

- Knowledge gap:
  - absence of an optimum strategy for genetic diagnosis of orofacial cleft.
- Research question:
  - what is the optimum strategy for genetic diagnosis of children with a cleft (lip, alveolar arch and) palate?

Feeding

- Knowledge gap:
  - the absence of research into the best method of feeding babies with clefts of the lip and palate.
- Research question:
  - What is the best way to administer food immediately after birth and immediately after a procedure in children with a cleft (lip, alveolar arch and) palate?

Lip and palate closure in patients with clefts of the lip and palate

- Knowledge gap:
  - there is uncertainty about the best moment for closure of the cleft lip and cleft alveolar arch respectively in children with a cleft (lip, alveolar arch and) palate.
  - there is uncertainty about the best surgical technique for closure of the cleft lip and cleft alveolar arch respectively in children with a cleft (lip, alveolar arch and) palate.
- Research question:
  - what is the best moment for closure of the cleft lip and cleft alveolar arch respectively in children with a cleft (lip, alveolar arch and) palate?
  - what is the best surgical technique for closure of the cleft lip and cleft alveolar arch respectively in children with a cleft (lip, alveolar arch and) palate?

Hearing problems in patients with clefts of the lip and palate

- Knowledge gap:
    - there is uncertainty about the (un)favourable effects of early insertion of tympanostomy tubes specifically in children with clefts of the lip and palate.
- Research question:
    - what are the (un)favourable effects of early insertion of tympanostomy tubes compared to a wait-and-see approach in children with a cleft (lip, alveolar arch and) palate or alternative forms of treatment?

Hypernasality in patients with clefts of the lip and palate

- Knowledge gap:
    - there is uncertainty about the best diagnostic strategy for determining and analysing velopharyngeal insufficiency (VPI) in children with a cleft (lip, alveolar arch and) palate.
    - there is uncertainty about the best surgical technique for treatment of velopharyngeal insufficiency (VPI) in children with a cleft (lip, alveolar arch and) palate.
- Research question:
    - what is the best diagnostic strategy for determining and analysing velopharyngeal insufficiency (VPI) in children with a cleft (lip, alveolar arch and) palate?
    - what is the best surgical technique for the treatment of velopharyngeal insufficiency (VPI) in children with a cleft (lip, alveolar arch and) palate?

Bone grafting procedure in patients with clefts of the lip and palate

- Knowledge gap:
    - there is uncertainty about the best moment to perform a bone grafting procedure in children with a cleft lip and alveolar arch or with a cleft lip, alveolar arch and palate.
    - there is uncertainty about the type of bone transplant in the bone grafting procedure in a patient with a cleft lip and alveolar arch (with or without a cleft palate).
- Research question:
    - what is the best moment to perform a bone grafting procedure in children with a cleft lip and alveolar arch (with or without a cleft palate)?
    - what is the best surgical technique for closure of the cleft lip and cleft alveolar arch in children with a cleft lip and alveolar arch or a cleft lip, alveolar arch and palate?

Orthodontic treatment

- Knowledge gaps:
    - there is uncertainty about when ventral traction of the maxilla should be applied in children with a cleft (lip, alveolar arch and) palate, due to an absence of long-term results in which patients were monitored until facial growth was complete.
    - there is uncertainty about which retention equipment is most effective in the long term in children with a cleft (lip, alveolar arch and) palate for

retaining the tooth position that has been achieved and the arch form of the maxilla.

- Research question:
    - is there a preference for a certain technique of ventral traction to the maxilla?
    - which retention device is the most effective in the long term for children with a cleft (lip, alveolar arch and) palate with regard to retention of the tooth position that has been achieved and the arch form of the maxilla?

Rhinoplasty

- Knowledge gap:
    - there is uncertainty about which treatment strategy for rhinoplasty achieves the best (final) result in children with a cleft lip, alveolar arch and palate.
- Research question:
    - what are the long-term results of a rhinoplasty (primary and secondary) performed at age < 18 years compared to a rhinoplasty (primary and secondary) performed at age > 18 years in children with a cleft (lip, alveolar arch and) palate?

Psychosocial guidance for patients with clefts of the lip and palate

- Knowledge gap:
    - there is uncertainty about the moments during the development of the child at which psychosocial guidance can best take place.
- Research question:
    - what is the effectiveness of psychosocial guidance as part of a multi-disciplinary team approach for children with clefts of the lip and palate and their parents?

Appendix 3 Report on invitational conference

Date: Monday 14 October 2013
Time: 18:00 - 21:00
Location: Domus Medica in Utrecht

Present: C. Breugum (UMC Utrecht); H. de Veye (UMC Utrecht); M. van den Boogaard (UMC Utrecht); D. Bitterman (UMC Utrecht); M.Muradin (UMC Utrecht); M. Braam (Haga Hospital); C. Moues-Vink (Medical Centre Leeuwarden); D. van Dam (Medical Centre Leeuwarden); K. Heijdenrijk (Medical Centre Leeuwarden); J. Dijkstra-Putman (Medical Centre Leeuwarden); W. Borstlap (UMC St Radboud); M. Nienhuijs (UMC St Radboud); R. Admiraal (UMC St Radboud); J. te Rijdt (Isala Zwolle); M. Tellier (Isala Zwolle); L. van Adrichem (Erasmus MC Rotterdam); M. Koudstaal (Erasmus MC Rotterdam); J. de Gier (Erasmus MC Rotterdam); E. Ongkosuwito (Erasmus MC Rotterdam); C. van der Horst (Academic Medical Center Amsterdam); J. Nolte (Academic Medical Center Amsterdam); J. Vehof (Rijnstate); M. Rüttermann (UMCG); D. Booi (Maastricht University Medical Center); J. Burgers (NHG); C. Prahl (VUmc); B. Prahl (BOSK); S. Savitri (Achmea); A. Mink van der Molen (chairman of the guideline committee); T. van Barneveld (Knowledge Institute of Medical Specialists); P. Broos (Knowledge Institute of Medical Specialists)

Brief outline of the guideline process
At the end of 2012, a subsidy application was submitted to the Quality Funds Foundation for Medical Specialists (SKMS) for the development of the multi-disciplinary guideline on orofacial clefts. This project was initiated and financed by the NVPC, with co-funding from the Netherlands Association of ENT Surgery and Head & Neck Surgery, the Netherlands Association of Oral Diseases and Maxillofacial Surgery (NVMKA) and the Netherlands Association of Orthodontists (NVvO). The NVSCA supports this project and will be represented in the guideline task force that is responsible for the development of this guideline. This project will run from May 2013 – May 2015 and it will be supported by the Knowledge Institute of Medical Specialists.

This invitational conference has been organised to hear from the field parties present at this conference about the bottlenecks in the care surrounding the treatment of patients with clefts of the lip and palate and to create an inventory of the points of attention/suggestions for the guideline that will be developed. The aim was also to prioritise these bottlenecks and points of attention. Following on from this invitational conference, two focus groups with patients will be organised to obtain input from the patient perspective.

This guideline offers space for the development of 16 clinical questions. As the guideline covers the entire course of treatment from 0 to 18 years, it was decided to divide this into 4 phases:

- Phase 1: 0 – 12 months
- Phase 2: 1 – 4 years

- Phase 3: 4 – 8 years
- Phase 4: 9 – 18 years

Substantive discussion
During the invitational conference, Dr Mink van der Molen gave a short presentation about the four main phases of the treatment and listed the potential bottlenecks. This was followed by a brief discussion based on these bottlenecks, to which the participants could add their opinions. In addition, topics such as the organisation of care, transparency of the quality of care (registration of outcome parameters), visitation and implementation of the guideline were discussed. The point-by-point elaboration of this discussion is provided below. A brief description of the bottlenecks that were suggested and additional points for discussion submitted by the representatives present is provided below.

Phase 1: ***0 to 12 months***

- ***Feeding if a cleft palate is found to be present after birth;***
  This topic was deemed relevant for the guideline by the representatives that were present.

- ***Which clinical genetic tests are indicated if a child is born with clefts of the lip and palate;***
  This topic was deemed relevant for the guideline by the representatives that were present, possibly with a specific emphasis on cost-effectiveness.

- ***The use of "pre-surgical nasal alveolar moulding";***
  This topic was deemed **not** relevant for the guideline by the representatives that were present.

- ***Timing and order and techniques for the closure of the cleft alveolar arch and palate;***
  This topic was deemed relevant for the guideline by the representatives that were present.

- ***(Pierre) Robin sequence; watchful waiting (posture, etc.), indication tongue-lip adhesion, madibule distraction;***
  This topic was deemed relevant for the guideline by the representatives that were present, but relatively rare and often part of a syndromal problem. Following a discussion, it was decided – in view of the need to prioritise – not to include Pierre Robin and other syndromal problems (such as 22q11.2 DS) in this guideline.

Phase 2: ***1 to 4 years***

- ***Middle ear problems with orofacial cleft (when to perform audiogram, treatment of glue ears, tympanostomy tubes);***
  This topic was deemed relevant for the guideline by the representatives that were present. Those present indicated that this topic should be considered in a broader context and that it is therefore better to refer to "ear problems". In addition, it was noted that "ear problems" are also a relevant topic in Phase 1.

- ***Speech-language development with orofacial cleft, treatment of open-nosed speech (role of speech therapist, timing, pre-op examination, indication, technique);***
  This topic was deemed relevant for the guideline by the representatives that were present. Topics specifically mentioned for the clinical questions include:
  - Use of a cranially or caudally pedicled pharynx posterior wall flap.
  - The use of lipofilling.

Phase 3: ***4 to 8 years***

- ***Orthodontic treatment before and after the bone grafting surgery;***
  This topic was deemed relevant for the guideline by the representatives that were present, with specific attention for the use of orthodontic treatments before and after the closure of the cleft inn the alveolar arch.

- ***Timing of the bone grafting surgery;***
  This topic was deemed relevant for the guideline by the representatives that were present.

- ***The best surgical technique for bone grafting (bone from pelvic crest or chin, artificial bone (tri-calcium phosphate) or bone induction (BMP2)). Unilateral versus bilateral;***
  This topic was deemed relevant for the guideline by the representatives that were present.

Phase 4: ***9 to 18 years***

- ***Determining the indication for more extensive orthogantic surgery (including Le Fort I osteotomies) after puberty.***
  This topic was deemed relevant for the guideline by the representatives that were present. The following specific bottlenecks were mentioned with regard to Le Fort I:
  - When should the treatment stop?
    Is the significance that parents and child (patient) attach to the result of - for example - a Le Fort 1, but also other (extra) procedures, the same as that of the treating physician? In other words, the desired moment to stop the treatment may differ between patient and treating physician. Next, the possible need for time-out moments in the treatment pathway were mentioned, in which the treating physician and patient evaluate the treatment and discuss subsequent steps. Those present deemed it desirable to give attention to this aspect in the guideline.
  - In addition to the aforementioned discussion, the following question was posed “what should we do with the quality measurement if a patient rejects further treatment?”. One of those present noted that the WHO and ACPA have published documents describing minimum requirements for (quality) documentation.
  - Technical: distraction versus classic Le Fort I.

- ***The nose of cleft patients***
  This topic was suggested by the representatives that were present and deemed relevant for the guideline. The following specific bottlenecks were mentioned with regard to this topic:
    - timing of any procedure that takes place.
    - for which indications should you treat young patients.

- ***The use of implants to replace any missing teeth (complete set of teeth versus long-term complications and costs)***
  This topic was deemed **not** relevant for the guideline by the representatives that were present. There are choices that need to be made in this pathway, but other bottlenecks have a higher priority.

- ***Psychological aspects of clefts of the lip and palate (parents of child 0-18)***
  This topic was deemed relevant for the guideline by the representatives that were present and it should be noted that this also applies to Phase 1, 2 and 3.

- ***Final evaluation 18 years. What should be documented from 0-18 years. Outcome parameters***
  This topic was deemed relevant for the guideline by the representatives that were present and it should be noted that the final evaluation should actually be performed at the age of 21 years (or even later). The guideline should include a description of which quality information (outcome parameters) needs to be measured and when, whilst only measuring at age 18 years is deemed insufficient.

Other topics

In addition to the discussion points described above, various individuals suggested additional bottlenecks that will be discussed briefly below.

- ***Extent and scope of the guideline***
  In his presentation, Mink van der Molen indicated that this guideline project has sufficient budget to answer 16 clinical questions. Questions were raised about whether 16 clinical questions would be sufficient to cover the entire treatment pathway for orofacial clefts. However, Van Barneveld emphasised that bottlenecks will be discussed in this guideline and that this should not be seen as a manual for the treatment of clefts of the lip and palate.

- ***Implementation of the guideline***
  An implementation plan will be drafted with this guideline. The actual implementation of the guideline falls beyond the scope of the assignment given to the guideline task force and will take place under the responsibility of the NVSCA. It should be noted that the NVSCA does not have any experience in such implementation.

- ***Quality of care***
  All the representatives present acknowledge the need for inclusion of the aspect “quality of care” in this guideline. An open discussion was held about whether this will have consequences in future for the number of cleft teams and/or

possible collaboration between cleft teams. The aspects listed below in relation to quality of care were discussed:

- *How to measure quality?*
  The guideline should include a description of which quality information (outcome parameters) needs to be measured and when. The option of measuring quality through the use of PROMs is considered an important option.
- *Variations in practice*
  The BOSK states that the main priority for the patient is that the quality of care improves and that uniformity of treatment between the cleft teams is not essential for this. In response, Mink van der Molen emphasises that this guideline is intended to reduce any undesirable variations in practice (i.e. variation that is not evidence-based), whilst offering sufficient freedom for an individualised approach to the treatment.
- *Volume standards*
  Van Barneveld asked those present whether the guideline should focus on volume standards. The general impression of those present is that knowledge and quality are more than volume/production alone. For example, specific ongoing training and refresher courses, conference visits, fellowships, etc. are also important. It was noted that setting a hard volume standard is less desirable, but "exposure" can be an important quality determinant. The representative from Achmea stated that there is a lower limit regarding volume in order to measure quality of care reliably.
- *Standardisation*
  Minimum standards regarding expertise within cleft teams.

- ***Other suggested bottlenecks***
  - From the patient perspective, a desire was expressed to focus on the information provided to parents about the various treatment options.
  - The inclusion of patient information in the guideline.
  - Educational materials and information for the general practitioner.
  - Focus on cost considerations in the guideline.
  - Special dentistry.
  - Organisation of care and method of collaboration between disciplines.
  - What to do about oral hygiene.
  - How to handle a cleft palate versus a bilateral cleft lip, alveolar arch and palate versus unilateral.

Prioritisation of bottlenecks

Finally, those present were asked to prioritise the bottlenecks by listing the most relevant bottleneck and the least relevant bottleneck.

- Most relevant bottleneck
  - Evaluation moments during and after the treatment pathway (mentioned 8x).
  - Timing of the closure of the cleft alveolar arch and palate (mentioned 8x).

    - How and when to measure quality, including PROMS (mentioned 6x).
    - Hearing and speech (mentioned 5x).
    - Need for a generalistic guideline that is not too detailed (mentioned 2x)
    - Requirements regarding composition and organisation of cleft teams (mentioned 2x)
    - Surgical techniques (mentioned 2x)
    - Guidance offered to patient and parents (psychosocial and social) (mentioned 2x)
    - Exposure requirement instead of volume standards (mentioned 1x)
    - Patient summary (mentioned 1x)
    - Uniformity of treatment plan without competition between cleft teams (mentioned 1x)
    - Osteotomy in the late phase (mentioned 1x)
- Least relevant bottleneck
    - NAM
    - Robin
    - Implants
    - Other syndromes

Follow-up agreements

Two patient focus groups will be organised as a follow-up to this invitational conference.

This report will be presented to all invited parties. At a later stage in the process, the (draft) guideline will also be presented to these parties for comments.

Appendix 4 Report of focus group meeting

Date: Thursday 15 May 2014 (18:30 – 21:00)
Location: Domus Medica, Utrecht
Present: Teus van Barneveld (KiMS); Pieter Broos (KiMS); Henriette de Veye (Guideline Committee, UMC Utrecht); 2 cleft patients; 8 parents of a cleft patient.

1) Opening

Teus van Barneveld opened the meeting and provided a brief explanation about the aim of the guideline and how this meeting fits into this. During this meeting, the experiences and expectations of the care were discussed with a number of patients. The following questions were included in the focus group discussion:

- What do you expect from your treating physician regarding the diagnosis, treatment, information and guidance?
- How could the treatment pathway be improved?
- Which bottlenecks have you experienced? And which good/positive points have you experienced that should definitely be conserved?

2) Report of group discussion

A number of general topics and questions were discussed during the meeting, as explained below.
The discussion started with the general question "What would be a good addition to the care":

- *"The use of an 'experiential expert' active from/within the teams would be a good addition. This can occur at different levels; sometimes offering practical support and sometimes emotional support. The offer should be made, because sometimes it can be quite difficult to ask.*
- *"Feedback to the parents about what was discussed in the multi-disciplinary meeting. You want to be certain that the communication between the specialists is good and you want to know what was discussed, so that you know what is coming next."*
- *"The need for an approachable access point for any questions."*

<u>Experiences and information supply needs</u>

In response to the question about how the care could be improved, the patients indicated that there is a need for clear information and substantiation of choices. A number of quotes are provided below:
"Why does one hospital close the hard palate at such an early stage whilst another does not? As patients, we don't know why there are so many differences and why certain choices are made. A cleft team should - at the very least - be able to explain why they make certain choices. My doctor said: go with what feels best for you."
"Doctors contradict each other. Initially the doctors said they did not think plates were an option, but later they were suddenly talking about plates. They do not explain why certain choices are or aren't made. They are unable to explain it and contradict each other."

Teus van Barneveld indicated that the development of the guideline was created (partially) as a result of this need. The guideline developers have noticed that there is significant variation between the different protocols. One of the objectives of the guideline is to create an inventory of the proof/evidence that is available and how to do this. Furthermore, the aim is to reach clear agreements when there is insufficient evidence to make a strong recommendation.
One of the patients noted that she gets the feeling that everyone is very attached to the protocols. After all, each treatment and each child is different and unexpected things can happen.
Question Teus van Barneveld: Where do you find your information?

- *"We primarily obtain the information from the websites of the various cleft teams."*
- *"We had enough time to choose a cleft team, because we were adopting a child with a cleft. To us it was important that the plastic surgeon was experienced. And we compared protocols and contacted cleft teams by telephone."*
- *"There is a lack of independent information provision."*

Conclusion: the patients would like to see less variation in treatments (based on evidence) and better information provision. If more research were to be performed, then everyone would gladly participate. One parent indicated that taking part in research creates uncertainty and therefore would prefer not to take part.

Choice of cleft team and differences in treatment pathway

The fact that there is no unanimous treatment pathway for a child with clefts of the lip and palate was discussed in detail. Patients and parents acknowledge that this is due to the fact that the treatment of a patient with a cleft is a "unique process", but they find the differences in protocols frustrating. When asked which points differ the most, the following points were mentioned:

- Moment of surgery
- Palate plate
- Method of suturing
- Taping or not (the team in Utrecht cannot even agree as a team)
- Different teams for multi-disciplinary consultations and different treatment methods
- Duration of hospital admission after bonegrafting surgery
- Feeding after surgery
- In Nijmegen, they discourage breastfeeding
- Difference in the number of patients being treated by the cleft teams

Parents currently have the feeling that there is not enough reliable, independent information and cleft teams are often uncooperative when parents explore other options.
"When you start shopping around, the cleft teams will start pitting themselves against each other. Sometimes they even try to reel you in. What they should be doing is explain why they make certain choices and why other teams make a different choice. For example, the expertise of the plastic surgeon is essential for the result. Doctors should really be referring patients to each other."
"If you do not stand up for yourself as a parent, then they do not tell you anything. Some parents don't really stand up for themselves and effectively hand their child over to the doctor. In that case they won't tell you anything."

Question Teus van Barneveld: Would you actually like to have a choice?
"Not really. As patient/parent, we are not properly equipped to obtain the correct information. At the moment the differences are too big and this makes you uncertain and causes you to start shopping around. A unanimous protocol would be best."

Start of the treatment pathway

Parents have different experiences relating to the period just prior to birth and the weeks after the birth.

- *"We first requested a meeting during the pregnancy and two cleft nurses visited us at home 2 weeks after the birth. They came to give us information and offer psychological support. We found this very pleasant."*
- *"We were not aware before the birth that our child would be born with a cleft. As a result we experienced a whole range of emotions in the first weeks. In the period between birth and the first appointment it was not possible to find reliable information. 3 weeks is really quite long, from an emotional perspective. There was definitely a need for timely information, but that is very different now with prenatal screening."*
- *"Initially, during the pregnancy, I missed having a meeting with the clinical geneticist. We were shown a lot of pictures of surgeries that were not due to take place for some time."*
- *"Good experience, had a consultation within 7 days."*
- *"Had a consultation with the cleft team within 10 days. A situation developed in which they immediately deviated from the protocol. We were unable to change gears during the conversation and had a lot of questions afterwards. It was a surprise to us that it was possible to deviate from the protocol. Perhaps the rigid protocols create the wrong expectations, when in fact this should always be accompanied by a conversation. And there is a need for a well-dosed supply of information. For example, if you are having a second child with a cleft then the information that you require is different."*
- *You also require different information when you are adopting a child, because the parents have limited information about their child. They do not know what type of cleft their child has. An adoption consultation is offered in Arnhem."*
- *Conversation going from one doctor to the next: "A disadvantage of having a conversation that takes place going from one doctor to the next is that questions will arise at a later stage for a doctor that you have already seen."*
- *"It is better to have a conversation with several professionals at once. An initial meeting with an entire cleft team is quite overwhelming."*

Question: How should we organise the first weeks after birth?

- *"There should be a fixed point of contact in the cleft team, who contacts you just before the birth and who you can contact if you have any questions, for example about feeding."*
- *"Each cleft team should have a social worker or psychologist and this is also stated in the guideline on prenatal screening for orofacial clefts."*

Screening for psychosocial development and psychological support

We are curious about the need for psychological support. Is there a need for screening of psychosocial development and if so, at which moments?

- A unanimous "yes" from all those present.
- *"Sometimes parents will think that everything is fine, but children can suddenly experience problems."*
- *"In Tilburg, there is a support group for patients attending high school, under the supervision of a psychologist."*
- *"Screening for psychosocial support is most needed from the age of about 8-10 years. This is the phase in which the child realises that it has a cleft. Further screening when the child starts puberty may also be necessary. Actually, you would ideally perform the screening one year after the child has started high school. This allows you to detect changes other than the normal changes faced by those starting high school."*
- *"Screening at the end of the treatment pathway (from 18 years): this depends a little on the situation."*

Question: which moments do parents think are important to receive psychological support for themselves and their child (beyond prenatal and birth)?

- *"After the operations"*
- *"When their child changes."*
- *"Does not necessarily have to be a set moment. But puberty might be a good time, because your child will start changing a lot in those years."*
- *"It is important that this option is offered by the cleft team. It should be open for discussion and the parents should be aware of it."*
- *"How should you ensure that your child becomes resilient? As parents, you need to decide when this is necessary. Screening would be useful for this."*

Genetic diagnostics

Question: what are your experiences, should this be standard procedure?

- *"I was scared about taking part in a large study. People are scared about life insurance and mortgages, etc."*
- *"There is a need for a conversation with the clinical geneticist."*
- *"Sometimes you hear from other patients being treated by other teams that they are not even aware that the clinical geneticist exists."*
- *"The offer should at least be made, so that you as a parent at least have the option."*

Other topics

At the end of the meeting, the participants were asked whether there were any other topics that they would like to discuss.

- **Speech therapy:** *"It is good that these examinations take place, but I wonder how much the cleft team communicates with the local speech therapist. Referral to a speech therapist with experience in clefts is recommended."*
- **Tube feeding after birth:** "*Some information about this topic should be included in the guideline. Perhaps the various cleft teams can reach unanimous agreements about this. There are a lot of things that you can try before you need*

to start tube feeding, but this is not offered everywhere and some teams start tube feeding immediately."

- **Breastfeeding:** *Perhaps the various cleft teams can reach unanimous agreements about this. For example about when you can start trying to latch on. Please also include recommendations about when it is pointless to try."*
- **External cooperation:** *I have noticed that - as a parent of a child with a cleft - I often need to chase after information. For example, information about visiting the dentist for the first time. I did not know that I was allowed to contact the cleft team immediately about an ear infection."*
- **External cooperation:** *"Cleft teams should have a social map of the care that is available just beyond the cleft team."*
- **External cooperation:** *"Education of the child health centres, they are really lacking a lot of knowledge about feeding and speech. Also applies to general practitioners and - for example - maternity nurses and child health nurses. These professionals are the first to ask parents questions."*
- **ENT:** Uncertainty/ambiguity about when to remove tonsils. Provide clarity in the guideline.

3) Round of questions and closing.

There were no comments during the round of questions.

Appendix 5 Standard texts and standards regarding acoustic nasometry

1) Nasometry

1.1 Text and standards up to 8 years

Normal text
Miep is op school
Nu gaat zij kleuren
Zij tekent de juf
Dat wordt heel mooi
Juf geeft Miep stickers

Denasal text
Jos heeft feest
Hij is jarig
Hij krijgt veel cadeautjes
Ook is er taart
De taart heeft vijf kaarsjes
Jos blaast ze uit

Nasal text
Mama gaat naar oma
Zij neemt een mand mee
In de mand zijn bananen
En ook mandarijnen
Oma heeft honger
Ze neemt een mandarijn

The standards

Normal text:	17 – 34%
Hyponasal text:	4 - 22 %
Hypernasal text:	41 - 65%

1.2 Text and standards from 8 years

Normal text
Papa en Marloes staan op het station. Ze wachten op de trein. Eerst hebben ze een kaartje gekocht. Er stond een hele lange rij, dus dat duurde wel even. Nu wachten ze tot de trein er aan komt. Het is al vijf over drie, dus het duurt nog vier minuten. Er staan nog veel meer mensen te wachten. Marloes kijkt naar links. In de verte ziet ze de trein al aankomen.

Denasal text
Het is zaterdag. Els heeft vrij. Ze loopt door de stad. Het is prachtig weer, de lucht is blauw. Op straat ziet ze Bart op de fiets. Hij wacht voor het rode licht. Als Bart haar ziet, zwaait hij.
Els loopt weer verder. Bij de bakker koopt ze brood, bij de slager koopt ze vlees. Als het vijf uur is, gaat ze terug, zodat ze weer op tijd thuis is.

Nasal text

Vanmorgen ging meneer van Dam naar de groenteman. Namelijk om een ons mandarijnen te kopen. Aan zijn arm nam hij een mand mee om de mandarijnen in te doen. Na een minuut of tien stond meneer van Dam in de winkel en hij nam een ons mandarijnen mee en ook maar meteen negen bananen en een mooie ananas. Met zijn mand aan de arm ging hij toen snel naar huis.

The standards

	Normal text		Denasal text		Nasal text	
	Ave	S.D.	Ave	S.D.	Ave	S.D.
Nasality	32.83	5.84	12.31	5.21	54.02	8.04

The Range (+/- 2 S.D.)

	Normal text	Denasal text	Nasal text
Nasality	21.2 – 44.4	1.89 – 22.73	38.94 – 70.10

Appendix 6 Standard Expressions for Nasal Endoscopy and Video Fluoroscopy

1 Name of the child
2 Expressions for mirror test:
- Papapapapa
- Pipipipipi
- Kakakakaka
- Kikikikiki
- Fffffffff
- sssssss,
- ieeeeee
- oeeeee
- Piet zit op de stoep

3 Counting from 1 to 10
4 Sentence level: several sentences from the denasal and normal nasometry text:
- Miep is op school
- Nu gaat zij kleuren
- Jos heeft feest
- Hij is jarig
- Hij krijgt veel cadeautjes

Appendix 7 Evidence tables

Chapter 4 Feeding of patients with clefts of the lip and palate

Table Exclusion after reading the full article

Author and year of publication	Reason for exclusion
Batista 2011	Full tekst in Spanish
Brine 1994	Included in Besell 2011
Darzi 1996	Included in Besell 2011
Farronato 2014	Does not meet selection criteria
Glenny 2004	Does not meet selection criteria (protocol of systematic review)
Maserei 2007a	Included in Besell 2011
Noguiera 2012	Does not meet selection criteria (conference abstract)
Prahl 2005	Included in Besell 2011
Shaw 1999	Included in Besell 2011

Evidence table for systematic review of RCTs and observational studies (intervention studies)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Besell 2011 [individual study characteristics deduced from [1st author, year of publication]] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs *Literature search up to October 2010* **A**: Brine 1994 **B**: Darzi 1996 **C**: Masarei 2007 **D**: Prahl 2005 **E**: Shaw 1999 Study design: RCT [parallel / cross-over], Setting and Country: United Kingdom Source of funding: Non-commercial	Inclusion criteria SR: 1) randomized controlled trials using either true or quasi methods of random allocation 2) patients: babies born with cleft lip or palate up to the age of 6 months from term 3) intervention: modified bottles, cups, spoons, pumps, positions, techniques and/or teats (to supplement breastfeeding or instead of breastfeeding), obturating plates or maternal advice or support. Any intervention could be compared to any other or to unmodified equipment or advice. 4) Outcomes: primary: growth. Secondary: development, parental satisfaction Exclusion criteria SR: 1) patients: babies born with syndromes	Describe intervention: **A**: squeezable nurser **B**: breastfeeding (postsurgical) **C**: presurgical orthopaedics or maxillary orthopedics **D**: passive acrylic plate 24 hours/day, maintained until soft palate closure **E**: squeezable bottle with Nuk orthodontic teat	Describe control: **A**: rigid bottle with standard cross-cut nipple **B**: spoon-feeding (postsurgical) **C**: no presurgical orthopaedics **D**: no plate **E**: rigid bottle with Nuk orthodontic teat	End-point of follow-up: **A**: 18 months **B**: 6 weeks after surgery **C**: 12 months of age **D**: 12 months of age **E**: 12 months of age For how many participants were no complete outcome data available? (intervention/control) **A:** no drop-outs listed, no reasons for attrition given **B**: no dropouts in study **C**: dropouts not reported **D**: reasons for dropout not reported **E**: dropouts listed and described in full	Weight Defined as. Difference in Increase in weight in kg *Squeezable bottle versus rigid bottle* After 6 months Pooled effect (random effects model): -0.10 [95% CI -0.42 to 0.23] favoring squeezable bottle Heterogeneity (I^2): 48% After 12 months (random effects model): -0.15 [95% CI -0.53 to 0.22] favoring squeezable bottle Heterogeneity (I^2): 78% *Breast feeding versus spoon feeding* After 6 weeks: Pooled effect (1 study, not applicable): 0.47 [95% CI 0.20 to 0.74] favoring breastfeeding Heterogeneity (I^2): not applicable	Facultative: Brief description of author's conclusion There is a moderate level of evidence that in infants with cleft lip and/or palate using squeezable bottles for feeding results in a similar weight gain and height as feeding from rigid bottles. There is a low level of evidence that in infants with cleft lip and/or palate breastfeeding results in a higher weight gain when compared to spoon-feeding. There is a moderate level of evidence that in infants with cleft lip and/or palate the use of a feeding plate results in a similar weight gain and height as not using a feeding plate.

		5 studies included <u>Important patient characteristics at baseline</u>: *Number of patients; characteristics important to the research question and/or for statistical adjustment (confounding in cohort studies); for example, age, sex, bmi, ...* <u>N, mean age</u> **A**: 37, 15 days **B**: 40, 4.4 months **C**: 50, from birth **D:** 54, 2 weeks **E:** 101, from birth <u>*Sex*</u>*:* **A**: 57% Male **B**: not stated **C**: 60% Male **D:** 76% Male **E:** 58% Male Groups comparable at baseline? Unclear				*Infant orthopaedics versus no infant orthopaedics* After 6 months Pooled effect (1 study, not applicable): -0.57 [95% CI -1.14 to 0.00] favoring maxillary orthopaedics Heterogeneity (I^2): not applicable After 12 months (random effects model): 0.10 [95% CI -0.53 to 0.73] favoring no maxillary orthopaedics Heterogeneity (I^2): 0% <u>Height</u> Difference between group sin cm *Squeezable bottle versus rigid bottle* After 6 months Pooled effect (random effects model): 0.20 [95% CI -0.59 to 0.98] favoring rigid bottle Heterogeneity (I^2): 33% After 12 months (random effects model): 0.21 [95% CI -0.72 to 1.14] favoring rigid bottle Heterogeneity (I^2): 74% *Infant orthopaedics versus no infant orthopaedics*	

						After 6 months Pooled effect (1 study, not applicable): -1.05 [95% CI -2.20 to 0.11] favoring infant orthopaedics Heterogeneity (I^2): 0% After 12 months (random effects model): -0.78 [95% CI -3.68 to 2.12] favoring infant orthopaedics Heterogeneity (I^2): not applicable <u>Head circumference</u> Difference between group sin cm *Squeezable bottle versus rigid bottle* After 6 months Pooled effect (random effects model): -0.28 [95% CI -0.70 to 0.14] favoring squeezable bottle Heterogeneity (I^2): 57% After 12 months (random effects model): -0.66 [95% CI -1.16 to -0.17] favoring squeezable bottle Heterogeneity (I^2): 80% *Infant orthopaedics versus no infant orthopaedics* After 6 months Pooled effect (1 study, not applicable):	

						0.30 [95% CI -0.66 to 1.26] favoring no infant orthopedics Heterogeneity (I^2): not applicable After 12 months (1 study, not applicable): 0.25 [95% CI -1.03 to 1.53] favoring no infant orthopedics Heterogeneity (I^2): not applicable <u>Parent satisfaction:</u> Squeezable versus rigid bottle: no significant difference in daily activities (24 hour log) between groups	
Goyal 2014 [individual study characteristics deduced from [1st author, year of publication]] PS., study	SR and meta-analysis of RCTs / cohort / case-control studies *Literature search up to January 2013* RCTs **A**: Brine 1994 **B**: Shaw 1999 **C**: Prahl 2005 **D**: Maserei 2007a Observational studies	Inclusion criteria SR: 1)articles that summarized the use of obturators and other feeding interventions in infants with clefts 2) published in English Exclusion criteria SR:- *26 studies included* <u>Important patient</u>	Describe intervention: **Not reported per study**	Describe control: **Not reported per study**	<u>End-point of follow-up</u>: **Not reported per study** <u>For how many participants were no complete outcome data available?</u> (intervention/control) **Not reported per study**	<u>Outcome measure-1</u> **Not reported per study**	<u>Facultative</u>: Brief description of author's conclusion: A pragmatic approach to feeding, plus using a combination of various interventions is recommended. Although a systematic search is performed, the evidence and outcome measures are

characteristics and results are extracted from the SR (unless stated otherwise)	**E**: Tisza 1962 **F**: Williams 1968 **G**: Paradise 1969 **H**: Paradise 1974 **I**:Campbell 1987 J: Claren 1987 K: Clarren 1987 L: Saunders 1989 M: Choi 1991 N: Richard 1991 O: Lang 1994 P: Trenouth 1996 Q: Kogo 1997 R: Oliver 1997 S: Turner 2001 T: Mizuno 2002 U: Da Silva Dalben 2003 V: Garcez 2005 W: Maserei 2007b X: Sabarinath 2008 Y: Britton 2011 Z: Ize-Iyamu 2011 ..... Study design: see above Setting and Country: India Source of funding: Not reported	characteristics at baseline: *Not reported* N, mean age **Not reported** *Sex:* **Not reported** Groups comparable at baseline? Unclear					not summarized systematically and no meta-analyses are performed due to heterogeniety of studies.

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series])

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Augsornwan 2013	Type of study: randomized controlled trial Setting: inpatients Country: Thailand Source of funding: non-commercial	Inclusion criteria: 1) patients with cleft lip and/or palate who were admitted to the participating hospital and provided informed consent Exclusion criteria: - N total at baseline: Intervention: 96 Control: 96 Important prognostic factors[2]: *For example* *age (months, mean):* *I: 4.4* *C: 4.2* *Sex:* *I: 60% M* *C: 61% M* *Bilateral cleft:* *I: 16%* *C: 16%* Groups comparable at baseline? Yes	Describe intervention (treatment/procedure/ test): Feeding with breast or bottle	Describe control (treatment/procedure /test): Feeding with spoon or syringe	Length of follow-up: 14 days after surgery in ward which surgery? Lip? Then 3-12 months as outpatients Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Surgical complications: (number of patients with complication at day 14) Wound dehiscence: I: 0 C: 1 P=0.32 Skin inflammation: I: 0 C: 2 P=0.32 Bleeding: I: 0 C: 0 P>0.05 Swelling: I: 1 C: 2 P=0.32 Patient satisfaction:	

						Parents more statisfied and patients more relaxed during feeding in the breast/bottle group (as measured by questionnaire and observations by researchers)	
Hughes 2013	Type of study: pilot study / randomized controlled trial Setting: inpatients Country: United Kingdom Source of funding: not reported	Inclusion criteria: 1) infants aged 5-10 months undergoing cleft palate repair *isolated cleft palate or cleft lip + palate) Exclusion criteria: 1) feeding difficulties 2) contra-indication for use of nasogastric tubes or opioid analgesia N total at baseline: Intervention: 18 Control: 23 Important prognostic factors[2]: *For example* *age ± SD (months):* *I: 6.4 ± 0.6* *C: 6.2 ± 0.9* *Sex:* *I: 39% M* *C: 35% M* Groups comparable at baseline? Yes	Describe intervention (treatment/procedure/ test): Nasogastric feeding	Describe control (treatment/procedure /test): Oral feeding	Length of follow-up: 24 hours after surgery Loss-to-follow-up: Not described Incomplete outcome data: Not described	Outcome measures and effect size (include 95%CI and p-value if available): Oral intake: (mL / kg of weight) I: 147 ± 55 C: 59 ± 33 Mean difference: -88 (95% CI: -115 - -61) Painful episodes: (median and range) I: 4.5 (0-13) C: 5 (0.14) p>0.10 Analgesic use was similar in both groups	
Ize-Iyamu 2001	Type of study: randomized (controlled?) trial	Inclusion criteria: 1) babies with cleft lip and palate (cleft extending to at least 2/3 of the hard palate) 2) babies could not latch onto	Describe intervention (treatment/procedure/ test): Feeding using a syringe	Describe control (treatment/procedure /test): Feeding using a cup	Length of follow-up: Until the age of 14 weeks Loss-to-follow-up: Not described	Outcome measures and effect size (include 95%CI and p-value if available): Weight gain:	Babies with clefts in the cup and spoon group recorded a higher difficulty in feeding and those with a weight loss

	Setting: outpatients Country: Nigeria Source of funding: no funding	breast or feeding bottle <u>Exclusion criteria</u>: - <u>N total at baseline</u>: Intervention: 38 Control: 19 <u>Important prognostic factors</u>[2]: *For example* *age ± SD: from birth* *Sex:* *I: 26% M* *C: 21% M* Groups comparable at baseline? Yes		and spoon	<u>Incomplete outcome data</u>: Not described	Breastfeeding only: I: 0-6 weeks: 0.2 kg 6-10 weeks: 0.8 kg* 10-14 weeks: 0.7 kg C: 0-6 weeks: 0.3 kg 6-10 weeks: 0.4 kg* 10-14 weeks: 0.4 kg Breastfeeding plus formula: I: 0-6 weeks: 0.3 kg 6-10 weeks: 0.6 kg 10-14 weeks: 1.2 kg* C: 0-6 weeks: 0.3 kg 6-10 weeks: 0.5 kg 10-14 weeks: 0.6 kg* * = p<0.05 Feeding time: I: 10 mL / 1.25 minute C: 10 mL / 2.08 minute P not reported	over 1 kg were reassigned to the syringe group
Jones 1988	Type of study: retrospective observational Setting: outpatients (2 centers) versus inpatients (1 center) Country: Ireland Source of funding: not reported	<u>Inclusion criteria</u>: 1) childen with a cleft lip and/or palate that were treated in 1 of the 3 participating hospitals 2) full term birth 3) no other congenital defects 4) no handicapping systemic defects 4) no genetic disorders 6) no respiratory distress 7) adequate hospital records of weight gain <u>Exclusion criteria</u>: - <u>N total at baseline</u>:	Describe intervention (treatment/procedure/ test): mother and baby were cared for in the community and followed up at regular intervals by the cleft team in outpatient clinics prior to admission for primary surgery.	Describe control (treatment/procedure /test): an inpatient mother-and-baby ward was established, where infants with clefts were cared for by mothers and nursing staff until the time for primary repair.	<u>Length of follow-up</u>: Age of 4 months <u>Loss-to-follow-up</u>: Unclear, not reported <u>Incomplete outcome data</u>: Unclear, not reported	Outcome measures and effect size (include 95%CI and p-value if available): Weight gain: (average g/week) Outpatients: Center 1: 163 Center 2: 151 Inpatients: Center 3: 134 p>0.05	

		Intervention: 94 Control:108 Important prognostic factors[2]: *Not reported* Groups comparable at baseline? Uncelar					
Kim 2009	Type of study: randomized controlled trial Setting: outpatients Country: South Korea Source of funding: no funding	Inclusion criteria: 1) patients with nonsyndromic cleft palate with or without cleft lip 2) who underwent cleft palate repair using the 2-flap palatoplasty technique 3) operated between 1991 and 1996 at the participating hospital Exclusion criteria: 1) submucous cleft 2) bilateral cleft 3) any other anomalies (syndromic clefts, craniofacial deformities, neurologic deficits) N total at baseline: Intervention: 42 Control: 40 Important prognostic factors[2]: *For example* *age ± SD:* *I:8.1 months* *C: 7.8 months* *Sex:* *I: 52% M* *C: 40% M*	Describe intervention (treatment/procedure/ test): Liquid foods provided in bottle with same nipple as used previously by the child	Describe control (treatment/procedure /test): Liquid foods provided by cup, spoon or syringe.	Length of follow-up: 2 months Loss-to-follow-up: Unclear, not described Incomplete outcome data: Unclear, not described	Outcome measures and effect size (include 95%CI and p-value if available): Oral intake: No significant difference between I and S for the first 5 days On day 6: I: 798 mL C: 586 mL P=0.042 Postoperative complications: I: 12% C: 13% P=1.00 Oronasal fistula: I: 4 (10%) C: 5 (13%) p>0.05 Weight gain: After 1 months: I: 6.4% C”5.1% P=0.47 After2 months: I: 10.3% C: 9.3% P=0.33	Author’s conclusion: Bottle-feeding had no adverse effect on the early postoperative course after palatoplasty including complication rate, oral intake and weigh gain. These findings suggest that an unrestricted feeding regimen is appropriate immediately after palatoplasty.

		Severity of palatal cleft (Veau 1-2 / Veau 3) *I: 48% / 52%* *C: 53% / 47%* *Labial cleft:* *I: 50%* *C: 60%* Groups comparable at baseline? Yes					
Masarei 2007a	Type of study: Setting: Country: Source of funding:	<u>Inclusion criteria</u>: <u>Exclusion criteria</u>: <u>N total at baseline</u>: Intervention: Control: <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *I:* *C:* *Sex:* *I: % M* *C: % M* Groups comparable at baseline?	Describe intervention (treatment/procedure/ test):	Describe control (treatment/procedure /test):	<u>Length of follow-up</u>: <u>Loss-to-follow-up</u>: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe) <u>Incomplete outcome data</u>: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)	Outcome measures and effect size (include 95%CI and p-value if available):	
Masarei 2007b	Type of study: Setting: Country: Source of funding:	<u>Inclusion criteria</u>: <u>Exclusion criteria</u>: <u>N total at baseline</u>: Intervention: Control:	Describe intervention (treatment/procedure/ test):	Describe control (treatment/procedure /test):	<u>Length of follow-up</u>: <u>Loss-to-follow-up</u>: Intervention: N (%) Reasons (describe)	Outcome measures and effect size (include 95%CI and p-value if available):	

		Important prognostic factors[2]: *For example* *age ± SD:* *I:* *C:* *Sex:* *I: % M* *C: % M* Groups comparable at baseline?			Control: N (%) Reasons (describe) Incomplete outcome data: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)		
Turner 2000	Type of study: prospective observational Setting: outpatients (1 center) Country: United States of America Source of funding: not reported	Inclusion criteria: 1) referral within the first 2 weeks of life 2) living within a 50-mile radius from the hospital 3) mother's willingness to maintain feeding records for each feeding 4) having mothers who wanted to breast-feed or provide breast milk for the infant 5) infant having a cleft of the hard and soft palate with or without lip involvement Exclusion criteria: N total at baseline: Intervention: 8 Each infant was its own control Important prognostic factors[2]: *For example* *4 infants with unilateral cleft of lip and palate* *2 infants with bilateral cleft of*	Describe intervention (treatment/procedure/ test): A 5-phase (A, B1, C1, B2, C2) withdrawal design was used with each infant serving as its own control. In phase A the baseline minutes to feed were obtained in 3 consecutive feedings. In the B1 phase the baseline minutes to feed were obtained for 3 feedings with the Haberman bottle. In the C1 phase minutes to feed with a palatal obturator and breast feeding were obtained for 3 feedings. In the B2 phase the obturator was again removed for 3 feedings and total time with Haberman	Describe control (treatment/procedure /test): See description in "Intervention" column	Length of follow-up: Until the age of 2 years Loss-to-follow-up: none Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Feed time (minutes): A: 48 B1: 34 C1: 15 B2: 32 C2: 16 P<0.05 Average volume of milk consumed (mL): B1: 37 C1: 67 B2: 37 C2: 76 P<0.05 Average volume of milk consumed per minute (mL/min): B1: 1.4 C1: 3.8 B2: 31.2 C2: 5.2 P<0.05	Infants served as their own controls. None of the mothers were able to sustain effective breastfeeding without additional interventions.

		lip and palate *2 infants with cleft palate only* Groups comparable at baseline? Not applicable	was recorded. In phase C2 the time to feed of 3 feedings with obturator and Haberman was obtained.			Weight: All subjects within -2 SD o Z-score of WHO standards for growth Average: Z-score: -0.8 (95% CI: -1.4 - -0.2) Height: All subjects within -2 SD o Z-score of WHO standards for growth Satisfaction of mothers: 6 high satisfaction 2 good satisfaction	

Notes:

1. Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures
2. Provide data per treatment group on the most important prognostic factors [(potential) confounders]
3. For case-control studies, provide sufficient detail on the procedure used to match cases and controls
4. For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders

Risk of bias table for intervention studies (randomized controlled trials)

Study reference (first author, publication year)	**Describe method of randomisation** [1]	**Bias due to inadequate concealment of allocation?** [2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?** [3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?** [3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?** [3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?** [4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?** [5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?** [6] (unlikely/likely/unclear)
Augsornwan 2013	"computer-generated by block of 8 randomization"	Unlikely	Likely	Likely	Likely	Unlikely	Unclear	Unlikely
Hughes 2013	"table of random numbers and block randomisation" allocation was by pre-prepared ordered envelopes	Unlikely	Likely	Likely	Likely	Unlikely	Unclear	Unclear
Ize-Iyamu 2001	"randomly assigned"	Unclear	Likely	Likely	Likely	Unlikely	Unclear	Unclear
Kim 2009	"randomly assigned"	Unclear	Likely	Likely	Unlikely	Unlikely	Unclear	Unclear

1. Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
2. Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..
3. Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4. Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.
5. If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear
6. Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Jones 1988	Unlikely	Unlikely	Unlikely	Unclear
Turner 2000	Unlikely	Likely	Unlikely	Unclear

Chapter 5 Lip and palate closure in patients with clefts of the lip and palate
Module: Timing of the lip and palate closure

Table of excluded studies (exclusion after assessment of full text).

Author and year of publication	Reason for exclusion
Berkowitz, 2005	Does not meet selection criteria
Da Silva Filho, 2000	Does not meet selection criteria (follow-up too short)
Deluke 1997	Does not meet selection criteria (case serie)
Farronato 2014	Does not meet selection criteria
Friede, 2001	Included in systematic review Liao, 2006
Fudalej, 2010	Does not meet selection criteria
Gerke 2014	Does not meet selection criteria (congress abstract)
Goodacre, 2003	Does not meet inclusion criteria (lip closure)
Hudson 1994	Does not meet selection criteria (review, not systematic)
Klintö, 2014	Does not meet selection criteria (follow-up too short)
Latham 2007	Does not meet selection criteria
Lohmander, 2011	Does not meet selection criteria
O'Gara, 1994	Does not meet selection criteria (follow-up too short)
Prasad, 2000	Does not meet selection criteria
Rohrich, 1996	Included in systematic review Yang, 2010 and Liao, 2005.
Rohrich 2000	Does not meet selection criteria (review, not systematic)
Silva, 2001	Included in systematic review Yang, 2010
Tanino, 1997	Does not meet selection criteria
Wada, 1990	Does not meet selection criteria
Willadsen, 2012	Does not meet selection criteria
Williams, 2011	Does not meet selection criteria
Ysunza, 2010	Does not meet selection criteria

Evidence table for systematic review of RCTs and observational studies (intervention studies)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Liao 2006 [individual study characteristics deduced from [1st author, year of publication]] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs / cohort / case-control studies *Literature search up to December 2004* **A**: Robertson and Jolleys 1974 **B**: Hotz 1978 **C**: Schweckendiek 1978 **D**: Hotz and Gnoinsky 1979 **E**: Blijdorp and Egyedi 1984 **F**: Bardach 1984 **G**: Ross 1987 **H**: Friede 1987 **I**: Noverraz 1993 J: Smahel 1994 K: Rohrich 1996 L: Friede 1999 M: Nandlal 2000 N: Friede and Enemark 2001 O: Swennen 2002 <u>Study design</u>: RCT [parallel / cross-	Inclusion criteria SR: 1) studies evaluating the effect of timing of hard palate repair on facial growth in patients with cleft lip and palate 2) studies in English Exclusion criteria SR: 1) case reports 2) case series (<10 patients) 3) studies with no comparison or control in sample *15 studies included* <u>Important patient characteristics at baseline</u>: <u>Number of patients</u> **A**: 40	Describe intervention: **A**: L+A+SP (3) **B**: L (6) → SP (18) **C**: SO (6-8) → L (7-9) → HP (144 – 168) **D**: L(6) → SP (18) **E**: L + HP(3) → SP (66-78) (Veau) **F**: SO (8) → L (8.6) → HP (158.4) **G**: 1) SO → HP (58-84) 2) HP, SP (21-33) 3) HP, SP (12-20) 4) HP, SP (<11) **H**: 1) L (2.5) --: SP (8.8) → L/N (18.1) 2) L+HP (2.1) → SP (7.6) → L/N (19.1) 3) L(2.9)→ SP (10.4) → L/N (19.8) **I**:1) L9^) → SP (13) → HP + A (113) 2) L(6) → SP (13) → HP (55) 3) L(6) → SP (13) → HP (18) (all modified vL) J: → HP (72) (Push-back) K: L (3.4) → SP (11.4) → HP (48.6) (VMF) L: L(2.1) → SP (8.1) → L/N	Describe control: **A**: L + SP (3) → HP 12-15 (PMF) **B**: L (3) → HP + SP (30-36) (PMF) **C**: - **D**: - **E**: L+HP (3) → SP (28-42) (Veau) **F**: - **G**: SP → HP **H**: L+HP (1.5) → HP (4.1) → SP (9.5) → L/N (20.5)-- **I**: L(6) → SP (13) J: → HP (48) (Push-back) K: L (3.4) → HP + SP(10.8) (Push-back) L: L/N (7.8) → SP (20.2) → HP (61.9) → A (114.8) M: L → HP + SP (8-24) N: L+HP (3) → SP (22) → A (119) O: SP (3) → L + HP (6.2) *Number is age in months* *L=lip* *L/N: lip/nose* *A= alveolus* *(H) (S) P = (hard) (soft)*	<u>End-point of follow-up</u>: Until the age of… (in years) **A**: 3 (lateral cephalograms); 4.5 (cast) **B**: 4-6 **C**: adult **D**: 5 **E**: adult **F**: 17.2 (range 12-24) **G**: 11 – 19.6 **H**: 7 **I**: 17.1 J: adult K: 18 L: 16 M: 10 (range 6-14) N: 15.9 O: 10 (range 8.8 – 11.2) <u>For how many participants were no complete outcome data available?</u> (intervention/control) Not reported in all studies (however, since the studies were cross-sectional or retrospective in nature, this is not applicable)	<u>Maxillary growth:</u> A total of 13 studies describes the effect of timing of hard palate repair on maxillary growth. Three studies concluded that the variation in timing of the hard palate repair do not affect the length of the maxilla significantly, whereas one study opposes this view. One study reports that the length of the effect of timing depends on the type of cleft and another that the results depend on the age at time of assessment. Seven studies conclude that variation in timing of hard palate repair does not affect protrusion of the maxilla, whereas another two oppose this view and one more study states that this depends on the age at assessment. Methodological deficiencies and heterogeneity of the studies prevented pooling of results and possibility to draw major conclusions.	<u>Facultative</u>: Methodological deficiencies and heterogeneity of the studies prevented pooling of results and possibility to draw major conclusions. Level of evidence: GRADE very Low

	over], cohort [prospective / retrospective], case-control **A**: cross-sectional **B**: cross-sectional **C**: cross-sectional **D**: longitudinal **E**: cross-sectional **F**: cross-sectional **G**: longitudinal **H**: cross-sectional **I**:mixed longitudinal J: cross-sectional K: cross-sectional L: mixed longitudinal M: cross-sectional N: longitudinal O: cross-sectional <u>Setting and Country</u>: United Kingdom <u>Source of funding:</u> Not reported	**B**: 53 **C**: 266 D: 46 E: 105 F: 78 G: 450 H: 49 I: 88 J: 24 K: 44 L: 37 M: 50 N: 60 O: 62 <u>*Sex*</u>*:* **A**: NR **B**: NR **C**: NR **D: NR** **E: NR** **F: 59% Male** **G: 100% Male** **H: 42% Male** **I: NR** **J: 100% Male** **K: 59% Male** **L: 42% Male** **M: NR** **N: 80% Male** **O: 65% Male** Groups comparable at baseline? Unclear	(17.2) → HP + A (102.5) M: 1) L → HP + SP (36-78) 2) L → HP + SP (24-36) N: L (2) → SP (8) → L/N (18) → HP + A (104) O: L (5.8) → HP (29.1) → SP (32.3) *Number is age in months* *L=lip* *L/N: lip/nose* *A= alveolus* *(H) (S) P = (hard) (soft) palate* *vL = von Langenbeck* *(P) (V) MF = (palatal) (vomerine) mucoperiosteal flap*	*palate* *vL = von Langenbeck* *(P) (V) MF = (palatal) (vomerine) mucoperiosteal flap*			
Nollet 2005 [individual study characteristics	SR and meta-analysis of [RCTs / cohort / case-control studies] *Literature search up to December*	Inclusion criteria SR: Exclusion criteria SR: *XX studies*	Describe intervention: **Early palatal closure (soft and hard) <3 years** **(E)** Not reported per study	Describe control: **Late palatal closure (soft and hard) >3 years** **(L)** Not reported per study	<u>End-point of follow-up</u>: **NR** <u>For how many participants were no complete outcome</u>	<u>GOSLON score</u> (1 very good, 5 very poor) GOSLON score: E: 2.9±0.4 L: 2.3 ± 0.2	<u>Facultative</u>: Brief description of author's conclusion: well-designed randomized clinical trials are required for further investigation of the

deduced from [1st author, year of publication]] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	*2003* **A**: Mars 1987 **B**: Mars 1992 **C**: Noverraz 1993 **D**: Hathorn 1996 **E**: Atack 1998 **F**: Leonard 1998 **G**: Johnson 2000 **H**: Morris 2000 **I**:Williams 2001 J: Williams 2001 K: DiBiase 2002 L: Pigott 2002 M: Chan 2003 N: Choudhary 2003 O: Bongaarts 2004 <u>Study design</u>: RCT [parallel / cross-over], cohort [prospective / retrospective], case-control <u>Setting and Country</u>: the Netherlands <u>Source of funding:</u> Not reported	*included* <u>Important patient characteristics at baseline</u>: *Number of patients; characteristics important to the research question and/or for statistical adjustment (confounding in cohort studies); for example, age, sex, bmi, ...* <u>N, mean age</u> **A**: 115 **B**: 149 **C**: 68 *D: 32* E: 46 F: 70 G: 54 H: 35 I: 452 J: 18 K: 44 L: 38 M: 40 N: 25 *O: 41* <u>*Sex*</u>*:NR* Groups comparable at			<u>data available?</u> (intervention/control) **NR**	P=0.002 % GOSLON score 4 and 5: E: 29 ± 14 L: 4 ± 4 P=0.002	optimal timing for palatal closure, since the methodological quality of the included studies is low and heterogeneity between studies is high. Level of evidence: GRADE low

		baseline? Unclear					
Yang 2010 [individual study characteristics deduced from [1st author, year of publication]] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of [RCTs / cohort / case-control studies] *Literature search up to November 2007* **A**: Ross 1987 **B**: Molsted 1992 **C**: Smahel 1993 **D**: Rohrich 1996 **E**: Silva Filho 2001 **F**: Silvera 2003 **G**: Corbo 2005 **H**: Stein 2007 **I**:Holland 2007 Study design: RCT **A**: cross-sectional **B**: cross-sectional **C**: cross-sectional **D**: cross-sectional **E**: cross-sectional **F**: longitudinal **G**: longitudinal **H**: longitudinal **I**: cross-sectional Setting and Country: Taiwan Source of funding: No funding	Inclusion criteria SR: Exclusion criteria SR: *XX studies included* Important patient characteristics at baseline: *Number of patients; characteristics important to the research question and/or for statistical adjustment (confounding in cohort studies); for example, age, sex, bmi, ...* Number of patients: **A**: 380 **B**: 95 **C**: 51 D: 44 E:75 F: 21 G: 21 H: 43 I: 82 **….** *Sex:*	Describe intervention: **A**: L (?) → SP + HP (<20) **B**: L (3) → SO (9) → HP (108) (V) (P)MF **C**: 1) L(6) → SP + HP (12) 2) L (6) → SP + HP (<24) **D**: L (3) → SP + HP (11) **E**: L (9) → SP + HP (19) **F**: L (3-11) → SP + HP (18) **G**: SP (3) → L + HP (6) → A (120) **H**: L (4) → SP (23) → HP (86) → A (127) **I**: L (?) → SP (12) → HP (84) *Number is age in months* *L=lip* *L/N: lip/nose* *A= alveolus* *(H) (S) P = (hard) (soft) palate* *vL = von Langenbeck* *(P) (V) MF = (palatal) (vomerine) mucoperiosteal flap* *? = unclear*	Describe control: **A**: L (>) → SP (?) → HP (<11-108) **B**: - **C**: L (5) → SP + HP (12) **D**: L (3) → SP (11) → HP (49) **E**: L + SP (5.5) → HP (20) **F**: L (5&8) → SP (18) → HP (72) **G**: L (4) → SP + HP (23) → A (150) **H**: L (?) → SP + HP (12) **I**: - *Number is age in months* *L=lip* *L/N: lip/nose* *A= alveolus* *(H) (S) P = (hard) (soft) palate* *vL = von Langenbeck* *(P) (V) MF = (palatal) (vomerine) mucoperiosteal flap* *? = unclear*	End-point of follow-up: (in years) **A**: 15 **B**: 8-10 **C**: 10 **D**: 17-18 **E**: 7 **F**: 12 **G**: 12 **H**: 18 **I**: adults …. For how many participants were no complete outcome data available? (intervention/control) Not reported in all studies (however, since the studies were cross-sectional or retrospective in nature, this is not applicable)	Maxillary growth Two studies evaluate the effect of stage of palate repair on the length of the maxilla. One study concludes that the stage of palate repair does not affect the length of the maxilla, whereas the other study opposes this view. Eight studies evaluate the effect of stage of palate repair on the protrusion of the maxilla. Seven studies conclude that the stage of palate repair does not affect the protrusion of the maxilla, whereas one study opposes this view. The difference in the palate repair timing between the stages varies considerably between studies (1-96 months).	Facultative: Pooling of results is not possible due to the heterogeneity of included studies. Furthermore, definitive conclusions about maxillary growth connot be drawn based on the results of current literature. Level of evidence: GRADE (very low

		A:100 % Male **B**: 58% Male **C**: 86% Male D: 59% Male E: 60% Male F: 62% Male G: 57% Male H: 67% Male I: 59% Male **….** Groups comparable at baseline? Unclear					

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series]

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Bartzela, 2010	Type of study: retrospective observational Setting: outpatients Country: the Netherlands Source of funding: not reported	Inclusion criteria: 1) patients with bilateral cleft lip and palate who underwent surgery in one of the participating centers 2) Caucasian ethnic background 3) no associated congenital malformations, syndromes or mental retardation 4) treatment from birth onward in the same center 5) born before 1996 Exclusion criteria: - N total at baseline: A: 56 B: 37 C: 107 Important prognostic factors[2]: - Groups comparable at baseline? unclear	Describe intervention (treatment/procedure/test): Center A: Birth: infant orthopaedics (1.5 yrs), nose plugs (2.5 yrs) 3 months: bilateral lip adhesion 6 months: soft palate closure (center's own technique) 18 months: definitive bilateral lip and nose repair (center's own technique) 8 years: one-side alveolar bone grafting 8.5 years: hard palate closure with alveolar bone grafting of second side Center B: Birth: infant orthopaedics with extraoral strapping (9.2 months) 7 months: one-stage lip closure (modified Manchester)	Describe control (treatment/procedure/test): See Intervention column, 3 different center protocols were compared	Length of follow-up: Until at least 11 years of age Loss-to-follow-up: 23/204 (11%) at 12 years Incomplete outcome data: 23/204 (11%)	Outcome measures and effect size (include 95%CI and p-value if available): Bauru-BCLP yardstick score: assesses dental arch relationship Linear regression analysis for increments at different age intervals. Center C is reference category 6-12 years Center B: 10% (95% CI: -0.4% - 214%), p=0.041 Center A: 4% (95% CI: -7% - 15%) p=0.53 9-12 years Center B: 13% (95% CI: 3% - 27%) p=0.009 Center A: 6% (95% CI: -3% - 16%) p=0.21 6 – 9 years Center B: -4% (95% CI: -11% - 3%) Center A: -.2% (95% CI: -7% - 8%) p=0.95	Author's conclusion: Despite different treatment protocols, dental arch relationships in final scores at age 9 and 12 years. Delaying hard palate closure and employing infant orthopaedics did not appear to be disadvantageous in the long run. Premaxillary osteotomy employed in center B appeared to be associated with less favourable development of the dental arch relationship between 9 and 12 years.

			14 months: Von Langenbeck soft palate closure 10 years: hard palate closure and bilateral alveolar bone grafting and osteotomy of the premaxilla <u>Center C:</u> 3 months: straight-line lip closure and hard palate closure on one side 5 months: straight-line lip closure and hard palate closure on the other side 19 months: Von Langenbeck soft palate closure 10 years: bilateral alveolar bone grafting				
Friede 2001	Type of study: retrospective observational Setting: outpatients (2 centers) Country: Sweden and Denmark Source of funding: not reported	<u>Inclusion criteria</u>: 1) nonsyndromic patients with unilateral cleft palate treated in one of the two participating centers <u>Exclusion criteria</u>: - <u>N total at baseline</u>: Early closure (E): 29 Delayed closure (D): 30 <u>Important prognostic factors</u>[2]: *Sex:* *E: 83% M* *C: 77% M*	Describe intervention (treatment/procedure/test): early hard palate closure: vomer flap procedure at 3 months together with lip closure and then a pushback procedure at 22 months	Describe control (treatment/procedure/test): late hard palate closure: velum repair at 8 months and then hard palate closure at 8.5 years together with bone grafting of alveolar cleft	<u>Length of follow-up</u>: Until 16 years of age <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Maxillary growth: (Lateral röntgencephalograms) Children that had undergone early hard palate closure generally had more retrognathic faces (more maxillary retrusion and thus less facial convexity) than those who underwent late hard palate closure. The ANB angle only became negative in the patients who	All E surgeries performed in one center and all D surgeries perfomed in another center.

		Groups comparable at baseline? unclear				underwent late hard-palate closure and only in the older (14-16 years) age groups. The anterior vertical development of the maxilla was most satisfactory in patients who underwent delayed closure of the hard palate. Overall, the midfacial development was more favourable in the delayed hard palate closure group.	
Fudalej, 2011	Type of study: prospective observational Setting: outpatients Country: Poland, Czech Republic, the Netherlands Source of funding: non-commercial	Inclusion criteria: 1) children with non-syndromic complete unilateral cleft lip and palate with and without simonart's bands treated at the participating hospitals in Warsaw and Nijmegen Exclusion criteria: - N total at baseline: Intervention: 61 Control: 97 Important prognostic factors[2]: *For example* *age ± SD:* *I:* 11.2 years *C:* 8.7 years *Sex:*	Describe intervention (treatment/procedure/test): Warsaw protocol: 6-12 months: one-stage lip, soft and hard palate closure 9-11 years: bone grafting	Describe control (treatment/procedure/test): Nijmegen protocol: 0-6 months: infant orthopaedics 6-12 months: lip closure (Millard) 12-14 months: soft palate closure; Modified von Langenbeck 9-11 years: bone grafting and hard palate closure	Length of follow-up: Until 11 years Loss-to-follow-up: unclear Incomplete outcome data: unclear	Outcome measures and effect size (include 95%CI and p-value if available): EUROCRAN index used to grade dental arch relationship and palatal morphology of dental casts Dental arch: grade 1 (best) to 4 (worst) I: 2.58 (95% CI: 2.52 – 2.82) C: 1.97 (95% CI: 1.79 – 2.15) P<0.001 Palatal morphology: grade 1 (good) to 3 (worst) I: 1.79 (95% CI: 1.68 – 1.90) C: 1.96 (95% CI: 1.85 – 2.07) P=0.047	Author's conclusion: The dental arch relationship following one-stage repair was less favourable than the outcome of three-stage repair. The palatal morphology following one-stage repair, however, was more favourable than the outcome of three-stage repair

		I: 67% M *C: 77% M* Groups comparable at baseline? yes					
Goodacre 2003	Type of study: prospective observational Setting: outpatients (4 centers) Country: United Kingdom Source of funding: not reported	Inclusion criteria: 1) patients born in one of the participating hospitals with cleft palate or healthy control patient born around the same time Exclusion criteria: 1) multiple births 2) gestational age <36 months 3) birth weight <2.25kg 4) presence of any syndrome N total at baseline: Early lip closure: 34 (42 in experiment 3) Late lip closure: 29 (43 in experiment 3) Healthy controls: 80 Important prognostic factors[2]: *Not reported* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): Early lip closure At median 4.5 days (range 0-19)	Describe control (treatment/procedure/test): Late lip closure At median 18 days (range 2-152)	Length of follow-up: 12 months Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Static attractiveness as rated by surgeons postoperatively (experiment 1) Mean difference (early – late): -0.10 (95% CI: -2.3 – 0.44, p=0.54) Static attractiveness as rated by laypersons postoperatively (experiment 2) Mean difference (early – late): -0.11 (95% CI: -0.42 – 0.11, p=0.47) Dynamic attractiveness as rated by laypersons at 12 months (experiment 3) Mean difference (early – late): 0.08 (95% CI: -0.11 – 0.28, p=0.41)	
Grobbelaar 1994	Type of study: prospective observational Setting: outpatients (1	Inclusion criteria: 1) children with a cleft palate registered at the participating clinic Exclusion criteria:	Describe intervention (treatment/procedure/test): Palate closure perfomed	Describe control (treatment/procedure/test): Palate closure	Length of follow-up: Median 9.6 years (range 3-24) Loss-to-follow-up: 290 registered at clinic	Outcome measures and effect size (include 95%CI and p-value if available): Velopharyngeal insufficiency:	Other speech results except for velopharyngeal insufficiency not reported stratified by timing of operation.

	center) Country: South Africa Source of funding: not reported	 N total at baseline: Early closure: 77 Late closure: 107 Important prognostic factors[2]: *Not reported* Groups comparable at baseline?	before 6 months Dorrance: 13 Wardill: 14 Perko: 13 Furlow: 11 Von Langenbeck: 26	perfomed after 6 months Dorrance: 12 Wardill: 27 Perko: 6 Furlow: 9 Von Langenbeck: 47	37 never returned for surgery 50 never returned after their operation 19 attended only once Incomplete outcome data: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)	 Early closure: 4/77 Late closure: 9/107 P<0.05	
Gundlach 2013	Type of study: retrospective observational Setting: outpatients (3 centers) Country: Germany / United States of America Source of funding: no funding	Inclusion criteria: 1) non-syndromal patients with complete unilateral clefts of lip, alveolus and palate Exclusion criteria: - N total at baseline: One-stage closure (O): 35 (center A and B) Two stage closure (T): 50 (center C) Important prognostic factors[2]: *O: 7-9 year olds: 18* *15-17 year olds: 32* *T: 7-9 year olds: 18* *15-17 year olds: 17* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): Labioplasty at 3 months (Triangular Flap Method, modification on Tennison's Stencil Method) Veloplasty at 12-18 months (Two Flap Technique, modification of Veau's two-pedicled palatal flaps)	Describe control (treatment/procedure/test): Labioplasty at 6 months (Waveline procedure) Veloplasty At 15-18 months in center B (n=24) At 3 years in center A (n=26) (Intravelar Veloplasty according to Kriens)	Length of follow-up: Until the age of 7-9 years n=36 Until the age of 15-17 years n=49 Loss-to-follow-up: Not described Incomplete outcome data: Not described	Outcome measures and effect size (include 95%CI and p-value if available): Maxillary growth: Anterior cross-bites: Least often in center A At 7-9 years P<0.05 Posterior cross-bites: Most often in center B At 15-17 years P<0.05 Constricted palates (or dental arches): Highest rate in center C At 7-9 years P<0.05 Speech: Success rates:	Speech results published earlier (1987) and briefly mentioned in Discussion section

						Center A: 70% Center C: 74% p>0.05	
Landheer 2010	Type of study: retrospective observational Setting: outpatients (one center) Country: Netherlands Source of funding: not reported	<u>Inclusion criteria</u>: 1) all consecutive children treated for cleft (lip and) palate, born between January 1 1988 and December 31 1997, who received cleft palate repair at the Utrecht Medical Center <u>Exclusion criteria</u>: - <u>N total at baseline</u>: Early closure of hard palate(1-stage): 121 Late closure of hard palate (2-stage): 154 <u>Important prognostic factors</u>[2]: *Only reported for group as a whole:* *Age at last follow-up: 12.5 ± 7.3 years* *Sex: 58%M* *Syndrome: 56 (20%)* *Cleft type (Veau): I : 6%* *II: 34%* *III: 40%* *IV: 56%* Groups comparable at	Describe intervention (treatment/procedure/test): Soft and hard palate closure at 6-9 months (1-stage repair)	Describe control (treatment/procedure/test): Soft and hard palate closure at 6-9 months Hard palate closure by a modified von Langenbeck procedure at 4-7 years; when the speech therapist felt that the open hard palate may influence speech. (2-stage repair)	<u>Length of follow-up</u>: Median 9.3 years, IQR: 7.2 years <u>Loss-to-follow-up</u>: Not described <u>Incomplete outcome data</u>: Two subanalyses were performed due to incomplete data for some of the 275 patients (DNR): -among patients with cleft repair in 2 stages -among patients with recorded preoperative cleft width	Outcome measures and effect size (include 95%CI and p-value if available): <u>Fistula:</u> Odds ratio of fistula formation in 2-stage repair versus 1-stage repair: 2.3 (95% CI: 1.2 – 4.3)	All patients underwent the cleft palate repair in 2 stages, unless the operating surgeon considered the cleft narrow enough to close in 1 operation. Thus the patients undergoing 1-stage repair had a narrower cleft to start with → selection bias.

		baseline? Unclear					
Kirschner 2000	Type of study: retrospective observational Setting: oupatients (1 center) Country: United States of Amerika Source of funding: not reported	Inclusion criteria: 1) Veau class III unilateral cleft lip and palate who underwent palatoplasty at the participating center Exclusion criteria: 1) moderate or severe hearing loss 2) associated major craniofacial malformations 3) associated syndromes 4) palate repair included primary posterior pharyngeal flap 5) unintentional oronasal fistulas N total at baseline: Early repair: 40 Late repair: 50 Important prognostic factors[2]: *For example* *age ± SD:* *E: 8.3 ± 3.2* *L: 8.7 ± 3.0* *Sex: not reported* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): Palate closure at 3-7 months Modified Furlow technique	Describe control (treatment/procedure/test): Palate closure after 7 months Modified Furlow technique	Length of follow-up: Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): No significant difference between the groups in terms of : Resonance Nasal air emission Velopharyngeal function	
Klintö 2014	Type of study: prospective observational Setting:	Inclusion criteria: 1) patients with complete unilateral cleft palate patients 2) monolingual speakers	Describe intervention (treatment/procedure/test): 1) TSC:	Describe control (treatment/procedure/test): OSC	Length of follow-up: Until the age of 3 years Loss-to-follow-up: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Speech:	In two-stage palate closure all patients were operated in one center and randomized to late or early hard palate closure. One-stage palate

	outatients (2 centers) Country: Sweden Source of funding: not reported	of Swedish <u>Exclusion criteria</u>: 1) known malformations or syndromes <u>N total at baseline</u>: Two-stage palate closed (TSC): 9 Two-stage open (TSO): 9 One stage closed (OSC): 10 <u>Important prognostic factors</u>[2]: *Not reported* Groups comparable at baseline? Unclear	Early soft palate repair with lip closure at 4.6 months (Scandleft soft palate repair) Hard palate closure at 12 months (cranially based vomer flap) 2) TSO: Early soft palate repair with lip closure at 4.6 months (Scandleft soft palate repair) Hard palate closure at 12 months (cranially based vomer flap)	Lip repair or adhesion at 3-6 months One stage palate repair at 14 months (intravelar veloplasty)	<u>Incomplete outcome data</u>: Not reported	Correct consonats, adjusted for age: Median (range) TSC: 76% (14-91%) TSO: 59% (3-92%) OSC: 86% (41-97%) P=0.06 Active cleft speech characteristics: Median (range) TSC: 16% (3-51%) TSO: 29% (4-64%) OSC: 6% (0-26%) P=0.015 Total number of phonological processes Median (range) TSC: 21 (6-72) TSO: 35 (9-76) OSC: 13 (4-44) P=0.033 Number of different types of phonological processes: Median (range) TSC: 8 (3-12) TSO: 9 (4-16) OSC: 6 (3-13) P=0.18 Hypernasality: lowest prevalence in OSC group, highest in TSO group (p=0.013) No significant differences in hyponasality or nasal air leakage between groups.	closure patients operated in another center. None of the patients received speech therapy

						Audiometry: Not reported	
O'Gara 1994	Type of study: prospective observational Setting: outpatients (1 center) Country: United States of Amerika Source of funding: not reported	Inclusion criteria: 1) babies born with non-syndromic complete unilateral cleft palate Exclusion criteria: - N total at baseline: Early closure (E): 11 Late closure (L): 12 Important prognostic factors[2]: *For example* *age ± SD:* *not reported* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): Palatoplasty before 12 months Techniques: von Langenbeck (55%), Wardill, V-Y pushback (27%), with or without levator reconstruction	Describe control (treatment/procedure/test): Palatoplasty after 12 months Techniques: von Langenbeck (67%), Wardill (17%), V-Y pushback , with or without levator reconstruction	Length of follow-up: Babies followed from 5 – 35 months Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Speech: Frequency of oral stops significantly higher in the early closure group after 11 months (p=0.02): 14-18 months E: 45±8 L: 15 ± 4 30-35 months: E: 62 ± 5 L: 34 ± 6 Frequencies of other speech features do not differ significantly between groups.	Each baby's readiness for palatoplasty was evaluated on an individual basis by the plastic surgeon of the team. The goal was to operate as early as possible, but with the greates chance of success.
Randag 2014	Type of study: retrospective observational Setting: outpatients Country: the Netherlands Source of funding: not reported (no financial conflict of	Inclusion criteria: Exclusion criteria: N total at baseline: One-stage closure (O): 24 Two-stage closure (T): 24 Important prognostic factors[2]: *Not reported* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): one-stage palate closure at 10 months lip closure at 3-6 months, soft palate was closed using intravelar veloplasty. Hard palate was closed using the von Langenbeck technique: a	Describe control (treatment/procedure/test): two-stage palate closure at 11 and 18 months lip closure at 3-6 months, soft palate was closed using intravelar veloplasty. Hard palatum was closed using the von Langenbeck technique:	Length of follow-up: Until 2.5 years of age Loss-to-follow-up: Only reported for one-stage closure group: 27/51 13: cleft of soft palate only 3 lost to follow-up 9 different mother tongue 15 insufficient language comprehension Incomplete outcome data: Not described	Outcome measures and effect size (include 95%CI and p-value if available): Speech: Articulation: number of correctly pronounced initial consonants: O: 9.7±4.5 T: 7.0 ± 3.8 P=0.03 Inadequate language production:	

	interest of authors reported either)		two-flap palatoplasty or a hybrid palatoplasty depending on the width of the cleft.	a two-flap palatoplasty or a hybrid palatoplasty depending on the width of the cleft		O: 1/24 (4%) T: 3/24 (13%) P=0.61 Resonance problems: O: 6/24 (26%) T: 8/24 (33%) P=0.75 Nasal air emissions: O: 12/24 (53%) T: 15/24 (63%) P=0.56 Good intelligibility: O: 10 (44%) T: 3 (19%) P=0.13 <u>Short term complications</u>: Postoperative haemorrhage O: 1/24 T: 4/24 p>0.05 No difference in other short term complications (DNR)	
Richard 2006	Type of study: randomized controlled trial Setting: outpatients Country: United Kingdom Source of funding: non-commercial	<u>Inclusion criteria</u>: 1) children with non-syndromic unilateral cleft palate 2) age 3-60 months <u>Exclusion criteria</u>: - <u>N total at baseline</u>: I: Posterior-anterior (P-A): 23 C: Anterior-posterior (A-	Describe intervention (treatment/procedure/test): Posterior – anterior order of palate closure (The anterior operation consisted of a lip repair by Millard rotation advancement, a nasal correction using the	Describe control (treatment/procedure/test): Anterior-posterior order of palate closure: (The anterior operation consisted of a lip repair by Millard rotation advancement, a nasal correction using the	<u>Length of follow-up</u>: Until the age of 4-6 years <u>Loss-to-follow-up</u>: I: 6/23 (26%) 1 died, 5 lost contact C: 4/24 (17%) 1 syndromic, 3 lost contact <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): <u>Maxillary growth:</u> No significant differences in cephalometric measurements between groups <u>Speech:</u>	No power analysis for sample size is presented. Bias due to imprecision?

		P): 24 <u>Important prognostic factors[2]</u>: *For example* *age* *I: 18.7 months* *C: 18.8 months* *Sex:* *I: 67% M* *C: 46% M* Groups comparable at baseline? Yes	McComb procedure and a hard palate repair by a single layer vomerine flap. The posterior operation consisted of a soft palate repair with medial von Langenbeck incisions. The two operations were undertaken 3 months apart with the first operation at 19 months of age.)	McComb procedure and a hard palate repair by a single layer vomerine flap. The posterior operation consisted of a soft palate repair with medial von Langenbeck incisions. The two operations were undertaken 3 months apart with the first operation at 19 months of age.)		No significant differences in speech between groups. <u>Hearing loss:</u> No significant differences in hearing status between groups. <u>Fistula formation:</u> No significant differences in prevalence of symptomatic fistulae between groups.	
Rohrich 1996	Type of study: retrospective observational Setting: outpatients (1 center study) Country: United States of America Source of funding: not reported	<u>Inclusion criteria</u>: 1) patients with unilateral and bilateral cleft of the alveolus and secondary palate born during the perion 1960 – 1969 and treated at the Oxfor Plastic Surgery Department <u>Exclusion criteria</u>: - <u>N total at baseline</u>: Early closure (E): 21 Late closure (L): 23 <u>Important prognostic factors[2]</u>: *For example* *age (range):* *E: 17 (15-19)* *L: 18 (14-21)* *Sex:* *E: 57% M*	Describe intervention (treatment/procedure/test): Cleft repair (Miljard rotation-advancement) at 3.4 months. Soft palate repair plus hard palate repair at 11 months using the modified three- or four-flap Wardill-Kilner procedure.	Describe control (treatment/procedure/test): Cleft repair (Miljard rotation-advancement) at 3.4 months. Soft palate repair at 11 months using short Veau flaps Second-stage hard palate closure with a vomer flap at 49 months.	<u>Length of follow-up</u>: Average 12.8 years <u>Loss-to-follow-up</u>: 91 patient operated between 1960 – 1969. In 1996 68 completed and returned questionnaire. 44 were randomly selected for interview and examination. <u>Incomplete outcome data</u>: Not described	Outcome measures and effect size (include 95%CI and p-value if available): <u>Speech:</u> Articulation errors: E: 5% L: 10% P not reported Nasal resonance: E: 30% L: 81% P<0.001 Hyponasality: More in L group (p<0.01, DNR) Nasal emission: No difference between groups (DNR) Speech intelligibility impaired:	All operative procedures in both groups were performed by the same plastic surgeon.

		L: 61 % M *Bilateral cleft type:* *E: 29%* *L: 30%* Groups comparable at baseline? Yes				E: 5% L: 35% P<0.02 Normal articulation patterns: no difference between groups (DNR) <u>Maxillary growth:</u> arch width: no difference between groups (DNR) anterior maxillary collapse: no difference between groups (DNR) posteriorly a relatively normal relationship at the molar level without maxillary collapse: no difference between groups (DNR) Maxillary hypoplasia: no difference between groups (DNR) Midfacial hypoplasia: no difference between groups (DNR) <u>Hearing:</u> No significant difference between E and L Tendency for severe hearing loss in L (DNR, p<0.50) <u>Complications:</u> Overall fistulas	

						E: 29% L: 61% P<0.05 Persistent fistula E: 5% L: 35% p<0.05 Overall palatal fistulas in unilateral cleft types: E: 27% L: 69% P<0.05	
Da Silva Filho 2000	Type of study: retrospective observational Setting: outpatients (2 centers) Country: Brazil Source of funding: not reported	Inclusion criteria: 1) patients with unilateral cleft palate treated in one of the participating centers Exclusion criteria: - N total at baseline: Early palate closure (E): 22 Delayed palate closure (D): 53 Important prognostic factors[2]: *Sex:* *I: 55% M* *D: 62% M* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): early palate closure lip repair at 3-27 months and palate repair at 12-44 months. (The exact type of surgery was not reported.)	Describe control (treatment/procedure/test): late hard palate closure: lip and soft palate repair at 5.5 months hard palate repair at 20 months (The exact type of surgery was not reported.)	Length of follow-up: Age 4-7 years Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Maxillary growth: (lateral röntgencephalograms) No significant difference between groups in any of the cephalometric measurements	All E surgeries performed in one center and all D surgeries perfomed in another center.
Trotman 1996	Type of study: retrospective observational	Inclusion criteria: 1) unilateral cleft palate patients treated in one of	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	Length of follow-up: Until the age of 10 years	Outcome measures and effect size (include 95%CI and p-value if available):	All O surgeries performed in one center and all T surgeries performed in

	Setting: outpatients Country: United States of America Source of funding: not reported	the two participating centers <u>Exclusion criteria</u>: 1) other congenital abnormalities 2) previous orthodontic treatment <u>N total at baseline</u>: One-stage (O): 43 Two-stage (T): 43 <u>Important prognostic factors</u>[2]: *Sex:* *O: 56% M* *T: 56% M* Groups comparable at baseline? Unclear	primary alveolar bone grafting with definite lip repair at 4-6 months and hard and soft palate repair at 6-12 months.	triangular flap lip repair at 3 months and staged surgeries of soft and hard palate completed by 18 months with no alveolar bone grafting. were studied.	<u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	<u>Maxillary growth:</u> (Lateral cephalometric radiographs) Patients in the center that used one-stage palatal closure had faces that were on average less maxillary protrusive compared with the faces of the non-grafted patients (intervention) other center. However in the two-stage center the mandible compensated for the maxillary protrusion by downward and backward rotation. Overall, a similar alveolar arch relationship was noted in both groups, although in the one-stage closure group the anterior facial height increased.	another center.
Wada 1990	Type of study: randomized controlled trial Setting: outpatients Country: Japan Source of funding: no funding	<u>Inclusion criteria</u>: 1) patients with unilateral or bilateral cleft palate <u>Exclusion criteria</u>: <u>N total at baseline</u>: One stage closure: Unilateral cleft: 14 Bilateral cleft: 8 Two stage closure: Unilateral cleft: 16 Bilateral cleft: 7	Describe intervention (treatment/procedure/test): Lip repair at 5 months by Tennison's procedure Mucoperiosteal palatal pushback procedure at 20 months (one-stage closure)	Describe control (treatment/procedure/test): Lip repair at 5 months by Tennison's procedure Primary veloplasty at 20 months Double overlapping palatal hingeflap	<u>Length of follow-up</u>: Until the age of 10 years <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not described	Outcome measures and effect size (include 95%CI and p-value if available): <u>Maxillary growth:</u> In the unilateral cleft palate patients the maxillary growth of the patients who underwent the two-stage closure was comparable to those of the non-cleft controls regarding depth and height of the maxilla, while the one-stage closure	

		Important prognostic factors[2]: *Not reported* Groups comparable at baseline? Unclear		procedure at 5 years 10 months (two-stage closure)		patients had aberrant maxillary development. For the patients with bilateral clefts, the maxillary growth was similar in the one-stage and two-stage palatal closure groups.	
Williams 2009	Type of study: RCT Setting: outpatients 91 center) Country: United States of Amerika and Brazil Source of funding: non-commercial	Inclusion criteria: 1) patients with cleft lip at palate, of age and in good health for surgery Exclusion criteria: 1) family and patient did not show up for scheduled surgery date 2) condition that could interfere with speech development N total at baseline: Early surgery (E): 181 Late surgery (L): 195 Important prognostic factors[2]: *Not reported* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): Palate closure at 9-12 months of age Spina – Furlow=35 Millard – Furlow= 43 Spina – von Langenbeck= 51 Millard – von Langenbeck= 52	Describe control (treatment/procedure/test): Palate closure at 15-18 months of age Spina – Furlow=48 Millard – Furlow= 47 Spina – von Langenbeck= 46 Millard – von Langenbeck= 54	Length of follow-up: Until at least the age of 4 years Loss-to-follow-up: After surgery 31/498 (6%) Reasons not described Incomplete outcome data: Not described	Outcome measures and effect size (include 95%CI and p-value if available): Odds ratio (OR) Speech: Hypernasality: E: 79% L: 73% OR (E versus L): 1.46 (95% CI: 0.84 – 2.54, p=0.12) Nasal air emission: E: 57% L: 54% OR (E versus L): 1.16 (95% CI: 0.72 – 1.85, p=0.49) Fistula formation: E: 44/181 L: 37 / 195 OR (E versus L): 1.37 (95% CI: 0.84 – 12.22, p=0.21)	Method of randomization and (presence or absence of) blinding unclear. Statistical analyses presented very adequately.
Ysunza 1998	Type of study: prospective observational Setting: outpatients	Inclusion criteria: 1) unilateral complete cleft of primary or secondary palate, patient normal in all other respects	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	Length of follow-up: Until the age of 4 years Loss-to-follow-up: 580 cleft palate cases reviewed	Outcome measures and effect size (include 95%CI and p-value if available): Speech:	Only included patients with cleft palate width I or II. Patients with postoperative fistulae excluded from study group.

	Country: Mexico Source of funding: not reported	2) cleft palate width I or II 3) patients were in adequate conditions for surgical repair at 6 months 4) surgery performed by standard surgical routine of clinic 5) speech evaluation performed at 48 months 6) underwent videopharyngoscopy and multiview videofluorocopy 7) linguistic development within normal limits 8) normal hearing as demonstrated by pure tone audiometry 9) maxillofacial growth evaluation performed at 48 months of age <u>Exclusion criteria</u>: 1) patients with postoperative fistulae <u>N total at baseline</u>: Early closure (E): 41 Late closure (L): 35 <u>Important prognostic factors</u>[2]: *Sex:* *I: 46% M* *C: 51% M* Groups comparable at baseline? Unclear	Minimal incision palatopharyngoplasty at 6 months of age	Minimal incision palatopharyngoplasty at 12 months of age	76 patients met all the inclusion criteria <u>Incomplete outcome data</u>: Not decribed	Articulation development below normal limits for patient's age in all cases. No significant difference between groups (DNR) <u>Maxillary growth:</u> No significant differences in maxillary or cephalometric parameters between the groups (DNR) Both group had anterior maxillary collapse but normal development of the posterior maxilla (DNR)	
Zemann	Type of study:	<u>Inclusion criteria</u>:	Describe intervention	Describe control	<u>Length of follow-up</u>:	Outcome measures and	All O surgeries performed in

2011	retrospective observational Setting: outpatients (2 centers) Country: Austria, Slovenia Source of funding: not reported	1) children with unilateral cleft palate treated in one of the participating centers Exclusion criteria: - N total at baseline: One-stage closure (O): 22 Two-stage closure (T): 32 Important prognostic factors[2]: *Sex:* *O: 59% M* *C: 66% M* Groups comparable at baseline? Unclear	(treatment/procedure/test): one stage palate closure: lip repair at 3 months by Millard one-stage palatal closure within 12 months by Veau	(treatment/procedure/test): two-stage palate closure: lip repair within 6 months by Tennison-Randall, soft palate repair at 12 months by intravelar velaplasty hard palate repair at 30 months by Veau	Age of 6-10 years Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	effect size (include 95%CI and p-value if available): Maxillary growth: (Lateral röntgencephalograms) no statistically significant difference in cephalometric parameters between the patients undergoing one-stage versus two-stage palate closure. However, in the one-stage closure center there was considerably normal saggital facial growth, with tendency to forward growth of the mandible. In the two-stage closure group there was a slight decrease in sagittal maxillary growth and mandibular growth with unchanged alveolar arch relation.	one center and all T surgeries perfomed in another center.

Table of quality assessment for systematic reviews of RCTs and observational studies

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Liao 2006	Yes	Yes	No	Yes	Not applicable	Yes	No	No	No
Nollet 2005	Yes	Yes	No	Yes	Unclear	No	Unclear	No	No
Yang 2010	Yes	Yes	No	Yes	Not applicable	Yes	No	No	No

1. Research question (PICO) and inclusion criteria should be appropriate and predefined
2. Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched
3. Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons
4. Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported
5. Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)
6. Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table etc.)
7. Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I^2)?
8. An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.
9. Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a “yes,” source of funding or support must be indicated for the systematic review AND for each of the included studies.

Risk of bias table for intervention studies (randomized controlled trials)

Study reference (first author, publication year)	**Describe method of randomisation**[1]	**Bias due to inadequate concealment of allocation?**[2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?**[4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?**[5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?**[6] (unlikely/likely/unclear)
Richard 2006	"randomly allocated, stratified by block randomization"	Unclear	Unclear	Unlikely	Unclear	Unlikely	Unclear	Unclear
Wada 1990	"randomly assigned"???	Unclear	Unclear	Unlikely	Unclear	Unlikely	Unclear	Unclear
Williams 2009	"block randomization plan" ???	Unclear	Unclear	Unlikely	Unclear	Unlikely	Unclear	Unclear

1. Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
2. Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..
3. Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignment influences the process of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4. Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.
5. If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear
6. Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Bartzela, 2009	Unlikely	Unlikely	Unlikely	Unclear
Friede 2000	Unlikely	Unlikely	Unlikely	Unclear
Fudalej, 2011	Unlikely	Unlikely	Unlikely	Unclear
Goodacre 2003	Unlikely	Unlikely	Unlikely	Unclear
Grobbelaar 1994	Unlikely	Unlikely	Unlikely	Unclear
Gundlach 2013	Unlikely	Unlikely	Unlikely	Unclear
Kirschner 1999	Unlikely	Unlikely	Unlikely	Unclear
Klintö 2014	Unlikely	Likely	Unlikely	Unclear
Landheer 2010	Likely	Unlikely	Unlikely	Likely
O'Gara 1994	Likely	Unlikely	Unlikely	Likely
Randag 2014	Unlikely	Likely	Unlikely	Unclear
Rohrich 1996	Unlikely	Unlikely	Unlikely	Unclear
Da Silva Filho 2000	Unlikely	Likely	Unlikely	Unclear
Trotman 1996	Unlikely	Unlikely	Unlikely	Unclear
Ysunza 1998	Unlikely	Likely	Unlikely	Unclear
Zemann 2011	Unlikely	Likely	Unlikely	Unclear

Table of excluded studies (exclusion after assessment of full text).

Author and year of publication	Reason for exclusion
Bartzela, 2011	Does not meet selection criteria (does not answer research question, compares center protocols, not surgical techniques).
Enemark, 1993	Does not meet selection criteria (palatum durum)
Flinn, 2005	Does not meet selection criteria (does not answer research question, compares center protocols, not surgical techniques).
Flores, 2008	Does not meet selection criteria (none of the relevant outcome measures reported)
Grobbelaar, 1994	Does not meet selection criteria (does not answer research question).
Hassan, 2005	Does not meet selection criteria (follow-up too short)
Holtmann, 1984	Does not meet selection criteria (follow-up too short)
Karling, 1998	Does not meet selection criteria (does not answer research question).
Kitagawa, 2003	Does not meet selection criteria (palatum durum)
Latham, 2007	Does not meet selection criteria (more of a timing than technique issue)
Lee, 2013	Does not meet selection criteria (palatum durum)
Leenstra, 1996	Does not meet selection criteria (follow-up too short)
Maggiuli, 2014	Does not meet selection criteria (outcome: maxillary growth, follow-up: 6 months postoperatively; too short to draw conclusions regarding maxillary growth)
Meazzini, 2008	Does not meet selection criteria (does not answer research question, compares center protocols, not surgical techniques).
Mølsted, 1993	Does not meet selection criteria (palatum durum)
Nasser, 2008	Does not meet selection criteria (palatum durum)
Nollet, 2007	Does not meet selection criteria (does not answer research question, compares center protocols, not surgical techniques).
Rose, 2001	Does not meet selection criteria (none of the relevant outcome measures reported)
Rossell-Perry, 2014	Does not meet selection criteria (describes uvular repair, not palatal repair)

Shaw, 1992	Does not meet selection criteria (not an original article)
Sommerlad, 2001	Does not meet selection criteria (does not answer research question, does not compare different surgical techniques).
Syafrudin Hak, 2011	Does not meet selection criteria (compares orthopaedic treatment not surgical techniques)
Tanino, 1997	Number of participants too low (<10 per group)
Trotman, 1996	Does not meet selection criteria (palatum durum)
Wada, 1990	Does not meet selection criteria (palatum durum)
Wermker, 2013	Does not meet selection criteria (study includes adult patients)

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series]

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Palatum molle							
Abdel-Aziz, 2011	Type of study: randomized controlled trial Setting: outpatients Country: Egypt Source of funding: not reported	Inclusion criteria: 1) patients with cleft soft palate without any other congenital anomalities 2) treated at participating hospital Exclusion criteria: - N total at baseline: Intervention: 24 Control: 22 Important prognostic factors[2]: *For example* *age ± SD:* *total group: 1 year 4 months (range 11 months – 3 years)* *Sex:* *Total group: 45% M* Groups comparable at baseline? unclear	Describe intervention (treatment/procedure/test): V-Y pushback technique for cleft palate repair	Describe control (treatment/procedure/test): Furlow double-oppsing Z-plasty for cleft repair	Length of follow-up: At least 1 year Until the age of 4 years Loss-to-follow-up: 60 patients included in total (number per group not mentioned) Speech assessment performed in I: 24, C: 22 Reasons for this not reported Incomplete outcome data: See above	Outcome measures and effect size (include 95%CI and p-value if available): Means and standard deviations of the auditory perceptual assessment in both treatment groups Nasality I: 0.88 ± 1.01 C: 0.27 ± 0.55 P=0.035 Glottal Articulatiomn I: 1.13 ± 1.04 C: 0.5 ± 0.74 P=0.029 Phatyngealization of fricatives: I: 1.00 ± 1.18 C: 0.55 ± 1.1 P=0.10 Nasal emission: I: 0.92 ± 1.1 C: 0.36 ± 0.73 P=0.049 Speech intelligibility	Author's conclusion: The Furlow Z-plkasty is better than the V-Y pushback technique in repair of clefts involving the soft palate as it has a higher success rate regarding speech outcome and velopharyngeal closure; also it has a lower operative tima and blood loss.

						I: 1.08 ± 1.25 C: 0.59 ± 1.1 P=0.14 Fistulae: I: n=2 C: n=0 p-value not reported	
Carroll, 2013	Type of study: retrospective observational Setting: outpatients Country: United States of Maerica Source of funding: no funding	<u>Inclusion criteria</u>: 1) chart review of all children who had cleft palate repaired by surgeons in a pediatric otolaryngology practice at the participating hospital <u>Exclusion criteria</u>: 1) lost to follow-up 2) documented ossicular chain 3) ear canal or external ear malformations 4) documented sensoneurial hearing loss 5) Treacher-Collins syndrome 6) craniofacial microsomia <u>N total at baseline</u>: 4-flap: 70 Double reverse Z-plasty: 24 V to Y: 24 Von Langenbeck: 20 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *NR* *Sex:* *Total: 64% M* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): 1) double reverse Z-plasty (Furlow) 2) V- to Y pushback (Wardil-Kilner) 3) 4 flap (elsewhere called 2-flap) 4) von Langenbeck technique	Describe control (treatment/procedure/test): See Intervention column	<u>Length of follow-up</u>: Until the age of 6 years <u>Loss-to-follow-up</u>: unclear <u>Incomplete outcome data</u>: unclear	Outcome measures and effect size (include 95%CI and p-value if available): 6-year postoperative pure tone average (PTA) score (median, range) 1) 11.7 (3.3 – 43.3) 2) 10.0 (1.7 – 33.3) 3) 15.0 (6.6 – 40.7) 4) 15.0 (6.7 – 61.7) P=0.046 for nr 2 (Furlow) Number of ventilation tubes placed (median, range) 1) 2.0 (0-7) 2) 2.5 (1-6) 3) 4.0 (1-4) 4) 3.0 (1-4) P=0.005 for 4-flap (1) versus V-Y (3)	Author's conclusion: The majority of children developed normal hearing by 6 years with palatoplasty and routine tube insertion. Double reverse z-plasty was associated with best outcome, but is not ideal for hard palate clefts.

Grobbelaar, 1995	Type of study: Prospective observational Setting: outpatients Country: South Africa Source of funding: not reported	Inclusion criteria: 1) patients with cleft of only the soft palate Exclusion criteria: 1) submucous clefts 2) bifid uvulas N total at baseline: Dorrance repair: 25 Wardill repair: 41 Perko: 19 Furlow Z-plasty: 20 Langenbeck: 79 Important prognostic factors[2]: *Age (months) at repair:* Dorrance repair: 6.5 Wardill repair: 8.1 Perko: 4.0 Furlow Z-plasty: 5.7 Langenbeck: 6.2 *Sex:* Dorrance repair: 32%M Wardill repair: 22% M Perko: 58% M Furlow Z-plasty: 40% M Langenbeck: 47% M Groups comparable at baseline? No	Describe intervention (treatment/procedure/test): 1) Dorrance repair 2) Wardill repair 3) Perko 4) Furlow Z-plasty	Describe control (treatment/procedure/test): Von Langenbeck	Length of follow-up: 3-24 years (median 9.6 years) Loss-to-follow-up: Not reported Incomplete outcome data: Not reported Reasons (describe)	Outcome measures and effect size (include 95%CI and p-value if available): Normal Speech: Dorrance repair: 22/25 Wardill repair: 40/41 Perko: 19/19 Furlow Z-plasty: 20/20 Langenbeck: 75/79	The Furlow Z-plasty and Perko repair yielded the best speech results.
Hassan, 2007	Type of study: Prospective observational Setting: oupatients Country: Egypt	Inclusion criteria: 1) patients with nonsyndromic cleft palate Exclusion criteria: 1) submucous cleft N total at baseline:	Describe intervention (treatment/procedure/test): Kriens technique	Describe control (treatment/procedure/test): Wardill-Kilner V-Y pushback	Length of follow-up: 2 years Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): For the Kriens palatoplasty there was a -greater tendency for resolution of secretory otitis	Kriens technique in cleft palate patients confers better functional results regarding velopharyngeal competence and Eustachian tube function.

	Source of funding: not reported	Intervention: 33 Control: 37 Important prognostic factors[2]: *For example* *age ± SD:* *I: 19-23 months* *C: 19 – 21 months* *Sex:* *I: 52% M* *C: 41% M* Groups comparable at baseline? unclear				media in the early postoperative period -less time required for extrusion of the grommet tube -lower incidence of secretory recurrent otitis media -lower incidence of postoperative velopharyngeal incompetence -higher incidence of palatal fistula	
Henkel, 2003	Type of study: randomized trial Setting: outpatients Country: Germany Source of funding: not reported	Inclusion criteria: 1) patients with complete cleft of the soft palate Exclusion criteria: - N total at baseline: Intervention: 12 Control: 12 Important prognostic factors[2]: *For example* *age ± SD: NR* *Sex:* *NR* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): Wave-line technique for intravelar veloplasty Age: 12 months Labioplasty: 6 months Repair of hard palate: 4-5 years Primary bone grafting: 11-13 years	Describe control (treatment/procedure/test): Classic intravelar veloplasty Age: 12 months Labioplasty: 6 months Repair of hard palate: 4-5 years Primary bone grafting: 11-13 years	Length of follow-up: Until the age of 4 years Loss-to-follow-up: No loss to follow-up reported Incomplete outcome data: In wave-line technique group 2/12 (17%) were too playful for examination on sound tests	Outcome measures and effect size (include 95%CI and p-value if available): Mouth breathing: I: 4/12 C: 8/12 p-value not reported Compensatory grimacing when speaking I: 1/12 C: 8/12 P<0.05 (α-ι) test negative I: 12/12 C: 8/12 P<0.05 Sounds: /l/, /n/, /d/, /t/ normal I: 6/10 C: 3/12 P<0.05	Author's conclusion: Primary repair of clefts of the soft palate using the wave-line is straightforward, safe and easy. On the basis of the present results, this technique seems superior to the classic intravela veloplasty.

						Sounds /z/, /s/ normal I: 6/10 C: 4/12 P<0.05	
McWilliams, 1995	Type of study: retrospective observational Setting: outpatients Country: United States of America Source of funding: not reported	Inclusion criteria: 1) cleft subjects treated in the participating center (type of cleft not specified) Exclusion criteria: - N total at baseline: Furlow: 63 Wardill: 12 Vn Langenbeck: 6 Other: 2 Important prognostic factors[2]: *Cleft palate only (Veau class I-II)* Furlow: 23 Wardill: 1 Vn Langenbeck: 3 Other: 2 *Unilateral cleft lip and palate (Veau class III)* Furlow: 28 Wardill: 9 Vn Langenbeck: 3 Other: 0 *Bilateral cleft lip and palate (Veau class IV)* Furlow: 12 Wardill: 2 Vn Langenbeck: 0 Other: 0	Describe intervention (treatment/procedure/test): 1) Furlow (24/63 had soft palate closure at the same time as lip adhesion) (soft palaea closure at 7.7 ± 4.1 months) 2) Wardill (soft palate closure at 10.3 ± 4.3 months) 3) von Langenbeck (soft palate closure at 10.3 ± 4.3 months) 4) Other (not specified but including intravelar veloplasties (soft palate closure at 10.3 ± 4.3 months)	Describe control (treatment/procedure/test): Group 2, 3 and 4 were considered as control for group 1 (see description in Intervention columns)	Length of follow-up: Furlow: until 7.7 years Other groups: Until 9.5 years Loss-to-follow-up: Not applicable (retrospective study) Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Hypernasality score (0-4, with 4 worst) I: 0.32 ± 0.74 C: 1.30 ± 1.34 P=0.001 Phonation (0-3 with 3 severe phonation problems) I: 0.38 ± 0.81 C: 0.35 ± 0.7 P<0.05 Articulation I: 0.02 ± 0.13 C: 0.40 ± 0.99 P=0.01 Total speech scores I: 1.70 ± 2.12 C: 3.20 ± 3.04 P=0.04 Pharyngeal flaps I: 8/63 (13%) C: 9/20 (45%) P=0.001	Author's conclusion: Subjects who had a Furlow repairs were superior in measures of hypernasality, articulation and speech scores; and fewer pharyngeal flaps were required for Furlow subjects.

		Groups comparable at baseline? unclear					
Spauwen, 1992	Type of study: Randomized trial Setting: outpatients Country: the Netherlands Source of funding: not reported	Inclusion criteria: 1) Children with any form of cleft palate Exclusion criteria: - N total at baseline: Intervention: 10 Control: 10 Important prognostic factors[2]: *Mean age (years) at first examination* *I: 2.8* *C: 3.2* *Sex: NR* *Type of cleft:* *I:* *UCLP: 2* *BCLP: 2* *CP: 6* *C:* *UCLP: 3* *BCLP: 2* *CP: 5* Groups comparable at baseline? unclear	Describe intervention (treatment/procedure/test): Von Langenbeck	Describe control (treatment/procedure/test): Furlow	Length of follow-up: 3.5 years Loss-to-follow-up: None Incomplete outcome data: NR	Outcome measures and effect size (include 95%CI and p-value if available): Nasality: I: absent: 10 C: absent: 5, moderate: 4, severe:1 P<0.01 there were no significant differences in respect of articulatory skills, language comprehension, language production as well as hearing	The Furlow technique proved to be superior to the von Langebeck technique in terms of speech sound: at a mean age of 3.5 years nasality and nasal escape were absent in almost all cases. However, there were no significant differences in respect of articulatory skills, language comprehension, language production as well as hearing. Technically the Furlow technique is more difficult to perform, particularly in wide clefts.
Williams, 2009	Type of study: randomized controlled trial Setting: outpatients	Inclusion criteria: 1) patients with complete unilateral cleft lip and palate Exclusion criteria: 1) failure of family to return to	Describe intervention (treatment/procedure/test): Furlow	Describe control (treatment/procedure/test): Von Langenbeck	Length of follow-up: Until the age of 4 years Loss-to-follow-up: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Hypernasality: Odds ratio (OR) Von	Author's conclusion: In this study the Furlow double opposing Z-palatoplasty resulted in significantly better velopharyngeal function for

	Country: United States of America / Brazil Source of funding: non-commercial	the hospital at assigned operation date 2) conditions impairing speech development (hearing problems, mental retardation) N total at baseline: Intervention: 134 Control: 201 Important prognostic factors[2]: *Furlow:* *Spina: 83, Millard: 90* *Operation at 9-12 months: 78* *Operation at 15-18 months: 95* *Von Langenbeck* *Spina: 97, Millard: 106* *Operation at 9-12 months: 103* *Operation at 15-18 months:100* Groups comparable at baseline? Unclear			Incomplete outcome data: Not reported	Langenbeck versus Furlow 0.54 (95% CI: 0.31 – 0.95) p=0.014 Nasal air emission Odds ratio (OR) Von Langenbeck versus Furlow 0.72 (95% CI 0.45 – 1.15) p=0.12	speech than the von Langenbeck procedure as determined by the perceptual cul-de-sac test of hypernasality.
Witt, 1999	Type of study: prospective observational Setting: oupatients Country: United States of America Source of funding: not reported	Inclusion criteria: 1) patients with cleft palate treated at participating center Exclusion criteria: - N total at baseline: Intervention: 14 Control: 14 Important prognostic factors[2]: *For example* *Bilateral cleft lip and palate*	Describe intervention (treatment/procedure/test): Palatoplasty with intravelar veloplasty	Describe control (treatment/procedure/test): Palatoplasty without intravelar veloplasty	Length of follow-up: Until the age of 12 years or older Loss-to-follow-up: none Incomplete outcome data: none	Outcome measures and effect size (include 95%CI and p-value if available): Velopharyngeal rating (0: best – IV: worst) at 12 years of age Intervention O: 7 I: 4 II: 0 III: 3 Control	Author's conclusion: The intravelar veloplasty and nonintravelar veloplasty had similar distribution of perceptual speech ratings at both 6-year and 12-year or older speech evaluations

		I: 5/14 *C: 4/14* *Incomplete cleft of secondary palate* *I: 2/14* *C: 3/14* Groups comparable at baseline? Yes				0: 4 I: 10 II: 0 III: 0 p>0.05	
Lip adhesion							
Chowdri, 1990	Type of study: randomised trial Setting: outpatients Country: India Source of funding: not reported	<u>Inclusion criteria</u>: 1) patients with unilateral cleft lip <u>Exclusion criteria</u>: - <u>N total at baseline</u>: Intervention: 58 Control: 50 <u>Important prognostic factors</u>[2]: *For example ag:* *I: 3.1* *C: 2.9* *Sex: NR* *Complete cleft:* *I: 38/58 (73%)* *C: 30/50 (60%)* *Associated cleft palate:* *I: 39/58 (67%)* *C: 32/50 (64%)* Groups comparable at baseline? yes	Describe intervention (treatment/procedure/test): Rotation advancement	Describe control (treatment/procedure/test): Triangular flap repair	<u>Length of follow-up</u>: 6 years <u>Loss-to-follow-up</u>: Follow-up period (years) and number of patients per period (reasons for dropout not described: 1-2: 11 2-3: 22 3-4: 35 4-5: 29 5-6: 11 <u>Incomplete outcome data</u>: As above	Outcome measures and effect size (include 95%CI and p-value if available): Comparison scores (esthetic results) Lip I: 38 ± 5 C: 39 ± 5 p>0.10 Nose I: 34 ± 4 C: 34 ± 4 p>0.80 Lip + Nose I: 71 ± 10 C: 73 ± 12 p>0.50	Author's conclusion: No significant difference was found in overall postoperative appearance of lip and nose between rotation-advancement and triangular flap repair. As a result we recommend either technique for unilateral cleft lip repair.

Da Silva Armatunga, 2004	Type of study: randomized trials Setting: outpatients Country: Sri Lanka Source of funding: not reported	Inclusion criteria: 1) patients with unilateral cleft lip Exclusion criteria: - N total at baseline: Millard: 18 Cronin: 21 Combined: 20 Important prognostic factors[2]: *For example* *age ± SD:* *unclear (age distribution reported)* *Sex:* *Millard: 61% M* *Cronin: 62% M* *Combined: 65% M* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): Millard procedure Cronin procedure	Describe control (treatment/procedure/test): Method combining Millard an Cronin Procedure	Length of follow-up: 3 months Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Cleft Lip Component Symmetry Index score Cupid's bow height Millard: 77 Cronin 86 Combined: 87 P<0.01 for Millard vs other 2 groups Vermillion height: Millard: 87 Cronin: 97 Combined: 97 P<0.01 for Millard vs other 2 groups Nostril height symmetry: Millard: 93 Cronin: 93 Combined: 92 P>0.05, reduced in all groups Nostril width: Millard: 96 Cronin: 99 Combined: 95 p>0.05 for Cronin vs other 2 groups	Author's conclusion: The advantages of Millard's and Cronin's methods, which are the most widely used methods of cleft lip repair; could be retained and the disadvantages eliminated to a degree by combining the 2 methods. A basic muscle repair could also be included in the new combined method.
Halli, 2012	Type of study: retrospective observational Setting: outpatients	Inclusion criteria: 1) patients with unilateral or bilateral cleft lip treated in a rural health center 2) written informed consent obtained from	Describe intervention (treatment/procedure/test): Millatrd's lip repair Skin edges sutured by 6-0	Describe control (treatment/procedure/test): Millard's lip repair Skin edges	Length of follow-up: 18 months Loss-to-follow-up: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Esthetic outcome criteria as judged by 5 observers	Author's conclusion: Amcrylate, when used as tissue hglue for skin closure in cleft lip repair, definitely has an edge over conventional suturing

	Country: India Source of funding: not reported	parents/guardians of patients <u>Exclusion criteria</u>: - <u>N total at baseline</u>: Intervention: 30 Control: 30 <u>Important prognostic factors</u>[2]: *For example* *age ± SD:* *unclear (age distribution reported)* *Sex:* *I: 40% M* *C: 53% M* *Bilateral cleft:* *I: 3%* *C: 0%* Groups comparable at baseline? Yes	prolene	approximated with Amcrylate	<u>Incomplete outcome data</u>: Not reported	Mean rank of all judges I: 15.04 C: 15.96 P<0.05 Parent questionnaire % Very satisfied when wound is healed I: 23% C: 57% p-value Not reported	techniques
Reddy, 2010	Type of study: prospective observational Setting: outpatients Country: India Source of funding: non-commercial	<u>Inclusion criteria</u>: 1) patients with complete unilateral cleft lip with or without cleft palate 2) nonsyndromic patients 3) operated before age of 5 years <u>Exclusion criteria</u>: - <u>N total at baseline</u>: 1) 400 2) 400 3) 400	Describe intervention (treatment/procedure/test): 1) Millard incision 2) Pfeifer incision	Describe control (treatment/procedure/test): 3) Afroze incision	<u>Length of follow-up</u>: 2-4 years <u>Loss-to-follow-up</u>: Complete follow-up <u>Incomplete outcome data</u>: Complete outcome data collection	Outcome measures and effect size (include 95%CI and p-value if available): With regard to white roll, vermilion border, scar, nostril symmetry, Cupid's bow and lip length, the Afroze incision gave superior results compared with Millard or Pfeifer incision. All three incisions showed comparable outcomes regarding alar base and alar dome.	Author's conclusion: The Afroze incision is superior regarding a broad spectrum of outcomes in a heterogenous population of patients with unilateral cleft lip

		Important prognostic factors[2]: *For example* *age ± SD:* *1) 2.2 ± 1.7* *2) 1.9 ± 1.7* *3) 1.7 ± 1.4* *Sex:* *1) 50% M* *2) 63% M* *3) 54% M* Groups comparable at baseline? Yes					

BCLP: bilateral cleft lip and palate; CP: cleft palate only; UCLP: unbilateral cleft lip and palate

Notes:

1. Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures
2. Provide data per treatment group on the most important prognostic factors [(potential) confounders]
3. For case-control studies, provide sufficient detail on the procedure used to match cases and controls
4. For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders

Risk of bias table for intervention studies (randomized controlled trials)

Study reference (first author, publication year)	**Describe method of randomisation** [1]	**Bias due to inadequate concealment of allocation?** [2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?** [3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?** [3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?** [3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?** [4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?** [5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?** [6] (unlikely/likely/unclear)
Palatum molle								
Abdel-Aziz, 2011	"randomly classified into two equal groups	Likely	Likely	Likely	Likely	Unlikely	Likely	Unlikely
Henkel, 2003	Each patient was assigned to one of the two groups following a previously determined succession	Likely	Likely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
Spauwen, 1992	"randomly allocated"	Likely	Unclear	Unclear	Unclear	Unlikely	Unlikely	Unlikely
Williams, 2009	Block randomization plan for 4 surgeons: each sequential set assigned to a surgeon was assigned to the 8 study groups at random	Likely	Likely	Unlikely	Unlikely	Unlikely	Unclear	Unlikely
Lip adhesion								
Chowdri, 1990	"simple random sampling procedure"	Likely	Likely	Unlikely	Likely	Unlikely	Unclear	Unclear
Da Silva	"randomly	Likely	Likely	Unlikely	Likely	Unlikely	Unclear	Unclear

Armatunga , 2004	allocated”							

1. Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
2. Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..
3. Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has “soft” (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4. Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.
5. If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear
6. Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Palatum molle				
Carroll, 2013	Unlikely	Unlikely	Unlikely	Unclear
Grobbelaar, 1995	Unlikely	Unlikely	Unlikely	Unclear
Hassan, 2007	Unlikely	Unlikely	Unlikely	Unclear
McWilliams, 1995	Unlikely	Unlikely	Unlikely	Unlikely
Witt, 1999	Unlikely	Unlikely	Unlikely	Unclear
Lip adhesion				
Halli, 2012				
Reddy, 2010	Likely (patients operated at age 2-3 years in India)	Unlikely	Unlikely	Unclear

7. Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.
8. 2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.
9. Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has “soft” (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
10. Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series]

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Ysunza, 2004	Type of study: randomized clinical trial Setting: Cleft palate clinic of hospital Country: Mexico Source of funding: Not reported	Inclusion criteria: Complete unilateral cleft lip and palate with no other medical conditions; Palate repair performed before 8 months of age; presence of VPI; age 5 to 10 Exclusion criteria: Hearing disorders N total at baseline: Intervention: 35 Control: 35 Important prognostic factors[2]: *Age in years range:* I: 4y 1m to 7y 10m C:4y 5m to 7y 7m Groups	I: A customized pharyngeal flap according to findings of videonasopharyngoscopy and multiview videofluoroscopy	C: Sphincter pharyngoplasty according to findings of videonasopharyngoscopy and multiview videofluoroscopy	Length of follow-up: I: 4 months C: 4 months Loss-to-follow-up: I: 0 C: 0	VPI resolution: I: 89% (n=31) C: 85% (n=30) P > 0.05 Velopharyngeal closure patterns Uniformly distributed between the two groups of patients. Complications: None of the patients presented serious complications concerning the risk of obstruction in the immediate postoperative period. No complications such as fistulae, dehiscence of the flap (pharyngeal flap) or flaps (sphincter pharyngoplasty), bleeding nor infection were detected in this series of patients.	The planning of the surgical procedure, in order to match the postoperative structure to the pre- operative velopharyngeal dimensions and movements visualized through VNP and MVVF, seems to be the most important aspect of the surgery for correcting residual VPI after palatal closure. This was done on individual basis in both groups.

		comparable at baseline? Yes					
Åbyholm, 2005	Type of study: randomized clinical trial Setting: Cleft palate clinic of hospital Country: US, Norway, UK Source of funding: National Institute of Dental and Craniofacial Research (US) and NW Regional Health Authority	<u>Inclusion criteria</u>: Complete unilateral cleft lip and palate with no other medical conditions; already undergone a primary repair of the palate (with or without a cleft lip or alveolus), aged between of 3 and 25 years with apparent VPI diagnosed by an experienced specialist speech pathologist at one of the participating centers <u>Exclusion criteria</u>: Hearing disorders <u>N total at baseline</u>: Intervention: 52 Control: 45 <u>Important prognostic factors</u>[2]: *Age in years range (3-7):* I: 48% C: 58% *Age in years range (8-14):* *I: 38%*	I: Pharyngeal flap	C: Sphincter pharyngoplasty	<u>Length of follow-up</u>: I: 12 months C: 12 months <u>Loss-to-follow-up</u>: I: 0 C: 0	<u>VPI resolution:</u> *3 months* I: 82% (n=26) C: 42% (n=13) P = 0.005 *12 months* I: 83% (n=43) C: 78% (n=35) P = 0.45 <u>Complications:</u> low complication rate, low reoperation rate, and no significant differences were detected between the two procedures. Both procedures rarely resulted in clinically significant sleep apnea, and that no difference was found in its long- term incidence.	

		C: 31% *Age in years range (15-25):* *I: 14%* *C: 11%* Groups comparable at baseline? Yes					

Notes:

1) Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures
2) Provide data per treatment group on the most important prognostic factors [(potential) confounders]
3) For case-control studies, provide sufficient detail on the procedure used to match cases and controls
4) For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders

Risk of bias table for intervention studies (randomized controlled trials)

Study reference (first author, publication year)	Describe method of randomisation[1]	Bias due to inadequate concealment of allocation?[2] (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?[4] (unlikely/likely/unclear)	Bias due to loss to follow-up?[5] (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?[6] (unlikely/likely/unclear)
Ysunza, 2004	Block randomization, unclear	unclear	unclear	unclear	unlikely	likely	unlikely	Unlikely
Åbyholm, 2005	computer-generated random numbers, with allocation concealment through sealed envelopes	unlikely	unlikely	unclear	unlikely	unlikely	likely	unLikely

1) Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
2) Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..
3) Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4) Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.

5) If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear
6) Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.

Chapter 9 Bone grafting procedure in patients with clefts of the lip and palate

Module: Naso-alveolar moulding (NAM)

Validity and Maintenance

The guideline task force consulted two registration platforms for trials - ClinicalTrials.gov and the International Clinical Trials Registry Platform of the World Health Organization - to determine whether there are any ongoing clinical trials about NAM. Two trials were registered (websites accessed 2 February 2018), but both of these trials had a very short follow-up (maximum of 6 months). Based on this information, the guideline task force does not expect any major developments in the near future and deems a revision period of 5 years justified.

Module	Document manager(s)	Year of authorisation	Next assessment of actuality of guideline	Frequency of assessment for actuality	Who will supervise the actuality?	Relevant factors for changes to recommendation
NVPC	NVvO, NVMKA, NVPC	2018	2023	5 years	NVPC	New relevant literature

Knowledge gaps

There has been insufficient research into whether naso-alveolar mo(u)lding in children with a complete unilateral or bilateral cleft lip, alveolus and palate has a permanent positive effect on the critical outcome measures defined by the guideline task force, namely the shape and functioning of the nose and the aesthetic result of the treatment. It has also not been proven that NAM facilitates lip surgery or improves the psychosocial wellbeing of the parents. In addition, the cost-effectiveness needs to be examined.

Indicators

The guideline task force has not defined any indicators as no scientific evidence of sufficiently high quality was found for NAM.

Implementation plan

The guideline task force has not drafted an implementation plan, as further scientific evidence to substantiate the usefulness of NAM is required.

Exclusion table

Table Exclusion after reading the full article

Author and year	Reason for exclusion
Abbott (2012)	Systematic review of observational studies
Abu-Rub (2005)	Retrospective study
Adachi (2013)	Intervention does not meet inclusion criteria
Adali (2012)	Retrospective study
Alajmi (2013)	Retrospective study
Alam (2013)	Retrospective study
Allareddy (2015)	Intervention does not meet inclusion criteria
Ball (1995)	Retrospective study
Barillas (2009)	Retrospective study
Barnwell (2011)	Not available
Bartzela (2010)	Intervention does not meet inclusion criteria
Bennun (2009)	Observational study
Berkowitz (1996)	Intervention does not meet inclusion criteria
Berkowitz (1999)	Retrospective study
Berkowitz (2004)	Intervention does not meet inclusion criteria
Berkowitz (2016)	Retrospective study
Bongaarts (2004)	Intervention does not meet inclusion criteria
Bongaarts (2006)	Intervention does not meet inclusion criteria
Bongaarts (2008)	Intervention does not meet inclusion criteria
Bongaarts (2009)	Intervention does not meet inclusion criteria
Broder (2016)	Observational study
Ceron-Zapata (2016)	Observational study
Chan (2003)	Intervention does not meet inclusion criteria
Chang (2010)	Retrospective study
Chang (2014)	Comparison does not meet inclusion criteria
Chen (2015)	Retrospective study
Cho (2001)	Intervention does not meet inclusion criteria
Cho (2006)	Retrospective study
Chou (2013)	Intervention does not meet inclusion criteria
Clark (2011)	Retrospective study
Dec (2013)	Intervention does not meet inclusion criteria
Dec (2013)	Descriptive study
Durwald (2007)	Intervention does not meet inclusion criteria
Ezzat (2007)	Comparison does not meet inclusion criteria
Flinn (2006)	Intervention does not meet inclusion criteria
Fuchigami (2014)	Intervention does not meet inclusion criteria
Furukawa (2011)	Poster
Garfinkle(2011)	Retrospective study
Grabowski (2006)	Retrospective study
Hak (2012)	Intervention does not meet inclusion criteria
Haque (2015)	Intervention does not meet inclusion criteria
Heidbuchel (1998)	Intervention does not meet inclusion criteria
van der Heijden (2013)	Pre-post comparison
Hosseini (2017)	Comparison does not meet inclusion criteria
Hsieh (2012)	Retrospective study
Jorge (2016)	Retrospective study
Kajii (2013)	Retrospective study
Karling (1993)	Retrospective study
Kecik (2009)	Pre- post comparison
Koh (2013)	Intervention does not meet inclusion criteria
Konst (1999)	Intervention does not meet inclusion criteria
Konst (2000)	Intervention does not meet inclusion criteria
Konst (2003)	Intervention does not meet inclusion criteria
Konst (2003)	Intervention does not meet inclusion criteria
Konst (2003)	Intervention does not meet inclusion criteria
Konst (2004)	Intervention does not meet inclusion criteria

Koya (2016)	Pre- post comparison
Kozelj (1999)	Intervention does not meet inclusion criteria
Kozelj (2000)	Intervention does not meet inclusion criteria
Kozelj (2007)	Retrospective study
Larson (1993)	Pre- post comparison
Laverde (2016)	Pre- post comparison
Lee (2008)	Retrospective study
Liao (2012)	Retrospective study
Liao (2014)	Retrospective study
Liou (2004)	Pre- post comparison
Liou (2007)	Pre- post comparison
Lohmander (2004)	Comparison does not meet inclusion criteria
Manosudprasit (2014)	Narrative review
Masarei (2007)	Intervention does not meet inclusion criteria
Maull (1999)	Retrospective study
Mazaheri (1993)	Pre- post comparison
Miliard (1999)	Retrospective study
Millard (1998)	Retrospective study
Mishima (1998)	Intervention does not meet inclusion criteria
Mishima (2003)	Intervention does not meet inclusion criteria
Mishra (2010)	Methods and results not well described
Molsted (1993)	Retrospective study
Molsted (1993)	Retrospective study
Monasterio (2013)	Retrospective study
Monasterio (2013)	Retrospective study
Murthy (2009)	Retrospective study
Murthy (2013)	Narrative review
Muzaffar (2001)	Retrospective study
Nakamura(2009)	Retrospective study
Natsume (1998)	Letter to the editor
Nazarian (2011)	Retrospective study
Noverraz (2015)	Intervention does not meet inclusion criteria
Noverraz (2015)	Intervention does not meet inclusion criteria
Pai (2005)	Pre- post comparison
Papadopoulos (2012)	Intervention does not meet inclusion criteria
Papay (1994)	Descriptive study
Patel (2012)	Case report
Patel (2015)	Retrospective study
Pfeifer (2002)	Retrospective study
Prahl (2001)	Intervention does not meet inclusion criteria
Prahl (2003)	Intervention does not meet inclusion criteria
Prahl (2005)	Intervention does not meet inclusion criteria
Prahl (2006)	Intervention does not meet inclusion criteria
Prahl (2008)	Intervention does not meet inclusion criteria
Prasad (2000)	Retrospective study
Punga (2013)	Observational study
Ritschl (2015)	Incorrect comparison
Roberts-Harry (1996)	Intervention does not meet inclusion criteria
Ross (1994)	Retrospective study
Ruiz-Escolano (2016)	Pre-post comparison
Russell (2011)	Retrospective study
Russell (2015)	Intervention does not meet inclusion criteria
Sabarinath (2010)	Pre-post comparison
Santiago (1998)	Retrospective study
Sasaki (2012)	Comparison does not meet inclusion criteria
Semb (2005)	Intervention does not meet inclusion criteria
Severens (1998)	Intervention does not meet inclusion criteria
Shay (2015)	Retrospective study
Shetty (2012)	Comparison does not meet inclusion criteria
Shetty (2016)	Comparison does not meet inclusion criteria

Singh (2005)	Pre-post comparison
Singh (2005)	Comparison does not meet inclusion criteria
Sischo (2015)	Intervention does not meet inclusion criteria
Sischo (2016)	Observational study
Spengler (2006)	Pre-post comparison
Spolyar (2015)	Retrospective study
Sulaiman (2013)	Intervention does not meet inclusion criteria
Suri (2012)	Retrospective study
Tan (2015)	Retrospective study
Tang (2016)	Pre- post comparison
Tollefson (2007)	Descriptive study
Urbanova (2016)	Intervention does not meet inclusion criteria
Uzel (2011)	Retrospective study
Wakami (2011)	Retrospective study
Yu (2013)	Did not present data on the effect size or association for the outcomes of interest
Zuhaib (2016)	Pre-post comparison

Evidence tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Liang (2018)	Type of study: Two-group parallel prospective clinical trial Setting: Chang Gung Craniofacial Center Country: Taoyuan (Taiwan) Source of funding: Not mentioned	Inclusion criteria: Patients with UCLP, no other craniofacial malformations or systemic diseases, primary lip closure at 3 to 4 months by the same surgeon using the Chang Gung modified rotation advancement technique without nasal cartilage dissection. Exclusion criteria: Not given N total at baseline: Intervention: 42 Control: 42 Important prognostic factors[2]: Age at lip closure (mean, range): I: 113 days (94 – 117 days) C: 109 days (93 – 115 days) Sex: I: 52.4% M C: 59.5% M	Describe intervention (treatment/procedure/test): NAM: oral plate with a nasal stent. The plate was placed in the mouth and the nasal stent wire was adjusted. Lip tape was used to narrow the cleft. The nasal molding stent was adjusted weekly, and the lower lateral cartilage was molded accordingly to resemble the normal alar shape. Treatment duration was 1 to 3 months until lip closure. Lip closure: Chang Gung modified rotation advancement technique. Nasal cartilage dissection was not performed. After lip closure a silicone nasal conformer was placed into the nostril for 6 months in both groups of patients.	Describe control (treatment/procedure/test): Participants in the control group had lip closure without NAM.	Length of follow-up: 4 to 5 years Loss-to-follow-up: No loss-to-follow-up Incomplete outcome data: No incomplete outcome data	Outcome measures and effect size (include 95%CI and p-value if available): Panel scoring of the bilateral alar base and symmetry of the nasal dome and nasolabial fold (full-face photographs), symmetry of the bilateral nasal dome and nostril, columella length and shape of the nostril sill and nose tip (submental oblique photograph). Average score (per participant): NAM = 66.62 ± 14.25 non-NAM = 66.31 ± 15.08 F = 0.009 P = 0.923	Only the baseline factors year of birth, surgical time, age at lip closure, gender and cleft sideness were given. Participants were not randomised to the treatment groups. Allocation of treatment was based on time of entry.

		Groups comparable at baseline? Yes (Age, sex and cleft sideness were comparable at baseline).					
Shetty (2017)	Type of study: Randomized controlled trial Setting: Nitte Meenakshi institute of craniofacial surgery Country: India Source of funding: None	Inclusion criteria: Non syndromic UCLP who presented up to 1 year of age Exclusion criteria: Not given N total at baseline: Intervention (n = 60) I: NAM initiated before 1 month of age (n = 20). II: NAM initiated at 1 to 6 months of age (n = 20). III: NAM initiated at 6 months to 1 year of age (n = 20). Control (n = 60) I: operation at 6 months of age II: operation between 6 and 9 months of age III: operation between 9 and 15 months of age	Describe intervention (treatment/procedure/test): NAM was performed until 6 months of age in subgroup I and at least 3 months in subgroup II and III. The maxillary arch was actively molded by selective trimming of the appliance and addition of a layer of soft acrylic to promote alveolar growth in the antero-medial direction. Once approximation of the alveolar segments was noted, passive molding was undertaken to retain the alveolar segments while forward growth of the lesser segment was stimulated. Maxillary arch collapse was prevented by addition of a soft liner over the palatal shelves and by applying lateral pressure on the arch. All impressions, casts, and PNAM appliances were made by the same investigator (R.K.A.). Lipclosure: modified rotation-advancement cheiloplasty in study group patients at completion of PNAM (at the age of 6 months in subgroup I, 6–9 months in subgroup II, and 9–15 months in subgroup III). To maintain uniformity, control group patients also underwent operation at the time of their	Describe control (treatment/procedure/test): Patients in the control group had lip closure and palate closure without NAM	Length of follow-up: 6 years Loss-to-follow-up: Not described Incomplete outcome data: No incomplete outcome data	Outcome measures and effect size (include 95%CI and p-value if available): Three maxillary distances measured on dental casts. NAM versus control (mean difference (95% CI) p-value): Comparison of change in maxillary arch dimensions measured on dental casts at T1 (= first visit), T2 (= before cheiloplasty), and T3 (= at 6 years). Between T1 and T2, T1 and T3, and T2 and T3: Subgroup I: ISD T1 versus T2 NAM -11.40 (1.70) Control 0.40 (0.50) P-value < 0.001	The participants were not randomised to the treatment groups.

		Important prognostic factors[2]: *Intervention (mean age at initiation (range)):* I: 11 days (range 1 - 28 days) II: 94 days (range 33 - 180 days) III: 235 days (range 180 - 365 days) Groups comparable at baseline? Unknown (no baseline table given)	corresponding study subgroups. Neither nasal dissection nor gingivoperiosteoplasty was carried out for any patient. Palatoplasty: Pushback procedure at 18 months of age in all patients. All surgeries were carried out by the same surgeon (V.S.)			T1 versus T3 NAM -13.25 (2.17) Control -12.80 (2.09) P-value 0.52 (NS) T2 versus T3 NAM -1.85 (0.71) Control -13.20 (1.77) P-value <0.001 ICW T1 versus T2 NAM -0.20 (0.77) Control 0.20 (0.41) P-value 0.06 (NS) T1 versus T3 NAM -0.50 (0.69) Control -3.70 (0.87) P-value <0.001 T2 versus T3 NAM -0.30 (0.47) Control -3.90 (0.79) P-value <0.001 PAW T1 versus T2 NAM 1.05 (1.32) Control 0.90 (0.31) P-value 0.63 (NS) T1 versus T3 NAM 4.20 (1.32) Control 3.90 (0.31) P-value 0.93 (NS)	

						T2 versus T3 NAM 3.15 (0.49) Control 3.00 (0.00) P-value 0.16 (NS) Subgroup II: ISD T1 versus T2 NAM -7.45 (1.28) Control 0.45 (0.51) P-value <0.001 T1 versus T3 NAM -12.25 (2.54) Control -12.45 (1.64)P-value 0.65 (NS) T2 versus T3 NAM -4.80 (1.58) Control -12.90 (1.50)P-value <0.001 ICW T1 versus T2 NAM -0.15 (0.37) Control 0.20 (0.41) P-value 0.009 T1 versus T3 NAM -0.65 (0.67) Control -2.95 (0.83) P-value <0.001 T2 versus T3 NAM -0.50 (0.51)	

						Control -3.15 (0.67) P-value <0.001 PAW T1 versus T2 NAM 0.75 (0.97) Control 0.85 (1.04) P-value 0.93 (NS) T1 versus T3 NAM 3.00 (1.26) Control 3.35 (1.09) P-value 0.36 (NS) T2 versus T3 NAM 2.25 (0.44) Control 2.50 (0.69) P-value 0.16 (NS) Subgroup III: ISD T1 versus T2 NAM -6.35 (1.31) Control 0.40 (0.50) P-value <0.001 T1 versus T3 NAM -11.55 (1.91) Control -11.95 (1.60) P-value 0.57 T2 versus T3 NAM -5.20 (1.61) Control -12.35 (1.34) P-value <0.001	

						ICW T1 versus T2 NAM -0.15 (0.37) Control 0.25 (0.44) P-value 0.005 T1 versus T3 NAM -1.35 (0.59) Control -2.65 (0.75) P-value <0.001 T2 versus T3 NAM -1.20 (0.41) Control -2.90 (0.72) P-value <0.001 PAW T1 versus T2 NAM 1.50 (0.61) Control 1.65 (0.81) P-value 0.50 T1 versus T3 NAM 3.25 (1.02) Control 2.85 (0.88) P-value 0.28 T2 versus T3 NAM 1.75 (0.72) Control 1.20 (0.41) P-value 0.007	

Risk of bias table for intervention studies (randomized controlled trials)

Study reference (first author, publication year)	**Describe method of randomisation**[1]	**Bias due to inadequate concealment of allocation?**[2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?**[4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?**[5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?**[6] (unlikely/likely/unclear)
Liang (2016)	Date of admission	Likely (randomization process was not blinded)	Likely (participants were not blinded)	Likely (care providers were not blinded)	Unlikely (outcome assessors were blinded)	Unlikely (the results of the predefined outcomes were reported)	Unlikely (no loss to follow-up reported in the study)	Unlikely (participants included in the analysis were also included in the trial)
Shetty (2017)	Not described	Likely (randomization process was not blinded)	Likely (participants were not blinded)	Likely (care providers were not blinded)	Unlikely (outcome assessors were blinded)	Unlikely (the results of the predefined outcomes were reported)	Unlikely (no loss to follow-up reported in the study)	Unlikely (participants included in the analysis were also included in the trial)

1. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.**
2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules.**
3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear.**
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Module: Timing of the bone grafting procedure

Table Exclusion after reading the full article

Author and year	Reason for exclusion
Kazemi, 2002	Narrative review
Shashua, 2000	Narrative review
Fudalej, 2011	Intervention not well described
Williams, 2003	Wrong comparison
Mueller, 2012	Incorrect intervention
Schultze-Mosgau, 2003	did not present data on the effect size or association for the outcomes of interest
Van der Meij, 2001	did not present data on the effect size or association for the outcomes of interest

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series]

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Nishihara, 2014	Type of study: Retrospective cohort study Setting: University hospital Country: Japan Source of funding: Not reported	Inclusion criteria: Complete unilateral cleft lip and palate who underwent SABG in the alveolar cleft from March 1991 to December 2002. Exclusion criteria: Patients with congenital malformation, with the cleft-adjacent lateral incisor, or with incomplete cleft lip. N total at baseline: Intervention: 16 Control: 9 Important prognostic factors[2]: *Age in years range:* I: 7.2 to 13.3 C:10.3 to 17.8	I: Secondary autogenous bone grafting before eruption of the canine according to Bergland methods.	C: Secondary autogenous bone grafting before eruption of the canine. Canine teeth had almost erupted at the time of bone grafting according to Bergland methods.	Length of follow-up: I: 12.9 years (range 9.7 to 20.2) C: 11 years (range 9.1 to 14.8) Measurement took place at 1 year and more than 4 years after the operation Loss-to-follow-up: I: 0 C: 0	Crown eruption at 4 years: I: 15/16 (94%) C: 9/9 (100%) Vertical heights at > 4 years: I: 56.8 ± 5.1 mm C: 56.7 ± 4.2 mm P>0.05 Rate of an acceptable bone bridge: I: 62.5% C: 88.8% P-value=0.158	

		Groups comparable at baseline? The canine angle was significantly smaller in the intervention group.					
Trindade-Suedam, 2012	Type of study: Prospective cohort study Setting: University hospital Country: Brazil Source of funding: Govermental (CAPES within the PRODOC program)	<u>Inclusion criteria:</u> Patients with complete unilateral cleft lip and palate operated on for a period of 3 months (February to May 2009), who underwent alveolar bone grafting <u>Exclusion criteria:</u> No return for the second or third examination. <u>N total at baseline:</u> Total group: 52 (not specified per group) <u>N in the analysis:</u> Intervention: 16 Control: 15 <u>Important prognostic factors2:</u> None described	SABG group: patients during mixed dentition operated on before or immediately after eruption of the permanent canine (10-13 y). All surgical procedures were performed according to the protocol proposed by Boyne and Sands (1972), in which particulate bone from the iliac crest was harvested.	TABG group: patients during permanent dentition (15-28y) All surgical procedures were performed according to the protocol proposed by Boyne and Sands (1972), in which particulate bone from the iliac crest was harvested	<u>Length of follow-up:</u> 2 months and 6-12 months <u>Loss-to-follow-up:</u> Total group: 19 (37%) Reasons Nineteen patients were excluded because they did not return for the second or third examination. In 2 instances, patients did not return because of extrinsic trauma to the bone graft resulting in complete bone loss.	Modified Bergland Index 1=excellent - 5=failure (95% CI): Buccal 2 months SAGB: 1.50 (0.63) TABG: 2.53 (1.64) Buccal 6-12 months SAGB: 1.38 (0.50) TABG: 2.93 (1.49) P<0.05 Intermediate 2 months SAGB: 1.56 (1.03) TABG: 2.60 (1.59) P<0.05 Intermediate 6-12 months SAGB: 1.75 (1.18) TABG: 2.93 (1.44) P<0.05 Palatal 2 months SAGB: 1.63 (1.09) TABG: 2.67 (1.63) P<0.05 Palatal 6-12 months SAGB: 1.63 (1.09) TABG: 2.80 (1.52) P<0.05 Bergland index 2 months (excellent/good): SAGB: 14 (86%) TABG: 9 (60%)	A post-hoc sub-group analysis was performed which was not pre specified in the methods section. A rational for the chosen cut off was missing. "TABG group subdivided into 2 groups according to age (patients 15-16 and 18-28 y), no patients classified as having failure conditions were observed in the first subgroup (15-16 y). In the second subgroup (18-28 y), 44% were ranked as having failure conditions." They put much weight on this subgroup analysis in the discussion and conclude that surgery performed at younger ages (15-16 y), even during permanent dentition, yields better outcomes.

		Groups comparable at baseline? As a definition of the study design, groups were not comparable on age. Unsufficient information was provided on other clinical characteristics.				Bergland index 6-12 months (excellent/good): SAGB: 12 (75%) TABG: 8 (53%) Bergland index 2 months (failure): SAGB: 0 (0%) TABG: 4 (26%) Bergland index 6-12 months (failure): SAGB: 0 (0%) TABG: 4 (26%)	
Miller, 2010	Type of study: Retrospective cohort study Setting: University hospital Country: United States Source of funding: US government work	Inclusion criteria: Patients undergoing alveolar cleft bone grafting from 2000 to 2008. Exclusion criteria: Not described. N total at baseline: Intervention: 61 Control: 38 Important prognostic factors[2]: *Mean age in years (range):* Total group: 8.8 (range 6 to 37) *Gender % male:* Total group: 68%	I: Grafting before complete eruption of the permanent central incisors	C: Grafting during or after complete eruption of the permanent central incisors	Length of follow-up: Variable between 1 week to 52 months Loss-to-follow-up: 28% (71 had appropriate imaging available no further information described).	Complications: I: 9.8% (pyogenic granuloma n=2, residual fistula n=2, residual alveolar defect without fistula n=1, and hip wound dehiscence n=1). C: 13.2% (residual fistula n=3, residual, alveolar cleft defect without fistula n=1, gingival hyperplasia n=1, and fibroma n=1). No statistically significant differences	The proportions of complication were on patient level. One patient with multiple complications was measured as one to calculate the percentage. This was present for one patient in the control group who must have had two complications.

		Groups comparable at baseline? No statistically significant differences (P <.05) were found between groups 1 and 2 in gender, ethnicity, cleft type, hospital stay, or length of follow-up. As a definition of the study design, groups were not comparable on age.					
Rawashdeh, 2007	Type of study: Prospective cohort study Setting: University hospital Country: Jordan Source of funding: Not reported	Inclusion criteria: Not described Exclusion criteria: The requirement for postoperative follow-up period was a minimum of 6 months. N total at baseline: Intervention: 30 Control: 32 Important prognostic factors[2]: *Mean age in years ± SD:* *I:10.3 ±?* *C:16.5 ±?*	I: Early SABG (before the eruption of the canine). The surgical technique utilized was based on principles of SABG described by Boyne and Sands. The bone used was autogenous cancellous bone harvested from the iliac crest.	C: Late SAGB (after the eruption ofthe canine). The surgical technique utilized was based on principles of SABG described by Boyne and Sands. The bone used was autogenous cancellous bone harvested from the iliac crest.	Length of follow-up: Average 2.8 years (range 0.6 to 5.5 years) Loss-to-follow-up: Not described Incomplete outcome data: Not described	Bony fill measured with the Kindelan grading scale: Unilateral cleft patients: *Grade 1:* I: 20 (90%) C: 20 (80%) *Grade 2:* I: 1 (5%) C: 3 (12%) *Grade 3:* I: 1 (5%) C: 2 (8%) *Grade 4:* I: 0 (0%) C: 0 (0%) Bilateral cleft patients: *Grade 1:* I: 9 (56.2%)	Only grade 1 SABG cases, which corresponded to Bergland types I and II, and Chelsea19 types A and C, were classified successful. There were no tests performed that evaluated the statistical difference between groups.

		Groups comparable at baseline? As a definition of the study design, groups were not comparable on age. Unsufficient information was provided on other clinical characteristics.				C: 8 (57.1%) *Grade 2:* I: 3 (18.8%) C: 2 (14.3%) *Grade 3:* I: 2 (12.5%) C: 0 (0%) *Grade 4:* I: 2 (12.5%) C: 4 (28.6%)	
Jia, 2006	Type of study: Prospective cohort study Setting: University hospital Country: China Source of funding: Not reported	Inclusion criteria: Patients with clefts who had secondary alveolar bone grafting between 1992 and 2001. Exclusion criteria: No follow-up or the cleft canine had not erupted at the time of the research. N total at baseline: Total group: 202 After exclusion of follow-up: Total group: 170 I (CLAP): 16 C (CLAP): 24 I (UCLP): 44 C (UCLP): 58	I: Secondary alveolar bone grafting before eruption of the canine according to the standardised method that was first described by Boyne and Sands. Subgroups for: CLAP: unilateral cleft lip and alveolar process alone UCLP: unilateral cleft lip and palate BCLP: bilateral cleft lip and palate.	C: Secondary alveolar bone grafting after eruption of the canine according to the standardised method that was first described by Boyne and Sands. Subgroups for: CLAP: unilateral cleft lip and alveolar process alone UCLP: unilateral cleft lip and palate BCLP: bilateral cleft lip and palate.	Length of follow-up: Average 1.9 years (range 1 to 8 years). Loss-to-follow-up: Not described Incomplete outcome data: Not described	Interdental septal height. Success rate defined as Bergland Type I and II (p-value provide for significant results): CLAP I: 15 (94%) C: 23 (96%) UCLP I: 42 (95%) C: 48 (83%) P-value = 0.049 BCLP I: 20 (91%) C: 23 (68%) p-value = 0.044 Interdental septal height. Failure rate defined as Bergland Type III and IV (p-value): CLAP I: 1 (6%) C: 1 (4%)	Minor wound dehiscences were reported too, but it was not specified in which group they had appeared. Patients with complications had poor postoperative oral hygiene.

		I (BCLP): 22 C (BCLP): 34 <u>Important prognostic factors[2]</u>: *age (range)* CLAP(all): 14 (8-33) UCLP(all): 15 (8-35) BCLP(all): 14 (8-24) *Gender % male:* CLAP(all): 47.5% UCLP(all): 58.8% BCLP(all): 64.3% <u>Groups comparable at baseline?</u> Patients characteristics were not specified for the contrast of interest (intervention at early vs. late eruption). As a definition of the study design, groups were not comparable on age.				UCLP I: 2 (5%) C: 10 (17%) BCLP I: 2 (9%) C: 11 (32%) Complications: Chronic infection of the graft, resulting in complete failure I: 1 C:5	
Dempf, 2002	Type of study: Retrospective cohort study Setting:	<u>Inclusion criteria</u>: Patients, who underwent an alveolar bone grafting at least 3	I: Secondary bone grafting during the mixed stage of dentition with autogenous iliac cancellous bone.	C: Tertiary bone grafting after completion of the second stage of dentition with autogenous iliac cancellous bone.	<u>Length of follow-up</u>: Not described <u>Loss-to-follow-up</u>: Total group: 39.3%	Oronasal fistulae: I: 0 C: 0 Bone Height 75-100%:	

	University hospital Country: Germany Source of funding: Not reported	years ago. <u>Exclusion criteria</u>: Spontaneous approximation of the alveolar arch segments tertiary osteoplasties needed to be performed only on those patients who had not already received a systematic therapy. <u>N total at baseline</u>: Total group: 140 procedures in 91 patients <u>Important prognostic factors</u>[2]: *Mean age in years ± SD:* *I:10.6 ± ?* *C: 21.3 ± ?* <u>Groups comparable at baseline?</u> Unclear, unsufficient information was given on patient characteristics. As a definition of the study design, groups were not comparable on	Osseous bridging of the clefted alveolus was attempted as a secondary osteoplasty in patients aged between 8 and 11 years in all cases in which a spontaneous approximation of the alveolar arch segment had not occurred.	Osseous bridging of the clefted alveolus was attempted as a secondary osteoplasty in patients aged between 8 and 11 years in all cases in which a spontaneous approximation of the alveolar arch segment had not occurred.	(procedure level) Reasons not described. Incomplete outcome data: Bone Height: I: 4 (6.7%) C: 0 (0%) Reason not described.	I: 25 (41.7%) C: 10 (40.0%) Bone Height 50–75%: I: 26 (43.3%) C: 7 (28.0%) Bone Height 25–50%: I: 4 (6.6%) C: 6 (24.0%) Bone Height 0–25%: I: 1 (1.7%) C: 2 (8.0%) Infraocclusion: I: 12 (48.0%) C: 14 (70.0%) No. infraocclusion: I: 13 (52.0%) C: 6 (30.0%) Loss of the dental implant: I: 0 C: 5 Complete loss of the grafted material was not observed.	

		age.					
Freihofer, 1993	Type of study: Retrospective cohort study Setting: University hospital Country: The Netherlands Source of funding: Not reported	Inclusion criteria: All patients with reconstructions of unilateral clefts and of clefts in patients with a bilateral deformity, with a follow-up time of at least 1 year and adequate documentation. Exclusion criteria: Patients with missing records or when it was not possible to reasonably incorporate them in one of the groups (unilateral cleft or cleft) N total at baseline Unilateral clefts (number of cleft sides): Intervention: 61 Control 1: 21 Control 2: 64 Control 3: 19 N total at baseline Bilateral clefts (number of cleft sides): Intervention: 32 Control 1: 21 Control 2: 46	I: Early secondary bone grafting. Reconstruction of the alveolar cleft before eruption of the canine through the alveolar bone. Transplant materials were mandibular symphysis, rib or iliac crest and one heterogeneous group containing calvarial bone, bone from the vomer, bank bone, lyodura and closures without a transplant.	C1: Late secondary bone grafting. Reconstruction of the alveolar cleft after eruption of the canine through the alveolar bone. C2: Late secondary bone grafting. Reconstruction of the alveolar cleft after eruption of the canine through the alveolar bone simultaneously with a midface osteotomy (defined as a (partial) Le Fort I or higher). C3: Tertiary bone grafting. Reconstruction of the alveolar cleft when secondary or closure during the osteotomy had failed. Transplant materials were mandibular symphysis, rib or iliac crest and one heterogeneous group containing calvarial bone, bone from the vomer, bank bone, lyodura and closures without a transplant.	Length of follow-up: At least one year (no further information reported). Loss-to-follow-up: No loss to follow-up as availability of one year follow-up was part of the inclusion criteria. Incomplete outcome data: No incomplete outcome data as availability of data for one year follow-up was part of the inclusion criteria.	Success rate defined as no oronasal communication and with at least 50 % of the bone graft height (unilateral clefts): I: 56/61 (92%) C1: 15/21 (71%) C2: 33/64 (52%) C3: 12/19 (62%) Success rate defined as no oronasal communication and with at least 50 % of the bone graft height (bilateral clefts): I: 29/32 (91%) C1: 15/21 (71%) C2: 18/46 (39%) C3: 10/32 (31%) Difference in success rate between time points (all clefts): Early grafting (Intervention) was significantly better than at all other points in time. The positive or negative effects of pre- and/or postoperative orthodontics were not studied.	Early secondary grafting of the alveolar cleft has a success rate of more than 90 % and is significantly better compared with all other timings. The treatment procedure, using rib, chin, ilium, or other bone for grafting, varied between patients, which might has affected the outcome. Surgeons closing bilateral clefts were more experienced than those closing unilateral ones.

		Control 3: 32 <u>Important prognostic factors[2]</u>: Not reported Groups comparable at baseline? Unclear, unsufficient information was given on patient characteristics. As a definition of the study design, groups were not comparable on age.					
Sindet-Pedersen, 1985	Type of study: Retrospective cohort study Setting: Community hospital Country: Denmark Source of funding: Not reported	<u>Inclusion criteria</u>: Patients diagnosed with cleft lip and alveolar process only, unilateral cleft lip palate and bilateral clefts involving the alveolar process with residual cleft in the alveolar process operated by secondary or late secondary bone-grafting. <u>Exclusion criteria</u>: Edentulous premaxilla, lack of follow-up (not	I: Secondary bone grafting before eruption of the canine Before bone-grafting, all patients underwent orthodontic treatment including transversal and/or sagittal expansion of the maxilla	C1: Secondary bone-grafting after eruption of the canine C2: Late secondary bone-grafting Before bone-grafting, all patients underwent orthodontic treatment including transversal and/or sagittal expansion of the maxilla	<u>Length of follow-up</u>: Average 7.2 months (range from 5.5 to 8.5 months) <u>Loss-to-follow-up</u>: 20/313 patients were excluded, with loss to follow amongst the reasons for exclusion. The exact number or reason for loss are not described.	Marginal bone level on teeth adjacent to the cleft. Total dental rehabilitation score value (1=optimal, 2=acceptable, 3=unacceptable, 4=no possibility of total dental rehabilitation): <u>Cleft lip and alveolar process only mean score value*:</u> I: 1.05 C1: 1.00 C2: 1.00 <u>Unilateral cleft-lip and palate mean score value*:</u> I: 1.10 C1: 1.41 C2: 1.58	

		specified), and atypical cleft diagnoses. <u>N total at baseline Cleft lip and alveolar process only:</u> Intervention: 19 Control 1: 11 Control 2: 2 <u>N total at baseline Unilateral cleft-lip and palate:</u> Intervention: 61 Control 1: 70 Control 2: 67 <u>N total at baseline Bilateral cleft-lip and palate:</u> Intervention: 16 Control 1: 24 Control 2: 23 <u>Important prognostic factors[2]</u>: *Mean age (range):* *I: 9.6 (5 – 14)* *C1: 13.5 (11 – 15)* *C2: 20.9 (16 – 38)* *Gender:* *I: 73% M* *C1: 71% M* *C2: 68% M* Minor oral surgery I: 58 (60%) C1: 43 (41%)				<u>Bilateral cleft-lip and palate mean score value*:</u> I: 1.16 C1: 1.58 C2: 1.96 <u>Cleft lip and alveolar process only mean score value*:</u> I: 100% C1: 100% C2: 100% <u>Unilateral cleft-lip and palate success rate*:</u> I: 98.4% C1: 88.6% C2: 77.6% <u>Bilateral cleft-lip and palate mean score value*:</u> I: 100% C1: 75% C2: 60.9% <u>Cleft lip and alveolar process only recurrence of fistula*:</u> I: 0 C1: 0 C2: 0 <u>Unilateral cleft-lip and palate recurrence of fistula *:</u> I: 0 C1: 3 C2: 10 <u>Bilateral cleft-lip and palate recurrence of fistula *:</u> I: 0 C1: 1 C2: 11	

		C2: 25 (27%) Groups comparable at baseline? As a definition of the study design, groups were not comparable on age. Unsufficient information was provided on other clinical characteristics.				*The results were presented on cleft level. Therefore the presented numbers exceed the number of included patients. Variation in treatment result between the 3 groups is statistically significant calculated by means of the "Chi-square test" for unilateral cleft-lip palate, and for bilateral clefts calculated on the basis of the number of clefts as well as the number of patients.	

Notes:

1. Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures
2. Provide data per treatment group on the most important prognostic factors [(potential) confounders]
3. For case-control studies, provide sufficient detail on the procedure used to match cases and controls
4. For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Nishihara, 2014	Likely: patient characteristics determined the timing of treatment. This leads to confounding by indication. Other characteristics were poorly described.	Unlikely: no patients were missing at follow up.	Likely: the outcome assessor could not be blinded for the timing of the intervention (radiographic pictures will show eruption).	Likely: there was no adjustment for prognostic factors.
Trindade-Suedam, 2012	Likely: patient characteristics determined the timing of treatment. This leads to confounding by indication. In addition, participants were selected based on their follow up period (31 out of the initial 52). For two drop-outs the reason was known to be related to the outcome of the intervention. Other characteristics were poorly described.	Unlikely: as a result of the inclusion criteria, there was a complete follow up.	Likely: the outcome assessor could not be blinded for the timing of the intervention (radiographic pictures will show eruption).	Likely: there was no adjustment for prognostic factors.
Miller, 2010	Likely: patient characteristics determined the timing of treatment. This leads to confounding by indication. Other characteristics were poorly described.	Likely: a substantial proportion of data was missing, without a specified reason.	Likely: the outcome assessor could not be blinded for the timing of the intervention (radiographic pictures will show eruption).	Likely: there was no adjustment for prognostic factors.
Rawashdeh, 2007	Likely: patient characteristics determined the timing of treatment. This leads to confounding by indication. In addition, participants were selected based on their follow up period which can introduce selection bias. No inclusion criteria were specified.	Unlikely: as a result of the inclusion criteria, there was a complete follow up.	Likely: the outcome assessor could not be blinded for the timing of the intervention (radiographic pictures will show eruption).	Unlikely: subgroups were defined for unilateral and bilateral palates.
Jia, 2006	Likely: patient characteristics determined the timing of treatment. This leads to confounding by indication. Additionally, participants were selected based on their follow up period (170 out of 202) which can introduce selection bias. Other characteristics were poorly described.	Unlikely: as a result of the inclusion criteria, there was a complete follow up.	Likely: the outcome assessor could not be blinded for the timing of the intervention (radiographic pictures will show eruption).	Unlikely: subgroups were defined for alveolar process alone, unilateral and bilateral palates.
Dempf, 2002	Likely: patient characteristics determined	Likely: a substantial proportion of data was	Likely: the outcome assessor could not be	Likely: there was no adjustment for

	the timing of treatment. This leads to confounding by indication. Other characteristics were poorly described.	missing.	blinded for the timing of the intervention (radiographic pictures will show eruption).	prognostic factors.
Freihofer, 1993	Likely: patient characteristics determined the timing of treatment. This leads to confounding by indication. Other characteristics were poorly described. In addition, reconstructions were selected based on minimal follow up documentation of one year ("a few patients are not incorporated in the series, mostly being adults who were not follow-up routinely").	Unlikely: no patients were missing at follow up.	Likely: the outcome assessor could not be blinded for the timing of the intervention (radiographic pictures will show eruption).	Unlikely: subgroups were defined for unilateral and bilateral palates and for different bone grafting material (chin, rib, ilium, other).
Sindet-Pedersen, 1985	Likely: patient characteristics determined the timing of treatment. This leads to confounding by indication. Other characteristics were poorly described.	Unlikely: 20 out of 313 patients were excluded for different reasons (edentulous premaxilla, lack of follow-up, atypical diagnosis).	Likely: the outcome assessor could not be blinded for the timing of the intervention (radiographic pictures will show eruption).	Unlikely: subgroups were defined for unilateral and bilateral palates and for different types of surgery.

1. Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.
2. Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.
3. Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4. Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.

Module: Technique of the bone grafting procedure

Table Exclusion after reading the full article

Author and year	Reason for exclusion
Guo, 2011	Does not match the clinical question
Van Hout, 2011	Does not meet the minimum reporting criteria for a review
Francis, 2013	Does not match the clinical question

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series]

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Alonso, 2010	Type of study: RCT Setting: Craniofacial Surgery Unit of the University of Sao Paulo Medical School and the CAIF (Assistance Center for Cleft Lip and Palate). Country: Brazil Source of funding: Not clearly stated. Absorbable collagen sponge and rhBMP-2 were provided (free of charge) by Dabasons Import Export Ltd. (Sa˜o Paulo, SP).	Inclusion criteria: 1) Preoperative orthodontic expansion of maxillary segments Exclusion criteria: Previous alveolar surgery, previous eruption of the canine, presence of comorbidities, or incomplete records N total at baseline: Intervention: 8 Control: 8 Important prognostic factors[2]: *Mean age:* 9 years and 6 months in both groups *Sex:* 9 male and 5 female. Distribution not reported *Bone height(mm):* I: 15.7±2.6 C: 16.1±1.66 P=0.595 *Preoperative defect*	InFuse bone graft (Sofamor-Danek, Memphis, Tenn.)impregnated with rhBMP-2	Traditional iliac crest cancellous graft	Length of follow-up: 12 months Loss-to-follow-up: Intervention: N=0 (0%) Control: N=0 (0%) Incomplete outcome data: Intervention: N=0 (0%) Control: N=0 (0%)	Bone filling percentage: *6 months* I: 59.6%±9.9 C: 75.4%±4.0 P=0.002 *12 months* I: 74.4%±10.8 C: 80.2%±4.1 P=0.176 Maxillary height (mm; percentage repair rate): *6 months* I: 8.5 ±2.6 (53.3%) C: 13.5 ±2.0 (83.3%) P=0.001 *12 months* I: 10.2±1.9 (65.0%) C: 13.9±1.4 (86.6%) P=0.001 Bone healing (postoperative defect volume mm^3) *6 months* I: 393.6±144.7 C: 260.4±98.8	

		(mm³): I: 974.8±236.8 C: 1052.4±326.0 P=0.595 <u>Groups comparable at baseline?</u> Yes				P=0.050 *12 months* I: 247.1±112.8 C: 207.8±77.9 P=0.432 <u>Morbidity:</u> I: patients (37.5%) developed significant swelling in the early postoperative period that was resolved uneventfully and not attributable to rhBMP-2 dose C: 7 patients (87.5%) complained of significant donor-site pain at week 2. <u>Mean length of stay:</u> I: 1 day postoperatively C: 3 days postoperatively <u>Dental eruption:</u> Routinely occurred in both groups. Not further described	
Canan, 2012	<u>Type of study:</u> RCT <u>Setting:</u> Assistance Center for Cleft Lip and Palate <u>Country:</u> Brazil <u>Source of funding:</u>	<u>Inclusion criteria</u>: Aged 8 to 15 years old, presenting uni-lateral cleft lip and/or palate with maxillary alveolar cleft defect <u>Exclusion criteria</u>: Not described <u>N total at baseline</u>: BMPG: 6	1) InFuse bone graft (Medtronic, Memphis, Tenn.)impregnated with rhBMP-2 (BMPG)	Traditional iliac crest cancellous graft (BGG)	<u>Length of follow-up</u>: 12 months <u>Loss-to-follow-up</u>: Intervention: N=0 (0%) Control: N=0 (0%)	<u>Bone filling percentage (%):</u> *3 months:* BMPG: 72.6±25.0 BGG: 75.6±20.0 P= 0.933 *6 months:* BMPG: 73.7±22.3 BGG: 76.0±18.2 P= 0.940	A third group (N=6) received periosteoplasty (PGG). The PPGshowed a lower volumeof boneformation in the assessment of 3 and 6 months. Because of clinical and ethical reasons, the continuity of patients from the PPG in the study was canceled after the 6-month measurement, and the patients were subjected to conventional bone grafting and the follow-up treatment was

	No financial support. Absorbable collagen sponge and rhBMP-2 were provided (free of charge) by Dabasons Import Export Ltd.	BGG: 6 Important prognostic factors[2]: *Mean age ± SD:* BMPG: 8.7±0.5 BGG: 10.8±2.3 *Preoperative defect (mean, mm^3):* BMPG: 471.8 BGG: 656.9 P=0.459 *Maxillary height noncleft side (mean, mm):* BMPG: 14.9 BGG: 13.6 P= 0.240 Groups comparable at baseline? Yes			Incomplete outcome data: Intervention: N=0 (0%) Control: N=0 (0%)	*12 months:* BMPG: 75.1±20.6 BGG: 78.0±15.1 P= 0.937 Maxillary height (percentage repair rate): *3 months:* BMPG: 55.4±10.6 BGG: 61.4±11.2 P= 0.429 *6 months:* BMPG: 58.9±11.5 BGG: 64.0±12.7 P= 0.699 *12 months:* BMPG: 64.2±14.6 BGG: 58.0±8.6 P= 0.818 Bone healing (postoperative defect volume mm^3) *3 months:* BMPG: 349.9±158.2 BGG: 493.8±309.2 P= 0.468 *6 months:* BMPG: 346.2±130.2 BGG: 502.9±311.4 P= 0.661 *12 months:* BMPG: 354.4±130.7 BGG: 520.5±310.3 P=0.589	ensured. Loss to follow-up not mentioned

						Cerebrospinal fluid density (Hounsfield units): *3 months:* BMPG: 72.6±25.0 BGG: 75.6±20.0 P= 0.933	
Thuaksuban, 2010	Type of study: RCT Setting: Dental Hospital, Prince of Songkla University Country: Thailand Source of funding: Supported by a grant for academic research from the Prince of Songkla University, Hatyai, Songkhla, Thailand.	Inclusion criteria: ASA class I patients, aged 9–12 years, with residual alveolar clefts Exclusion criteria: Bleeding disorders, bone and metabolic diseases, and not available for 2-year follow- up N total at baseline: Intervention: - 15 patients - 16 cleft sides Control: - 15 patients - 17 cleft sides Important prognostic factors[2]: *Mean age study population:* 10.2 years±1.2 *Gender* Male: n=10 Female: n=20 Groups comparable at baseline? Yes	A composite of deproteinized bovine bone (DBB) and autogenous cancellous bone harvested by a trephine bone collector. The ratio used was 1:1 of autogenous bone to DBB	Autogenous cancellous bone graft harvested from the anterior iliac crests by the conventional trapdoor approach	Length of follow-up: 24 months Loss-to-follow-up: Intervention: N= 2 (15.4%) Reasons: Lack of compliance, loss to follow-up Control: 1 N=1 (7.7%) Reasons: Lack of compliance, loss to follow-up Incomplete outcome data: Intervention: N= 2 (15.4%) Reasons: Lack of compliance, loss to follow-up	Postoperative pain (VAS) during 7 days: Not significantly different, but not specified Complications at donorsite Intervention: none reported Control: - paresthesia of the skin around the incision lines (n=1) - pain when walking (n=3) Complications at recipient site - Wound infection (I=1; C=1) - Wound dehiscence (I=3; C=1) Spontaneous eruption of canines: I: 5 teeth (42%) C: 5 teeth (50%) Decrease bone density after 24 months	This stufy used intraoral radiographs instead of computed tomography (CT) for evaluating bone graft quantities.

					Control: 1 N=1 (7.7%) Reasons: Lack of compliance, loss to follow-up	I: 27% C: 31% P > 0.05 <u>Decrease bone graft height</u> I: 24% C:24% P > 0.05	
Enemark, 2001	<u>Type of study:</u> Controlled Trial <u>Setting:</u> Aarhus Cleft Palate Institute <u>Country:</u> Denmark <u>Source of funding:</u> Not reported	<u>Inclusion criteria</u>: Not reported <u>Exclusion criteria</u>: Not reported <u>N total at baseline</u>: Intervention: 44 Control:57 <u>Important prognostic factors</u>[2]: *Age ± SD:* I: 9 years and 11 months C: 9 years and 10 months *Sex:* I: 73.9% M C: 70.2% M *UCLP complete* I: n=33 C: n=39 <u>Groups comparable at baseline?</u> Yes	Reconstruction of alveolar Cleft with mandibular bone	Reconstruction of alveolar Cleft with iliac crest bone	<u>Length of follow-up</u>: 4 years <u>Loss-to-follow-up</u>: No patients were lost to follow-up. <u>Incomplete outcome data</u>: No patients were lost to follow-up.	<u>Marginal Bone Level Scores (X^2):</u> I: 1.16 C:1.33 P=0.029 <u>Mean length of stay:</u> I: 3 to 4 days postoperatively C: 3 to 4 days postoperatively <u>Impaction of the cleft side canine after bone grafting:</u> I: 31.8% C: 35.1% P>0.05 <u>Average gingival retraction on cleft-side central incisor (X^2) :</u> I: 1.43 C:1.77 P= 0.512 <u>Complications immediately after surgery:</u>	The marginal bone level on cleft-related teeth was assessed on intraoral films and quantitated according to a 4- point scale previously described (Enemark et al., 1987).
Freihofer, 1993	Type of study: Retrospective	<u>Inclusion criteria</u>: All patients with	I: Reconstruction of the alveolar cleft before eruption of the canine	C1: rib bone as transplant material.	<u>Length of follow-up</u>:	Success rate defined as no oronasal	The timing of treatment, varied between patients, which might

	cohort study Setting: University hospital Country: The Netherlands Source of funding: Not reported	reconstructions of unilateral clefts and of clefts in patients with a bilateral deformity, with a follow-up time of at least 1 year and adequate documentation. <u>Exclusion criteria</u>: Patients with missing records or when it was not possible to reasonably incorporate them in one of the groups (unilateral cleft or cleft) <u>N total at baseline Unilateral clefts (number of cleft sides):</u> Intervention: 61 Control 1: 21 Control 2: 64 Control 3: 19 <u>N total at baseline Bilateral clefts (number of cleft sides):</u> Intervention: 32 Control 1: 21 Control 2: 46 Control 3: 32 <u>Important prognostic factors[2]</u>: Not reported Groups comparable at baseline? Unclear, unsufficient information was given	through the alveolar bone using chin bone as transplant material.	C2: iliac crest bone as transplant material. C3: heterogeneous group containing calvarial bone, bone from the vomer, bank bone, lyodura and closures without a transplant.	At least one year (no further information reported). <u>Loss-to-follow-up</u>: No loss to follow-up as availability of one year follow-up was part of the inclusion criteria. <u>Incomplete outcome data</u>: No incomplete outcome data as availability of data for one year follow-up was part of the inclusion criteria.	communication and with at least 50 % of the bone graft height (unilateral clefts): I: 35/36 (97%) C1: 38/46 (83%) C2: 39/71 (55%) C3: 4/12 (33%) Success rate defined as no oronasal communication and with at least 50 % of the bone graft height (bilateral clefts): I: 19/23 (83%) C1: 22/26 (84%) C2: 17/52 (33%) C3: 14/30 (47%) Difference in success rate between types of graft material (all clefts): Chin transplants gave significantly better results ($p<0.05$) than other transplants materials. Rib grafts gave significantly better results ($p<0.05$) than illium. The positive or negative effects of pre- and/or postoperative orthodontics were not studied.	has affected the outcome. Surgeons closing bilateral clefts were more experienced than those closing unilateral ones.

		on patient characteristics. Groups were not comparable on age.					

Notes:

1. Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures
2. Provide data per treatment group on the most important prognostic factors [(potential) confounders]
3. For case-control studies, provide sufficient detail on the procedure used to match cases and controls
4. For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders

Risk of bias table for intervention studies (randomized controlled trials)

Study reference (first author, publication year)	**Describe method of randomisation** [1]	**Bias due to inadequate concealment of allocation?** [2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?** [3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?** [3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?** [3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?** [4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?** [5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?** [6] (unlikely/likely/unclear)
Alonso, 2010	Not clearly described	unclear	unlikely	unclear	unclear	unlikely	unlikely	unlikely
Canan, 2012	Not clearly described	unclear	unlikely	unclear	unclear	unlikely	unlikely	unlikely
Thuaksuban, 2010	Not clearly described	unclear	unlikely	unclear	unclear	unlikely	unlikely	unlikely
Enemark, 2010	Not clear whether is it randomised	unclear	unlikely	unlikely	unclear	unlikely	unlikely	unlikely

1. Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
2. Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..
3. Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has “soft” (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4. Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.
5. If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear
6. Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.

Validity and Upkeep

Module[7]	Document manager(s)[8]	Year of authorisation	Next assessment of actuality of guideline[9]	Frequency of assessment for actuality[10]	Who will supervise the actuality?[11]	Relevant factors for changes to recommendation[12]
Orthognathic surgery in patients with clefts of the lip and palate: Le Fort I osteotomy versus distraction osteogenesis	NVPC, NVvO, NVMKA	2018	2023	5 years	NVPC	New relevant publications

Knowledge gaps

The effect of a classic Le Fort I osteotomy (LF1) - compared to distraction osteogenesis (DOG) - on speech development, relapse, revisional surgery, chewing function, malocclusion and post-operative position and relation of the bone and soft tissues in cleft patients has not been studied in sufficient detail.

Implementation

The guideline task force has not drafted an implementation plan, as more scientific evidence is required about the effects of a Le Fort I osteotomy compared to a distraction osteogenesis.

[7] Name of the module

[8] Document manager of the module (this can vary per module and can also be divided over several document managers)

[9] After maximum of five years

[10] Yearly, half-yearly, once every two years, once every five years

[11] managing association, shared managing associations, or (multi-disciplinary) task force remaining active

[12] Ongoing research, changes to reimbursement/organisation, availability of new products

Table exclusion after reading the full article

Author and year	Reason for exclusion
Zellner, 2017	Investigated the effect of another intervention in another patient population.
Shash, 2016	Investigated the effect of another intervention.
Pan, 2016	Investigated the effect of another intervention.
Bittermann, 2016	Investigated the effect of another intervention.

Evidence table

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Kloukos, 2016 (individual study characteristics deduced from Kloukos, 2016)	SR of six RCTs *Literature search up to February, 2016* **A:** Cheung, 2006 **B:** Chanchareonsook, 2007 **C:** Chua, 2010a **D:** Chua, 2010b **E:** Chua, 2012a **F:** Chua, 2012b Study design: **A – F:** Randomized Controlled Trial (RCT) Setting and Country: **A – F:** University hospital setting, Hong Kong Source of funding: (commercial / non-commercial / industrial co-authorship) **A – F:** (Not	Inclusion criteria SR: Randomized controlled trial comparing maxillary distraction osteogenesis to conventional Le Fort I osteotomy for the correction of cleft lip and palate maxillary hypoplasia in non-syndromic unilateral or bilateral cleft patient aged 15 years and older. Exclusion criteria SR: not stated *Six articles based on one study were included for this analysis.* Important patient	**A – F:** Intervention group[1] receiving maxillary distraction osteogenesis: a conventional Le Fort I was performed and maxilla was mobilised. Bilateral intraoral distractors were inserted and fixed on the zygomatic buttress and molar alveolar region. Distraction osteogenesis group: activation phase of distraction started on postoperative day 3 at a distraction rate of 1 mm/day in two rhythms until a class I incisal relationship was achieved.	**A – F:** Control group[1] of Le Fort I surgery: the maxilla was fully mobilised to the planned position. The mobilized maxilla was fixed by titanium miniplates at the zygomatic buttress and the pyriform region.	End-point of follow-up: **A**: 2 and 8 weeks and 3, 6 and 12 months postoperatively **B**: 3 months postoperatively **C**: 2 and 8 weeks, 3 and 6 months and 1,2,3,4 and 5 years postoperatively **D**: 3 months, 1 and 2 years postoperatively **E**: preoperatively and postoperatively at the 2nd to 8th week, 3 and 6 months, 1 and 2 years **F**: preoperatively and postoperatively at the 2nd week, 2,3 and 6 months, 1 and 2 years For how many participants were no complete outcome data available? (intervention/control) **A**: preliminary study (loss to follow-up: 5 participants 17.2%)) **B**: preliminary study (loss to follow-up: 3 participants (13.6%)) **C**: loss to follow-up: 0 participants (0.0%) **D**: loss to follow-up: 20	**Comparison: distraction osteogenesis versus orthognathic surgery** **C:** Outcome measure-1 Defined as skeletal stability (evaluated as the mean horizontal change of the maxilla at A-point) 5 years post-operatively, MD 4.80 (95%CI 0.41 – 9.19) 5 years post-operatively, MD (evaluated as the mean horizontal change of the maxilla at P point), MD 4.96 **D:** Outcome measure-2 Defined as resonance – hypernasality 4 months post-operatively, MD 0.75 (0.22 – 2.60) 17 months post-operatively, MD 0.11 (0.01 – 1.85) **D:** Outcome measure-3	This review found only one small randomised controlled trial concerning the effectiveness of distraction osteogenesis compared to conventional orthognathic surgery. The available evidence is of very low quality, which indicates that further research is likely to change the estimate of the effect. Based on measured outcomes, distraction osteogenesis may produce more satisfactory results; however, further prospective research comprising assessment of a larger sample size with participants with different facial characteristics is required to confirm possible true differences between interventions.

	stated)	<u>characteristics at baseline</u>: *Number of patients; characteristics important to the research question and/or for statistical adjustment (confounding in cohort studies); for example, age, sex, bmi, ...* <u>N, mean age</u> **A**: 29 patients randomized and analyzed, age range not reported **B**: 22 patients randomized and analyzed, age range 13 to 45 years old **C:** 47 patients randomized and analyzed, age range not reported **D:** 47 patients randomized, but only 22 analyzed, age range 16 to 22 **E:** 30 patients			participants (42.6%) **E**: loss to follow-up: 17 participants (56.7%) **F**: Many losses to follow-up	Defined as resonance – nasal emission 4 months post-operatively, MD 0.20 (0.01 – 3.74) 17 months post-operatively, MD 3.00 (0.14 – 66.53) **D:** <u>Outcome measure-4</u> Defined as velopharyngeal function – (no velopharyngeal incompetence or complete closure) 4 months post-operatively, MD 0.83 (0.44 – 1.54) 17 months post-operatively, MD 1.28 (0.65 – 2.52) **F:** <u>Outcome measure-5</u> Defined as maxillary advancement (evaluated as the advancement of Subspinale A-point (hard tissue)) 6 months post-operatively, MD 5.65 (P=0.003)	

		randomized, age range not reported **F:** 47 patients randomized, but only 39 analyzed, age range 16 to 22 <u>*Sex*</u>*:* **A**: 51.7% male **B**: 50.0% male **C**: sex not reported **D:** 50.0% male (from analysed participants) **E:** 56.7% male **F:** 51.3% male (from analysed participants)				12 months post-operatively, MD 5.27 (95%CI 2.53 – 8.01) 24 months post-operatively, MD 4.40 (95%CI 0.24 – 8.56) E: Outcome measure-6 Social Avoidance and Distress Scale (SADS) 3 months post-operatively MD -0.16 (95%CI -5.58, 5.26) 12 months post-operatively MD -0.58 (95%CI -4.95, 3.79) 24 months postoperatively MD -0.60 (95%CI -5.19, 3.99) E: Outcome measure-7 Cultural-Free Self-Esteem Inventory (CFSEI) 3 months post-operatively MD -2.28 (95%CI -4.85, 0.29(12 months post-	

						operatively MD -0.33 (95%CI -2.46, 1.80) 24 months post-operatively MD 0.17 (-2.11, 2.45) E: Outcome measure-8 Statisfaction with Life Scale (SWLS) 3 months post-operatively MD -0.49 (95%CI -4.26, 3.28) 12 months post-operatively MD 3.41 (95%CI -0.14, 6.96) 24 months post-operatively MD 2.95 (95%CI 0.14, 5.76)	

1) In the results is the control group the intervention group and vice versa.

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea et al., 2007; BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al, 2009; PLoS Med 6: e1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/not applicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Kloukos, 2016	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined.**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched.**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported.**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs).**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table et cetera).**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (for example Chi-square, I^2)?**
8. **An assessment of publication bias should include a combination of graphical aids (for example funnel plot, other available tests) and/or statistical tests (for example Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Chapter 10 Orthodontic treatment in patients with clefts of the lip and palate

Module: Ventral traction

Table exclusion after reading the full article

Author and year	Reason for exclusion
Ahn 2012	Does not meet inclusion criteria (follow-up too short).
Aizenbud 2012	Does not meet inclusion criteria.
Azeredo 2011	Does not meet inclusion criteria (congress abstract).
Baik 2009	Does not meet inclusion criteria (case-report).
Buschang 1994	Does not meet inclusion criteria (follow-up too short).
Chen 1996	Does not meet inclusion criteria (follow-up too short).
Chen 2007	Does not meet inclusion criteria (follow-up too short).
Chung 2013	Does not meet inclusion criteria (not relevant outcome variables).
Da Luz Vieira 2009	Does not meet inclusion criteria (follow-up too short).
Delaire 1973	Does not meet inclusion criteria (description of the technique).
Delaire 1976	Does not meet inclusion criteria (case-report).
Friede 1981	Does not meet inclusion criteria (case-report).
Gaggl 1999	Does not meet inclusion criteria.
Hickham 1991	Does not meet inclusion criteria (description of the technique).
Hoffmann 1986	Does not meet inclusion criteria (does not deal specifically with maxillary protraction)
Ishikawa 2000	Does not meet inclusion criteria (follow-up too short).

Jia 2006	Article written in Chinese
Jia 2008	Does not meet inclusion criteria (follow-up too short).
Liou 2005	Does not meet inclusion criteria (follow-up too short).
Maulina 2007	Does not meet inclusion criteria.
Mullerova 1994	Does not meet inclusion criteria.
Ramadan 2008	Does not meet inclusion criteria.
Ranta 1989	Does not meet inclusion criteria.
Rocha 2012	Does not meet inclusion criteria (case-report).
Sade 2010	Does not meet inclusion criteria (follow-up too short).
Sakamoto 2002	Does not meet inclusion criteria.
Sarnas 1987	Does not meet inclusion criteria (follow-up too short).
Sarnas 1998	Does not meet inclusion criteria.
Schultes 2000	Does not meet inclusion criteria.
Singla 2014	Does not meet inclusion criteria (follow-up too short).
So 1996	Does not meet inclusion criteria (follow-up too short).
Subtelny 2004	Does not meet inclusion criteria.
Tateishi 2001	Does not meet inclusion criteria.
Tindlund 1989	Does not meet inclusion criteria (follow-up too short).
Tindlund 1993	Does not meet inclusion criteria (follow-up too short).
Tindlund 1993	Does not meet inclusion criteria (follow-up too short).
Tindlund 1994	Does not meet inclusion criteria (follow-up too short).
Trotman 1994	Does not meet inclusion criteria.
Veleminska 2003	Does not meet inclusion criteria.
Vachiramon 2009	Does not meet inclusion criteria.
Yang 2012	Does not meet inclusion criteria (case-report).

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series]

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Borzabadie-Farahani 2014	Type of study: retrospective observational Setting: CLP centre Children's hospital Los Angeles Country: United States Source of funding: non-commercial	Inclusion criteria: 1) patients with unilateral cleft lip and palate (UCLP) 2) Class III malocclusions Exclusion criteria: - N total at baseline: Intervention: 18 Control: 17 Important prognostic factors[2]: *For example age (range):* I: 13-14 yr C: 13-14 yr *Sex:* I: 56% M C: 47% M Groups comparable at baseline? yes	Describe intervention (treatment/procedure/test): Late maxillary protraction during the night and fulltime Class III elastics after 8 weeks of suture loosening with weekly alternating rapid maxillary expansion and constriction with a Hyrax (Alt-RAMEC technique) until overcorrection to 3 mm positive overjet. Duration of treatment: 3-6 mo (mean 4.6 mo) 3-4 mo after point of overcorrection: removal of Hyrax and facemask and continuation with fixed appliances and Class III elast	Describe control (treatment/procedure/test): Orthodontic treatment in preparation for orthognathic surgery, no compensating extractions	Length of follow-up: From 13-14 until 17-18 years Loss-to-follow-up: Intervention: 1 1 (5%) Reason: not compliant with therapy Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): For explanation of abbreviations see figure 1 and 2. Significant differences in between groups for the following variables (table 3): SNA (°): 1.95 (95% CI: 0.75 – 3.15) A ⊥Na Perp (mm): 1.82 (95% CI: 0.86 – 2.77), CoA (mm): 2.92 (95% CI: 1.53 – 4.31), CoGn (mm): 3.55 (95% CI: 1.68 – 5.42), ANB(°): 3.13 (95% CI: 2.02 – 4.24), Wits (mm): 6.81 (95% CI: 4.44 – 9.18), Occl P-SN(°): -3.98 (95% CI: -5.99 - -1.98),	Author's conclusion: Late maxillary protraction produced a combination of skeletal changes (protraction of maxilla, improvement in the maxilla-mandibular skeletal relationship) and dental compensations (counterclockwise rotation of occlusal plane, retroclination of mandibular incisors) in patients with UCLP. Late maxillary protraction was also associated with some unwanted tooth movements (open bite tendency mandibular incisors overeruption).

						overjet (mm): 5.65 (95% CI: 4.11-7.19); IMPA (°): -5.77 (95% CI: -9.74 - -1.80) Late maxillary protraction created a slight open bite (0.66mm). Trends for overeruption of mandibular incisors and an increased lower face height (p=0.07 for both) were noted in the study group.	
Susami 2014	Type of study: retrospective observational Setting: outpatients Country: Japan Source of funding: not reported	Inclusion criteria: 1) Japanese patients with unilateral cleft lip and palate (UCLP) 2) treated with maxillary protraction (MP) in mixed dentition 3) followed until completion of growth (COG) Exclusion criteria: N total at baseline: Intervention: 11 Important prognostic factors[2]: *age (years):* *Start of MP:*	Describe intervention (treatment/procedure/test): Intra-oral maxillary lingual arch with buccal arms, Maxillary protraction (MP) with facemask during night (8-10hr). Force 150-200gF per side. MP was ceased when overbite became small and when patient's compliance became poor. Duration of treatment: mean 3y7m0	Describe control (treatment/procedure/test): Not applicable	Length of follow-up: Until completion of growth Average: 9 years 2 months Loss-to-follow-up: none Incomplete outcome data: Not described	Outcome measures and effect size (include 95%CI and p-value if available): *Also see table 2 in Results section.* Surgery: 5/11 patients eventually required orthognathic surgery A-posterior vertical line distance (A-PV) After MP: Forward movement 2.0mm (p<0.01) After COG: moved posterior in 7/11 cases (p>0.05) Point A-anterior vertical line distance (A-AV) After MP: Moved forward in 4/11 cases, negligible change After COG: moved posterior (p<0.001)	Author's conclusion: MP was effective as an early treatment for UCLP patients. However, its side effects showed a large variation and were in conflict with facial growth. Conscientious explanation of the expected effects and associated problems should be given to the patients/parents before its application.

		8y10m *End of MP: 12y5m* *After growth: 18y 0m* *Sex:* *I: 64% M* Groups comparable at baseline? Not applicable				<u>SNA</u> After MP: Moved forward in 5/11 cases, negligible change After COG: decreased ($p<0.01$) <u>SNB:</u> After MP: Decreased slightly ($p>0.05$) After COG: decreased ($p>0.01$) <u>Mandibular length (Cd-gn)</u> After MP: increased significantly After COG: increased ($p<0.01$) <u>Maxillary length (Cd-A)</u> After MP: Increased by 4.1mm ($p<0.001$) After COG: NR <u>HF-MP</u> After MP: increased in most cases ($p<0.01$) After COG: slightly increased ($p>0.05$) <u>Maxillary mandibular relationship (ANB)</u> After MP: large variation, overall change negligible After COG: decrease in 10/11 cases ($p<0.01$) <u>Difference between maxillary and mandibular length:</u> After MP: increased ($p<0.01$) After COG: increased ($p<0.001$)	

						Wits value After MP: improved, but p>0.05 After COG: U6-AV: After MP: forward movement 3.3mm (p<0.001) After COG: moved forward in most cases (p<0.05) Upper incisor: After MP: proclined significantly (p<0.01) After COG: no change on average Negative overjet After MP: improved (p<0.01) After COG: improved to normal limits in 6 patients that did not need surgery Mean overbite After MP: decreased (p<0.01) After COG: NR	

Notes:

1. Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures
2. Provide data per treatment group on the most important prognostic factors [(potential) confounders]
3. For case-control studies, provide sufficient detail on the procedure used to match cases and controls
4. For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Borzabadi-Farahani 2014	Unlikely	Unlikely	Unlikely	Unclear
Susami 2014	Unlikely	Unlikely	Unlikely	Unclear

1. Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.
2. Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.
3. Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4. Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.

Table Exclusion after reading the full article

Author and year	Reason for exclusion
Al-Gunaid, 2008	Does not meet inclusion criteria (description of the technique).
Bragger, 1991	Not clinically relevant (obsolete technique, patients did not receive bone grafting).
Carpentier, 2014	Does not meet inclusion criteria (does not answer research question).
Collins, 2013	Does not meet inclusion criteria (does not answer research question).
Curtis, 1968	Not clinically relevant (obsolete technique).
Duskowa, 2008	Does not meet inclusion criteria (does not answer research question).
Graf-Pinthus, 1970	Does not meet inclusion criteria (does not answer research question).
Hinz, 1986	Does not meet inclusion criteria (narrative review).
Holtgrave, 1989	Insufficient quality (surgical treatment nor described).
Iwata, 1992	Does not meet inclusion criteria (does not answer research question).
Johanson, 1974	Not clinically relevant (obsolete technique, patients did not receive bone grafting).
Li, 1997	Does not meet inclusion criteria (does not answer research question).
Li, 2004	Does not meet inclusion criteria (does not answer research question).
Li, 2007	Does not meet inclusion criteria (does not answer research question).
Li-xia, 2013	Does not meet inclusion criteria (does not answer research question).
Nicholson, 1989	Does not meet inclusion criteria (does not answer research question).
Ramstad, 1973	Not clinically relevant (obsolete technique, patients did not receive bone grafting).
Ramstad, 1997	Not clinically relevant (obsolete technique, patients did not receive bone grafting).
Rune, 1980	Does not meet inclusion criteria (does not answer research question).
Schoenaers, 2013	Does not meet inclusion criteria (not an original article).

Sheats, 1992	Does not meet inclusion criteria (narrative review).
Stoelinga, 1989	Does not meet inclusion criteria (does not answer research question).
Subtelny, 2004	Does not meet inclusion criteria (not an original article).

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies [cohort studies, case-control studies, case series]

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Marcusson, 2004	Type of study: prospective observational Setting: outpatients, University Hospital Country: Sweden Source of funding: non-commercial	Inclusion criteria: 1) patients with unilateral cleft lip and palate (UCLP) Exclusion criteria: 1) removable lingual appliance in the upper arch (n=6) 2) no study model at the baseline or at the follow-up examination (n=5) 3) orthodontic treatment, prosthodontic treatment or orthognathic surgery after baseline examination N total at baseline: Intervention A: 13 Intervention B: 11 Control: 15 Important	Describe intervention (treatment/procedure/test): A: Lip closure according to the Millard technique (3 months) Palatal closure according to the Wardill-Kilner technique (18 months) Orthodontic treatment with fixed appliances Bonded twisted retainer B: Lip closure according to the Millard technique (3 months) Palatal closure according to the Wardill-Kilner technique (18 months) Orthodontic treatment with fixed appliances Onlay or fixed bridge	Describe control (treatment/procedure/test): C: Lip closure according to the Millard technique (3 months) Palatal closure according to the Wardill-Kilner technique (18 months) Orthodontic treatment with fixed appliances No retention	Length of follow-up: Mean 5.6 (range 0.9 – 9.6) years Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Dental casts examined a scoring system developed by Huddart and Bodenham Means ± standard deviations are reported And p-values Maxillary canine width: A: -0.6 ± 0.6 B: -0.5 ± 0.8 C: -0.7 ± 0.9 p>0.05 Maxillary second premolar width: A: -1.7 ± 1.6 B: -1.7 ± 1.4 C: -1.6 ± 1.4 p>0.05 Maxillary first molar width: A: -1.1 ± 1.3 B: -1.4 ± 1.3 C: -1.7 ± 1.6 p>0.05	Author's conclusion: The occlusal score and the maxillary arch dimensions were reduced in all of the three groups, but there was no difference between the three groups. No power calculation for sample size provided.

		<u>prognostic factors[2]</u>: *Were reported for whole population, not per group* *age (range):* 25 (20-29) *Sex: 64% Male* Groups comparable at baseline? unclear				<u>Maxillary saggital length:</u> A: -0.6 ± 0.8 B: -0.6 ± 0.9 C: -1.0 ± 0.9 p>0.05 <u>Arch length cleft side:</u> A: -0.7 ± 0.9 B: -0.9 ± 0.7 C: -1.5 ± 1.3 p>0.05 <u>Arch length non-cleft side:</u> A: -1.0 ± 1.2 B: -1.1 ± 0.9 C: -1.1 ± 1.4 p>0.05 <u>Overjet:</u> A: -0.4 ± 0.7 B: -0.2 ± 1.2 C: -0.2 ± 0.6 p>0.05 <u>Overbite:</u> A: 0.0 ± 0.8 B: 0.0 ± 0.7 C: -0.3 ± 1.1 p>0.05	

Notes:

1. Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures
2. Provide data per treatment group on the most important prognostic factors [(potential) confounders]
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Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Marcusson, 2004	Unlikely	Unlikely	Unlikely	Unclear

1. Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.
2. 2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.
3. Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has “soft” (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4. Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.

Chapter 11 Rhinoplasty in patients with clefts of the lip and palate

Module: Rhinoplasty

Table of excluded studies (exclusion after assessment of full text).

Author and year of publication	Reason for exclusion
Chang, 2010	Does not meet selection criteria
Cussons, 1993	Does not meet selection criteria (follow-up too short)
Garri, 2005	Does not meet selection criteria (follow-up too short)
Hens, 2012	Does not meet selection criteria
Horswell, 1995	Does not meet selection criteria
Janiszewska-Olszowska, 2013	Does not meet selection criteria (follow-up too short)
Kim, 2004	Does not meet selection criteria (follow-up too short)
Kim, 2009	Does not meet selection criteria
Lu, 2012	Does not meet selection criteria (follow-up too short)
Mcheik, 2006	Does not meet selection criteria
Meazzini, 2010	Does not meet selection criteria
Offert, 2013	Does not meet selection criteria (follow-up too short)
Roberts-Harry, 1996	Does not meet selection criteria (follow-up too short)

Chapter 12 Psychosocial guidance for patients with clefts of the lip and palate

Module: Psychosocial guidance

Table of excluded studies (exclusion after assessment of full text).
Psychosocial interventions

Author and year of publication	Reason for exclusion
Collet, 2006	Does not meet inclusion criteria (does not answer research question).
Collet, 2007	Does not meet inclusion criteria (review, not systematic).
Damiano, 2010	Does not meet inclusion criteria (does not answer research question).
Douglas, 2012	Does not meet inclusion criteria (does not report the required outcome measures).
Grollemund, 2012	Article in French
Habersaat, 2013	Article in French
Hill, 2004	Does not meet inclusion criteria (does not answer research question).
Hunt, 2005	Does not meet inclusion criteria (does not answer research question).
Murray, 2008	Does not meet inclusion criteria (does not answer research question).
Nelson, 2012	Does not meet inclusion criteria (does not answer research question).
Pelchat, 2004	Included in systematic review Norman, 2014.
Shkoukani, 2014	Does not meet inclusion criteria (review, not systematic).

Psychosocial developement

Author and year of publication	Reason for exclusion
Berger, 2011	Does not meet selection criteria (does not answer research question).
Broder, 2013	Does not meet selection criteria (does not answer research question).
Collett, 2009	Does not meet selection criteria (does not answer research question).
Collett, 2010	Does not meet selection criteria (does not answer research question).

Conrad, 2014	Does not meet selection criteria (does not answer research question).
Endriga, 2003	Does not meet selection criteria (does not answer research question).
Maris, 1998	Already included in the systematic review by Hunt, 2005
Yu-Fen, 2000	Taiwanese population, not representative to draw conclusions about Dutch population
Zeytinoglu, 2012	Does not meet selection criteria (review, not systematic)

Evidence table for systematic review of RCTs and observational studies (intervention studies)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Norman, 2014 [individual study characteristics deduced from [1st author, year of publication]] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of [RCTs / cohort / case-control studies] *Literature search up to June 2013* **A**: Bessell, 2012 **B**: Newell, 2000 **C**: Maddern, 2006 **D**: Kapp-Simon, 2005 **E**: Pelchat, 2004 **F**: Kleve, 2002 **G**: Rpbinson, 1996 Study design: **A:** RCT **B:** RCT **C:** observational **D:** observational **E:** observational **F:** observational **G:** observational Setting and Country: United Kingdom Source of funding: Not reported	Inclusion criteria SR: 1) studies relating psychological interventions for children or adults with cleft lip and/or palate or parents of children with cleft lip and/or palate. 2) cleft lip and/or palate with or without cleft alveolus or individuals with syndromes with no developmental delay 3) randomized and non-randomized controlled trials and observational studies 4) interventions: all interventions addressing psychological adjustment 5) comparator: no intervention, other psychosocial intervention, or psychosocial intervention at a different point in time 6) outcome: measures related to psychosocial functioning Exclusion criteria SR: 1) studies containing <90% cleft palate patients, unless they reported results separately for those with cleft lip and/or palate or raw data for this subgroup was available upon request from authors.	Describe intervention: **A**: 8 weekly sessions, 60 minutes cognitive behavioural therapy (CBT) / social skills training (SST) **B**: CBT **C**: CBT **D**: SST group sessions **E**: CBT group sessions **F**: CBT **G**: SST	Describe control: **A**: no treatment **B**: no treatment **C**: no control **D**: waiting list control **E**: no control **F**: no control **G**: no control	End-point of follow-up: **A**: 6 months **B**: 3 months **C**: 6 months **D**: immediately after sessions **E**: immediately after sessions **F**: 6 months **G**: 6 months For how many participants were no complete outcome data available? (intervention/control) **A:** NR **B**: NR **C**: NR **D**: NR **E**: NR **F**: NR **G**: NR	Outcome measure-1 This review found no evidence to support any specific intervention.	Facultative: Brief description of author's conclusion Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question Level of evidence: GRADE (per comparison and outcome measure) including reasons for down/upgrading: No GRADE assessment possible since insufficient evidence for any intervention is provided Pooling not applicable due to large heterogeneity of studies.

		7 studies included <u>Important patient characteristics at baseline</u>: *Number of patients; characteristics important to the research question and/or for statistical adjustment (confounding in cohort studies); for example, age, sex, bmi, ...* <u>N, mean age</u> **A**: 8 patients, 18+ **B**: 106 patients, 18+ **C**: 29 patients, 5-16 years **D:** 20 patients, 12-14 years **E:** 76 parents, age NR **F:** 36 patients, 17-72 years **G:** 64 patients, adults <u>*Sex:*</u> **A**: 0% Male **B**: 11% Male **C**: 45% Male **D:** 45% Male **E:** 43% Male **F:** 25% Male **G:** 31% Male Groups comparable at baseline? Not applicable					

Table of quality assessment for systematic reviews of RCTs and observational studies

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Norman, 2014	Yes	Yes	No	Yes	Not applicable	Yes	No	No	No

1. Research question (PICO) and inclusion criteria should be appropriate and predefined
2. Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched
3. Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons
4. Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported
5. Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)
6. Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table etc.)
7. Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I^2)?
8. An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.
9. Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a “yes,” source of funding or support must be indicated for the systematic review AND for each of the included studies.

Appendix 8 Search justifications

Database	Search terms	Total
Medline (OVID) 1980-Nov. 2014 English, Dutch	1 cleft lip/ (12101) 2 Cleft Palate/ (17052) 3 ((gnatho* or cheilo* or palato) adj10 schisis):ti,ab(9) 4 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)):ti,ab(18012) 5 1 or 2 or 3 or 4 (24227) 12 exp Breast Feeding/ (27202) 13 Bottle Feeding/ (3361) 14 Palatal Obturators/ (1663) 15 exp Feeding Methods/ (38324) 16 (("special need*" or finger* or breast* or spoon* or nasogastric* or cup-and-spoon* or artificial* or syring* or intervention* or appliance*) adj3 (feed* or fed)):ti,ab(21306) 17 (breastfeeding or breast-feeding or breastmilk or breast-milk):ti,ab(32119) 18 (feeding adj3 (disorder* or skill* or problem* or difficult* or behavior* or behaviour* or failure* or pattern*)):ti,ab(14005) 19 (obturator* or botlle* or teat* or suck*):ti,ab(23726) 20 "Infant Nutritional Physiological Phenomena"/ (12799) 21 "Sucking Behavior"/ (2228) 22 "Syringes"/ (5207) 23 or/12-22 (130144) 24 5 and 23 (1154) 25 limit 24 to (yr="1980 -Current" and (dutch or english)) (593) 26 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (228748) 27 25 and 26 (16) 28 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*:ti,abor (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1453355) 29 25 and 28 (50) 30 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or prospective.tw. or Cross sectional.tw. or Cross-sectional studies/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (2119950) 31 25 and 30 (174) 32 27 or 29 or 31 (206) 33 27 or 29 (65) – 56 unique 34 31 not 33 (145) – 141 unique	361
Embase (Elsevier)	'cleft lip'/exp/mj OR 'cleft palate'/exp/mj OR ((gnatho* OR cheilo* OR palato) NEAR/10 schisis):ab,ti OR (alveolar NEAR/3 cleft*):ab,ti OR (orofacial NEAR/3 cleft*):ab,ti OR (cleft NEAR/3 lip*):ab,ti OR (cleft NEAR/3 palate*):ab,ti OR (cleft NEAR/3 maxilla*):ab,ti OR (oral NEAR/3 cleft):ab,ti AND ('breast feeding'/exp/mj OR 'infant feeding'/exp/mj OR 'feeding bottle'/exp OR 'palatal obturator'/exp OR 'sucking'/exp OR 'syringe'/exp OR (('special need' OR 'special needs' OR finger* OR breast* OR spoon* OR nasogastric* OR 'cup and spoon' OR artificial* OR syring* OR intervention* OR appliance*) NEAR/3 (feed* OR fed)):ab,ti OR breastfeeding:ab,ti OR 'breast feeding':ab,ti OR breastmilk:ab,ti OR 'breast milk':ab,ti OR (feeding NEAR/3 (disorder* OR skill* OR problem* OR difficult* OR behavior* OR behaviour* OR failure* OR pattern*)):ab,ti OR obturator*:ab,ti OR botlle*:ab,ti OR teat*:ab,ti OR suck*:ab,ti)	

	AND ([dutch]/lim OR [english]/lim) AND [1980-2014]/py (212) – 155 uniek AND 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp) OR 'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti NOT 'conference abstract':it)), AND 'clinical study'/exp (35) – 9 unique	

Chapter 5 Lip and palate closure in patients with clefts of the lip and palate

Module: Timing of the lip and palate closure

Database	Search terms	Total
Medline (OVID) 1980-present English	1 cleft lip/ (12101) 2 Cleft Palate/ (17052) 3 ((cheilo* or palato*) adj10 schisis).ti,ab. (9) 4 ((Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (oral adj3 cleft)).ti,ab. (17628) 5 1 or 2 or 3 or 4 (24098) 6 Cleft Palate/su [Surgery] (6084) 7 Cleft Lip/su [Surgery] (4885) 8 (closure* or surgery or "surgical repair").ti,ab. (877124) 9 palatoplast*.ti,ab. (651) 10 (millard or "vomerin* flap*" or langenbeck or furlow).ti,ab. (645) 11 6 or 7 or 9 or 10 (8160) 12 5 and 11 (7733) 13 limit 12 to (english language and yr="1980 -Current") (4391) 14 (Sagittal growth of the facial skeleton of 6-year-old children with a complete unilateral cleft of lip, alveolus and palate treated with two different protocols).m_titl. (1) 15 (Two-stage palatoplasty, is it still a valuable treatment protocol for patients with a cleft of lip, alveolus, and palate?).m_titl. (1) 16 14 or 15 (2) 17 (Protocols in cleft lip and palate treatment: systematic review).m_titl. (1) 18 (Effect on maxillary arch development of early 2-stage palatoplasty by modified furlow technique and conventional 1-stage palatoplasty in children with complete unilateral cleft lip and palate).m_titl. (1) 19 17 or 18 (2) 20 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (228748) 21 13 and 20 (57) – 56 unique 22 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1453355) 23 13 and 22 (319) 24 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or prospective.tw. or Cross sectional.tw. or Cross-sectional studies/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (2119950) 25 *Time Factors/ or Age Factors/ or (secondary or primary or tertiary or timing or age or late or early or delayed).ti. or stage.ti,ab. (1587435) 26 16 or 19 (4) 27 23 not 21 (310) – 292 unique	516

Embase (Elsevier)	'cleft lip'/exp/mj OR 'cleft palate'/exp/mj OR ((cheilo* OR palato) NEAR/10 schisis):ab,ti OR (orofacial NEAR/3 cleft*):ab,ti OR (cleft NEAR/3 lip*):ab,ti OR (cleft NEAR/3 palate*):ab,ti OR (oral NEAR/3 cleft):ab,ti AND (closure*:ab,ti OR surgery:ab,ti OR 'surgical repair':ab,ti OR palatoplast*:ab,ti OR millard:ab,ti OR (vomerin NEAR/2 flap*):ab,ti OR langenbeck:ab,ti OR furlow:ab,ti) AND [english]/lim AND [embase]/lim AND [1980-2014]/py AND ('meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp)) (26) – 20 unique AND ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it (230) – 148 unique	

Module: Technique for lip and palate closure

Database	Search terms	Total
Medline (OVID) 1980-present English	1 cleft lip/ (12101) 2 Cleft Palate/ (17052) 3 ((cheilo* or palato*) adj10 schisis).ti,ab. (9) 4 ((Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (oral adj3 cleft)).ti,ab. (17628) 5 1 or 2 or 3 or 4 (24098) 6 Cleft Palate/su [Surgery] (6084) 7 Cleft Lip/su [Surgery] (4885) 8 (closure* or surgery or "surgical repair").ti,ab. (877124) 9 palatoplast*.ti,ab. (651) 10 (millard or "vomerin* flap*" or langenbeck or furlow).ti,ab. (645) 11 6 or 7 or 9 or 10 (8160) 12 5 and 11 (7733) 13 limit 12 to (english language and yr="1980 -Current") (4391) 14 (Sagittal growth of the facial skeleton of 6-year-old children with a complete unilateral cleft of lip, alveolus and palate treated with two different protocols).m_titl. (1) 15 (Two-stage palatoplasty, is it still a valuable treatment protocol for patients with a cleft of lip, alveolus, and palate?).m_titl. (1) 16 14 or 15 (2) 17 (Protocols in cleft lip and palate treatment: systematic review).m_titl. (1) 18 (Effect on maxillary arch development of early 2-stage palatoplasty by modified furlow technique and conventional 1-stage palatoplasty in children with complete unilateral cleft lip and palate).m_titl. (1) 19 17 or 18 (2) 20 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (228748) 21 13 and 20 (57) – 56 uniek 22 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or	516

	doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1453355) 23 13 and 22 (319) 24 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or prospective.tw. or Cross sectional.tw. or Cross-sectional studies/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (2119950) 25 *Time Factors/ or Age Factors/ or (secondary or primary or tertiary or timing or age or late or early or delayed).ti. or stage.ti,ab. (1587435) 26 16 or 19 (4) 27 23 not 21 (310) – 292 unique	
Embase (Elsevier)	'cleft lip'/exp/mj OR 'cleft palate'/exp/mj OR ((cheilo* OR palato) NEAR/10 schisis):ab,ti OR (orofacial NEAR/3 cleft*):ab,ti OR (cleft NEAR/3 lip*):ab,ti OR (cleft NEAR/3 palate*):ab,ti OR (oral NEAR/3 cleft):ab,ti AND (closure*:ab,ti OR surgery:ab,ti OR 'surgical repair':ab,ti OR palatoplast*:ab,ti OR millard:ab,ti OR (vomerin NEAR/2 flap*):ab,ti OR langenbeck:ab,ti OR furlow:ab,ti) AND [english]/lim AND [embase]/lim AND [1980-2014]/py AND ('meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp)) (26) – 20 uniek AND ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it (230) – 148 unique	

Chapter 7 Hearing problems in patients with clefts of the lip and palate

Database	Search terms	Total
Medline (OVID) English. 2000-Oct. 2014	1 cleft lip/ (11952) 2 Cleft Palate/ (16865) 3 ((gnatho* or cheilo* or palato) adj10 schisis).ti,ab. (9) 4 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (17751) 5 1 or 2 or 3 or 4 (23931) 6 Middle Ear Ventilation/ (2150) 7 grommet*.ti,ab. (500) 8 exp Hearing Aids/ (13356) 9 ((oto* or audit* or hearing or cochlear) adj3 (prosthes* or implant*)).ti,ab. (10521) 10 ((oto* or ear*) adj3 implants*).ti,ab. (775) 11 ((ventilation or tympan* or oto* or audit* or hearing or cochlear or ear*) adj6 tube*).ti,ab. (9603) 12 6 or 7 or 8 or 9 or 10 or 11 (28522) 13 5 and 12 (214) 14 limit 13 to (english language and yr="2000 -Current") (90) 15 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (223143) 16 14 and 15 (5) 17 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1423054) 18 14 and 17 (11) 19 18 not 16 (8) 20 16 or 19 (13) – 13 unique 21 14 not 20 (77) – 75 unique	109
Embase (Elsevier)	'cleft lip'/exp/mj OR 'cleft palate'/exp/mj OR ((gnatho* OR cheilo* OR palato) NEAR/10 schisis):ab,ti OR (alveolar NEAR/3 cleft*):ab,ti OR (orofacial NEAR/3 cleft*):ab,ti OR (cleft NEAR/3 lip*):ab,ti OR (cleft NEAR/3 palate*):ab,ti OR (cleft NEAR/3 maxilla*):ab,ti OR (oral NEAR/3 cleft):ab,ti AND ('middle ear ventilation'/exp/mj OR 'hearing aid'/exp/mj OR ((oto* OR audit* OR hearing OR cochlear) NEAR/3 (prosthes* OR implant*)):ab,ti OR ((oto* OR ear*) NEAR/3 implants*):ab,ti OR ((ventilation OR tympan* OR oto* OR audit* OR hearing OR cochlear OR ear*) NEAR/6 tube*):ab,ti OR grommet*:ab,ti) AND [english]/lim AND [embase]/lim AND 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp) OR 'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti NOT 'conference abstract':it) AND [2000-2014]/py) AND [2000-2014]/py – 15 referenties, 12 unique Miscellaneous: 73 references, 19 unique	

Chapter 8 Hypernasality in patients with clefts of the lip and palate

Module: Diagnosis of hypernasality

Database	Search terms	Total
Medline (Ovid) 2000-present English	1 Cleft Palate/ (17834) 2 ((palato or cheilo-gnatho-palato) adj10 schisis).ti,ab. (7) 3 (cleft adj3 palate*).ti,ab. (15224) 4 "Velopharyngeal Insufficiency"/ (1517) 5 (Velopharyngeal adj3 (Insufficienc* or function* or dysfunction* or incompetence*)).ti,ab. (1486) 6 1 or 2 or 3 or 4 or 5 (22996) 12 "Voice Disorders"/ or Articulation Disorders/ or Speech intelligibility/ (9226) 13 "Voice Quality"/ (4657) 14 (nasality or hypernasality or nasalance or articulation or (nasal adj3 emission) or (speech adj3 production)).ti,ab. (11234) 15 12 or 13 or 14 (21838) 16 ("speech assessment" or nasopharyngoscop* or "speech evaluation" or nasometr* or nasendoscop* or endoscop* or video* or mri or "magnetic resonance imaging").ti,ab. (457931) 17 "Speech Articulation Tests"/ (891) 18 exp Articulation Disorders/di [Diagnosis] (1037) 19 Nasopharynx/pp [Physiopathology] (195) 20 Speech Disorders/di [Diagnosis] (1990) 21 Endoscopy/ (42575) 22 exp Fluoroscopy/ (13986) 23 exp Magnetic Resonance Imaging/ (334868) 24 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (652142) 25 6 and 15 and 24 (517) 26 limit 25 to (english language and yr="2000 -Current") (275) – 245 unique	245

Module: Treatment of hypernasality

Database	Search terms	Total
Medline (OVID) 1966-April 2014 English	1 Cleft Palate/ (17834) 2 ((palato or cheilo-gnatho-palato) adj10 schisis).ti,ab. (7) 3 (cleft adj3 palate*).ti,ab. (15224) 4 "Velopharyngeal Insufficiency"/ (1517) 5 (Velopharyngeal adj3 (Insufficiency or function or dysfunction or incompetence)).ti,ab. (1470) 6 1 or 2 or 3 or 4 or 5 (22988) 7 "Voice Disorders"/ or Articulation Disorders/ or speech intelligibility/ (9226) 8 "Voice Quality"/ (4657) 9 (nasality or hypernasality or nasalance or articulation or (nasal adj3 emission)).ti,ab. (8677) 10 7 or 8 or 9 (19644) 11 6 and 10 (1182) 12 (pharyngoplast* or furlow).ti,ab. (644) 13 Reconstructive Surgical Procedures/ or Otorhinolaryngologic Surgical Procedures/ (37051) 14 ("palatal closure*" or palatoplast*).ti,ab. (873) 15 "Surgical Flaps"/ or "Adipose Tissue"/tr (54234) 16 "intravelar veloplasty".ti,ab. (81) 17 surgery.fs. (1648736) 18 12 or 13 or 14 or 15 or 16 or 17 (1661890) 19 exp "rehabilitation of speech and language disorders"/ (8900) 20 "speech therap*".ti,ab. (2268) 21 19 or 20 (10237) 22 limit 11 to english language (1056) 23 18 or 21 (1670565) 24 22 and 23 (694) 35 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or	10 SR

	((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (231161) 36 24 and 35 (6)	
Embase (Elsevier)	('cleft palate'/exp/mj OR 'palatopharyngeal incompetence'/exp/mj OR (cleft NEAR/3 palate*):ab,ti OR (velopharyngeal NEAR/3 (insufficiency OR function OR dysfunction OR incompetence)):ab,ti) AND (pharyngoplast*:ab,ti OR 'palatal closure':ab,ti OR palatoplast*:ab,ti OR 'intravelar veloplasty':ab,ti OR 'speech therapy':ab,ti OR 'speech therapist':ab,ti OR 'palatoplasty'/exp/mj OR 'speech therapy'/exp/mj) AND [english]/lim AND ('voice disorder'/exp/mj OR 'nasal speech'/exp/mj OR 'hypernasality'/exp/mj OR ('speech disorder'/exp/mj AND [1966-2013]/py) OR nasality:ab,ti OR hypernasality:ab,ti OR nasalance:ab,ti OR articulation:ab,ti OR (nasal NEAR/3 emission):ab,ti OR 'speech'/exp), AND 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp) AND 9 references, 4 unique	

Database	Search terms	Total
Medline (OVID) 1966-April 2014 English	1 Cleft Palate/ (16412) 2 ((palato or cheilo-gnatho-palato) adj10 schisis).ti,ab. (7) 3 (cleft adj3 palate*).ti,ab. (13962) 4 "Velopharyngeal Insufficiency"/ (1328) 5 (Velopharyngeal adj3 (Insufficiency or function or dysfunction or incompetence)).ti,ab. (1268) 6 1 or 2 or 3 or 4 or 5 (21131) 13 "Voice Disorders"/ or Articulation Disorders/ (5860) 14 "Voice Quality"/ (4317) 15 (nasality or hypernasality or nasalance or articulation or (nasal adj3 emission)).ti,ab. (8128) 16 13 or 14 or 15 (16016) 17 6 and 16 (966) 18 (pharyngoplast* or furlow).ti,ab. (531) 19 Reconstructive Surgical Procedures/ or Otorhinolaryngologic Surgical Procedures/ (31823) 20 ("palatal closure*" or palatoplast*).ti,ab. (736) 21 "Surgical Flaps"/ or "Adipose Tissue"/tr (46934) 22 "intravelar veloplasty".ti,ab. (63) 23 surgery.fs. (1553661) 24 18 or 19 or 20 or 21 or 22 or 23 (1564457) 25 exp "rehabilitation of speech and language disorders"/ (8477) 26 "speech therap*".ti,ab. (2136) 27 25 or 26 (9725) 28 limit 17 to english language (846) 29 24 or 27 (1572711) 30 28 and 29 (532) 40 Articulation Disorders/ (1474) 41 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (204692) 42 30 and 41 (5) 43 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study	310

	or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1348724) 44 30 and 43 (51) – 49 uniek 45 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or prospective.tw. or Cross sectional.tw. or Cross-sectional studies/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (1959958) 46 30 and 45 (262) 47 46 not (42 or 44) (226) – 225 unique	
Embase (Elsevier)	'cleft palate'/exp/mj OR 'palatopharyngeal incompetence'/exp/mj OR (cleft NEAR/3 palate*):ab,ti OR (velopharyngeal NEAR/3 (insufficiency OR function OR dysfunction OR incompetence)):ab,ti AND ('voice disorder'/exp/mj OR 'nasal speech'/exp/mj OR 'hypernasality'/exp/mj OR ('speech disorder'/exp/mj AND [1966-2013]/py) OR (nasality:ab,ti OR hypernasality:ab,ti OR nasalance:ab,ti OR articulation:ab,ti OR (nasal NEAR/3 emission):ab,ti AND [1966-2013]/py)) AND (pharyngoplast*:ab,ti OR 'palatal closure':ab,ti OR furlow OR palatoplast*:ab,ti OR 'intravelar veloplasty':ab,ti OR 'speech therapy':ab,ti OR 'speech therapist':ab,ti AND [1966-2013]/py OR 'palatoplasty'/exp/mj OR 'speech therapy'/exp/mj) AND [english]/lim AND [embase]/lim Filter SR: 1,) 0 unique Filter RCT: 42, 10 unique Major clinical studies: 57, 21 unique	

Chapter 9 Bone grafting procedure in patients with clefts of the lip and palate

Module: Naso-alveolar moulding (NAM)

Database	Search terms	Total
Medline (OVID) 1993-Aug 2017 English	1 cleft lip/ (13642) 2 Cleft Palate/ (19053) 3 ((gnatho* or cheilo* or palato) adj10 schisis).ti,ab. (12) 4 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft) or (unilateral adj3 cleft) or (bilateral adj3 cleft) or (complete unilateral adj3 cleft) or (complete bilateral adj3 cleft) or alveolus).ti,ab,kf. (23545) 5 1 or 2 or 3 or 4 (29530) 6 (Effectiveness of pre-surgical infant orthopedic treatment for cleft lip and palate patients: a systematic review and meta-analysis).m_titl. (1) 7 Nasoalveolar molding in cleft care: is it efficacious?.m_titl. (1) 8 (Presurgical orthopaedic nasoalveolar molding in cleft lip and palate infants: a comparative evaluation of cases done with and without nasal stents).m_titl. (1) 9 6 or 7 or 8 (3) 10 5 and 9 (3) 11 ((nasoalveolar adj3 mo*) or ("nasal alveolar" adj3 mo*) or (alveolar adj3 mo*) or ((naso-alveolar or "naso alveolar") adj3 mo*) or NAM or ((infant* or neonatal or early) adj3 ortho*) or ((preoperative* or pre-operative*) adj3 ortho*) or ((presurgical or pre-surgical) adj3 ortho*)).ti,ab,kf. (9617) 12 5 and 11 (759) 13 limit 12 to (english language and yr="1993-current") (518) 14 9 and 13 (3) 15 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (339014) 16 13 and 15 (16) 17 ((clinical adj3 pathway) or (clinical adj3 pathways) or (practice adj3 parameter) or (practice adj3 parameters)).ti,ab,kw. or algorithms/ or care pathway.ti,ab,kw. or care pathways.ti,ab,kw. or clinical protocols/ or Consensus/ or Consensus Development Conference.pt. or Consensus Development Conference, NIH.pt. or Consensus Development Conferences as Topic/ or Consensus Development Conferences, NIH as Topic/ or critical pathway/ or guidance.ti,ab. or guideline*.ti. or guidelines as topic/ or practice guidelines as topic/ or Health Planning Guidelines/ or practice guideline/ (533506) 18 13 and 17 (16) 19 16 or 18 (31) 20 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1765581) 21 13 and 20 (70) 22 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ or comparative study.pt. or comparative.ti. (4422433) 23 13 and 22 (208) 24 21 not 19 (58) – 55 unique 25 23 not (21 or 19) (151) – 150 unique	479
Embase (Elsevier)	(((('cleft lip'/exp/mj OR 'cleft palate'/exp/mj OR (((gnatho* OR cheilo* OR palato) NEAR/10 schisis):ab,ti) OR ((alveolar NEAR/3 cleft*):ab,ti) OR ((orofacial NEAR/3 cleft*):ab,ti) OR ((cleft NEAR/3 lip*):ab,ti) OR ((cleft NEAR/3 palate*):ab,ti) OR ((cleft NEAR/3 maxilla*):ab,ti) OR ((oral NEAR/3 cleft):ab,ti) OR alveolus:ab,ti) AND ('nasoalveolar molding'/exp OR (((nasoalveolar NEAR/3 mo*):ti,ab) OR (('nasal alveolar' NEAR/3 mo*):ti,ab) OR ((alveolar NEAR/3 mo*):ti,ab) OR ((('naso alveolar' OR 'naso alveolar') NEAR/3 mo*):ti,ab) OR nam:ti,ab OR (((infant* OR neonatal OR early) NEAR/3 ortho*):ti,ab) OR (((preoperative* OR 'pre operative*') NEAR/3 ortho*):ti,ab) OR (((presurgical OR 'pre surgical') NEAR/3 ortho*):ti,ab))) AND (english)/lim AND (embase)/lim AND (1993-2017)/py) ('meta analysis'/exp OR 'meta analysis' OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/exp OR 'systematic review') OR ('practice guideline'/exp OR ((clinical	

	NEAR/3 pathway*):ti,ab) OR ((practice NEAR/3 parameter*):ti,ab) OR 'care pathway*':ti,ab OR guidance:ti,ab OR guideline*:ti)))) (38) – 27 unique (('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it)) (125) – 87 uniek AND 'major clinical study'/de NOT 'conference abstract':it (154) – 129 unique	

Module: Timing of the bone grafting procedure

Database	Search terms	Total
Medline (OVID) 2000-March 2014 English, Dutch	2 cleft lip/ (11526) 3 Cleft Palate/ (16337) 4 ((gnatho* or cheilo* or palato) adj10 schisis).ti,ab. (9) 5 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (17051) 6 2 or 3 or 4 or 5 (23102) 7 Alveolar Bone Grafting/ (8) [MESH-term vanaf 2014] 8 Cleft Lip/su [Surgery] (4689) 9 limit 8 to yr="1960 - 2013" (4528) 10 exp orthognathic surgical procedures/ (970) 11 limit 10 to yr="2010 - 2013" (902) 12 Osteotomy/ or osteoplasty.ti,ab. or osteotom*.ti,ab. (32137) 13 limit 12 to yr="1960 - 2009" (25752) 14 Bone Transplantation/ (24962) 15 (bone adj3 (grafting or transplantation)).ti,ab. (33498) 16 (alveolar adj3 graft*).ti,ab. (599) 17 ("alveolar cleft" adj3 reconstruction).ti,ab. (24) 18 "alveolar cleft bone graft".ti,ab. (5) 19 16 or 17 or 18 (614) 20 6 and 19 (448) 21 7 or 9 or 11 or 13 or 14 or 15 or 16 or 17 or 18 (82213) 22 6 and 21 (5258) 23 limit 22 to (yr="2000 -Current" and (dutch or english)) (1807) 24 *Time Factors/ or Age Factors/ (367740) 25 23 and 24 (136) 26 (secondary or primary or tertiary).ti. (294626) 27 (eruption adj4 (canine* or cuspid*)).ti,ab. or Cuspid/ (7107) 28 (timing or age).ti. (147497) 29 (late or early or delayed).ti. (290337) 30 24 or 26 or 27 or 28 or 29 (1041313) 31 23 and 30 (445) 32 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (201509) 33 31 and 32 (7) 34 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1336737) 35 31 and 34 (38) 36 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or	255

	studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Prospective.tw. or Longitudinal.tw. [Onder exp cohort studies/ vallen ook longitudinale, prospectieve en retrospectieve studies] (1713778) 37 31 and 36 (232) 49 33 or 35 (43) 50 37 not 49 (205) – 204 unique	
Embase (Elsevier)	'cleft lip'/exp/mj OR 'cleft palate'/exp/mj OR ((gnatho* OR cheilo* OR palato) NEAR/10 schisis):ab,ti OR (alveolar NEAR/3 cleft*):ab,ti OR (orofacial NEAR/3 cleft*):ab,ti OR (cleft NEAR/3 lip*):ab,ti OR (cleft NEAR/3 palate*):ab,ti OR (cleft NEAR/3 maxilla*):ab,ti OR (oral NEAR/3 cleft):ab,ti AND ('alveolar bone grafting'/exp/mj OR 'orthognathic surgery'/exp/mj OR 'cleft lip'/exp/mj/dm_su OR 'cleft palate'/exp/mj/dm_su OR 'bone graft'/exp/mj OR (bone NEAR/3 (grafting OR transplantation)):ab,ti OR (alveolar NEAR/3 graft*):ab,ti OR ('alveolar cleft' NEAR/3 reconstruction*):ab,ti) AND ('time'/exp OR secondary:ti OR primary:ti OR tertiary:ti OR (eruption NEAR/4 (canine* OR cuspid*)):ab,ti OR 'canine tooth'/exp OR timing:ti OR age:ti OR late:ti OR early:ti OR delayed:ti) AND ([dutch]/lim OR [english]/lim) AND [embase]/lim AND [2000-2014]/py AND ('meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) OR ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it) 28 references. 8 unique	

Database	Search terms	Total
Medline (OVID) 1980-June 2014 English, Dutch	1 cleft lip/ (11666) 2 Cleft Palate/ (16512) 3 ((gnatho* or cheilo* or palato) adj10 schisis).ti,ab. (9) 4 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (17286) 5 1 or 2 or 3 or 4 (23377) 6 Alveolar Bone Grafting/ (27) 7 Cleft Lip/su [Surgery] (4742) 8 limit 7 to yr="1960 - 2013" (4576) 9 exp orthognathic surgical procedures/ (1049) 10 limit 9 to yr="2010 - 2013" (961) 11 Osteotomy/ or osteoplasty.ti,ab. or osteotom*.ti,ab. (32931) 12 limit 11 to yr="1960 - 2009" (26046) 13 Bone Transplantation/ (25353) 14 (bone adj3 (grafting or transplantation)).ti,ab. (33880) 15 (alveolar adj3 graft*).ti,ab. (608) 16 ("alveolar cleft" adj3 reconstruction).ti,ab. (24) 17 "alveolar cleft bone graft".ti,ab. (5) 18 15 or 16 or 17 (623) 19 5 and 18 (455) 20 6 or 8 or 10 or 12 or 13 or 14 or 15 or 16 or 17 (83289) 21 5 and 20 (5318) 22 limit 21 to (yr="1980 -Current" and (dutch or english)) (3317) 23 *Time Factors/ or Age Factors/ (372610) 24 (secondary or primary or tertiary).ti. (299494) 25 (eruption adj4 (canine* or cuspid*)).ti,ab. or Cuspid/ (7179) 26 (timing or age).ti. (150143) 27 (late or early or delayed).ti. (295400) 28 23 or 24 or 25 or 26 or 27 (1057726) 29 22 and 28 (842)	445

	30 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (209087) 31 29 and 30 (10) 32 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1365705) 33 29 and 32 (56) 34 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Prospective.tw. or Longitudinal.tw. [Onder exp cohort studies/ vallen ook longitudinale, prospectieve en retrospectieve studies] (1753554) 35 29 and 34 (399) 43 31 or 33 (64) – 63 unique 44 35 not 43 (356) – 354 unique	
Embase (Elsevier)	'cleft lip'/exp/mj OR 'cleft palate'/exp/mj OR ((gnatho* OR cheilo* OR palato) NEAR/10 schisis):ab,ti OR (alveolar NEAR/3 cleft*):ab,ti OR (orofacial NEAR/3 cleft*):ab,ti OR (cleft NEAR/3 lip*):ab,ti OR (cleft NEAR/3 palate*):ab,ti OR (cleft NEAR/3 maxilla*):ab,ti OR (oral NEAR/3 cleft):ab,ti AND ('alveolar bone grafting'/exp/mj OR 'orthognathic surgery'/exp/mj OR 'cleft lip'/exp/mj/dm_su OR 'cleft palate'/exp/mj/dm_su OR 'bone graft'/exp/mj OR (bone NEAR/3 (grafting OR transplantation)):ab,ti OR (alveolar NEAR/3 graft*):ab,ti OR ('alveolar cleft' NEAR/3 reconstruction*):ab,ti) AND ('time'/exp OR secondary:ti OR primary:ti OR tertiary:ti OR (eruption NEAR/4 (canine* OR cuspid*)):ab,ti OR 'canine tooth'/exp OR timing:ti OR age:ti OR late:ti OR early:ti OR delayed:ti) AND ([dutch]/lim OR [english]/lim) AND [embase]/lim AND [1980-2014]/py AND ('meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) OR ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it) 41 references, 8 unique Plus 20-sr- sensitieve search	

Module: Technique of the bone grafting procedure

Database	Search terms	Total
Medline (OVID) 2000-March 2014 English, Dutch	1 cleft lip/ (11526) 2 Cleft Palate/ (16337) 3 ((gnatho* or cheilo* or palato) adj10 schisis).ti,ab. (9) 4 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (17051) 5 1 or 2 or 3 or 4 (23102) 6 Alveolar Bone Grafting/ (8) 7 Cleft Lip/su [Surgery] (4689) 8 limit 7 to yr="1960 - 2013" (4528) 9 exp orthognathic surgical procedures/ (970) 10 limit 9 to yr="2010 - 2013" (902) 11 Osteotomy/ or osteoplasty.ti,ab. or osteotom*.ti,ab. (32137) 12 limit 11 to yr="1960 - 2009" (25752) 13 Bone Transplantation/ (24962) 14 (bone adj3 (grafting or transplantation)).ti,ab. (33498) 15 (alveolar adj3 graft*).ti,ab. (599) 16 ("alveolar cleft" adj3 reconstruction).ti,ab. (24) 17 "alveolar cleft bone graft".ti,ab. (5) 18 15 or 16 or 17 (614) 19 5 and 18 (448) 20 6 or 8 or 10 or 12 or 13 or 14 or 15 or 16 or 17 (82213) 21 5 and 20 (5258) 22 limit 21 to (yr="2000 -Current" and (dutch or english)) (1807) 27 "donor site*".ti,ab. (10183) 28 iliac.ti,ab. (28488) 29 hip.ti,ab. (89452) 30 Chin/ (3080) 31 chin.ti,ab. (4472) 32 Mandible/ (36248) 33 (mandible adj3 graft).ti,ab. (63) 40 Bone Substitutes/ (6702) 41 "bone substitute*".ti,ab. (2122) 42 27 or 28 or 29 or 30 or 31 or 32 or 33 or 40 or 41 (173296) 43 21 and 42 (500) 44 limit 43 to (yr="2000 -Current" and (dutch or english)) (245) 45 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (201509) 46 44 and 45 (8) 47 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1336737) 48 44 and 47 (18) 49 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ [Onder exp hohrt studies vallen ook longitudinale, prospectieve en retrospectieve studies] (1849736)	158

	50 44 and 49 (127) 51 46 or 48 (25) 52 50 not 51 (120) 53 from 51 keep 1-25 (25) 54 from 52 keep 1-120 (120)	
Embase (Elsevier)	('cleft lip'/exp/mj OR 'cleft palate'/exp/mj OR ((gnatho* OR cheilo* OR palato) NEAR/10 schisis):ab,ti OR (alveolar NEAR/3 cleft*):ab,ti OR (orofacial NEAR/3 cleft*):ab,ti OR (cleft NEAR/3 lip*):ab,ti OR (cleft NEAR/3 palate*):ab,ti OR (cleft NEAR/3 maxilla*):ab,ti OR (oral NEAR/3 cleft):ab,ti) AND ('alveolar bone grafting'/exp/mj OR 'orthognathic surgery'/exp/mj OR 'cleft lip'/exp/mj/dm_su OR 'cleft palate'/exp/mj/dm_su OR 'bone graft'/exp/mj OR (bone NEAR/3 (grafting OR transplantation)):ab,ti OR (alveolar NEAR/3 graft*):ab,ti OR ('alveolar cleft' NEAR/3 reconstruction*):ab,ti) AND ('donor site':ab,ti OR 'donor sites':ab,ti OR iliac:ab,ti OR hip:ab,ti OR chin:ab,ti OR 'bone substitute':ab,ti OR 'bone substitutes':ab,ti OR ((mandible NEAR/3 graft*):ab,ti AND [2000-2014]/py) OR 'chin'/exp OR 'mandible'/exp OR 'iliac crest'/exp) AND meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de AND ([dutch]/lim OR [english]/lim) AND [embase]/lim AND [2000-2014]/py OR ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti NOT 'conference abstract':it 20 references, 7 unique	
PubMed	As supplied by publisher (grafting alveolar clefts) AND publisher[sb]) 6 references	

Database	Search terms	Total
Medline (OVID) 1980-May 2014 English, Dutch	1 cleft lip/ (11666) 2 Cleft Palate/ (16512) 3 ((gnatho* or cheilo* or palato) adj10 schisis).ti,ab. (9) 4 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (17286) 5 1 or 2 or 3 or 4 (23377) 6 Alveolar Bone Grafting/ (27) 7 Cleft Lip/su [Surgery] (4742) 8 limit 7 to yr="1960 - 2013" (4576) 9 exp orthognathic surgical procedures/ (1049) 10 limit 9 to yr="2010 - 2013" (961) 11 Osteotomy/ or osteoplasty.ti,ab. or osteotom*.ti,ab. (32931) 12 limit 11 to yr="1960 - 2009" (26046) 13 Bone Transplantation/ (25353) 14 (bone adj3 (grafting or transplantation)).ti,ab. (33880) 15 (alveolar adj3 graft*).ti,ab. (608) 16 ("alveolar cleft" adj3 reconstruction).ti,ab. (24) 17 "alveolar cleft bone graft".ti,ab. (5) 18 15 or 16 or 17 (623) 19 5 and 18 (455) 20 6 or 8 or 10 or 12 or 13 or 14 or 15 or 16 or 17 (83289) 21 5 and 20 (5318) 22 limit 21 to (yr="2000 -Current" and (dutch or english)) (1863) 27 "donor site*".ti,ab. (10371) 28 iliac.ti,ab. (28903)	240

	29 hip.ti,ab. (92009) 30 Chin/ (3119) 31 chin.ti,ab. (4555) 32 Mandible/ (36623) 33 (mandible adj3 graft).ti,ab. (64) 34 27 or 28 or 29 or 30 or 31 or 32 or 33 (170121) 35 22 and 34 (237) 40 Bone Substitutes/ (6834) 41 "bone substitute*".ti,ab. (2167) 42 27 or 28 or 29 or 30 or 31 or 32 or 33 or 40 or 41 (176981) 43 21 and 42 (506) 45 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (209087) 47 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1365705) 49 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ [Onder exp hohrt studies vallen ook longitudinale, prospectieve en retrospectieve studies] (1894734) 53 limit 43 to (yr="1980 -Current" and (dutch or english)) (407) 54 45 and 53 (10) 55 47 and 53 (26) 56 49 and 53 (202) 57 54 or 55 (35) 58 56 not 57 (189)	
Embase (Elsevier)	AND ('cleft lip'/exp/mj OR 'cleft palate'/exp/mj OR ((gnatho* OR cheilo* OR palato) NEAR/10 schisis):ab,ti OR (alveolar NEAR/3 cleft*):ab,ti OR (orofacial NEAR/3 cleft*):ab,ti OR (cleft NEAR/3 lip*):ab,ti OR (cleft NEAR/3 palate*):ab,ti OR (cleft NEAR/3 maxilla*):ab,ti OR (oral NEAR/3 cleft):ab,ti) AND ('alveolar bone grafting'/exp/mj OR 'orthognathic surgery'/exp/mj OR 'cleft lip'/exp/mj/dm_su OR 'cleft palate'/exp/mj/dm_su OR 'bone graft'/exp/mj OR (bone NEAR/3 (grafting OR transplantation)):ab,ti OR (alveolar NEAR/3 graft*):ab,ti OR ('alveolar cleft' NEAR/3 reconstruction*):ab,ti) AND ('donor site':ab,ti OR 'donor sites':ab,ti OR iliac:ab,ti OR hip:ab,ti OR chin:ab,ti OR 'bone substitute':ab,ti OR 'bone substitutes':ab,ti OR ((mandible NEAR/3 graft*):ab,ti AND [2000-2014]/py) OR 'chin'/exp OR 'mandible'/exp OR 'iliac crest'/exp) AND ([dutch]/lim OR [english]/lim) AND [embase]/lim AND [1980-2014]/py AND meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de AND OR ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti NOT 'conference abstract':it 25, 10 unique	
PubMed	As supplied by publisher (grafting alveolar clefts) AND publisher[sb]) 6 references	

Module: Le Fort I osteotomy versus distraction osteogenesis

Database	Search terms	Total
Medline (OVID) 1948-may 2017 English, Dutch	1 cleft lip/ (11546) 2 Cleft Palate/ (16366) 3 ((gnatho* or cheilo* or palato) adj10 schisis).ti,ab. (9) 4 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (17090) 5 1 or 2 or 3 or 4 (23144) 6 Osteotomy/ (23295) 7 limit 6 to yr="1960 - 2009" (19735) 8 Osteotomy, Le Fort/ (1430) 9 "Le Fort".ti,ab. (1620) 10 8 or 9 (2339) 11 5 and 10 (294) 12 ((Maxillary adj3 Distraction) or (Distraction adj3 Osteogenesis)).ti,ab. (2711) 13 Osteogenesis, Distraction/ (3232) 14 12 or 13 (3832) 15 5 and 14 (314) 16 11 or 15 (477) 17 limit 16 to (dutch or english) (422) 18 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (202346) 19 17 and 18 (9) 20 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or clinic$ trial$1.tw. or (clinic$ adj trial$1).tw. or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo$.tw. or randomly allocated.tw. or (allocated adj2 random$).tw.) not (animals/ not humans/) (1089633) 21 17 and 20 (19) 22 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or prospective.tw. or Cross sectional.tw. or Cross-sectional studies/ (Exp cohort studies also include longitudinal, prospective and retrospective studies) (1947068) 23 17 and 22 (157) 24 21 not 19 (16) 25 19 or 24 (25) SR & RCT 26 23 not 25 (147) – 147 unique	
Embase (Elsevier)	'cleft lip'/exp/mj OR 'cleft palate'/exp/mj OR ((gnatho* OR cheilo* OR palato) NEAR/10 schisis):ab,ti OR (alveolar NEAR/3 cleft*):ab,ti OR (orofacial NEAR/3 cleft*):ab,ti OR (cleft NEAR/3 lip*):ab,ti OR (cleft NEAR/3 palate*):ab,ti OR (cleft NEAR/3 maxilla*):ab,ti OR (oral NEAR/3 cleft):ab,ti AND ('maxilla osteotomy'/exp/mj OR 'le fort':ab,ti OR (maxillary NEAR/3 distraction*):ab,ti OR (distraction NEAR/3 osteogenesis):ab,ti OR 'distraction osteogenesis'/exp/mj) AND ((dutch)/lim OR (english)/lim) AND (embase)/lim AND ('meta analysis'/exp OR 'meta analysis' OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/exp OR 'systematic review') 'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti NOT 'conference abstract':it)) OR 'major clinical study'/exp 29 SR/RCT, 12 unique 23 major clinical study, 6 unique	

Module: Ventral traction

Database	Search terms	Total
Medline (OVID) No limitations on language or period	1 cleft lip/ (11926) 2 Cleft Palate/ (16839) 3 ((gnatho* or cheilo* or palato) adj10 schisis).ti,ab. (9) 4 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (17749) 5 1 or 2 or 3 or 4 (23922) 9 Malocclusion, Angle Class III/ (2578) 10 ("Class III" and (Angle* or malocclusion* or bite*)).ti,ab. (1832) 11 (underbite* or under-bite* or reverse-bite or prognath*).ti,ab. (2019) 12 Maxilla/gd (1014) 13 "Maxillofacial Development"/ (6625) 14 (Malocclusion or Retrognathia).ti,ab. (7130) 15 Retrognathia/ (1619) 16 9 or 10 or 11 or 12 or 13 or 14 or 15 (18016) 17 5 and 16 (1581) 18 exp Orthodontic Appliances, Functional/ (2499) 19 exp Orthodontic Appliances, Removable/ (4358) 20 exp Orthodontics/ (44483) 21 ("growth modif*" and (jaw or maxilla*)).ti,ab. (33) 22 (("fixed appliance*" or brace*) and orthodontic*).ti,ab. (1044) 23 ((extraoral or extra-oral or maxillary) and (traction or protraction)).ti,ab. (689) 24 "chin cap*".ti,ab. (68) 25 ((facemask* or face-mask* or "reverse head-gear" or "reverse headgear") and orthodontic*).ti,ab. (63) 26 ((orthopedic* or orthopaedic*) and (dental or orthodontic* or facial)).ti,ab. (2219) 27 "Palatal Expansion Technique"/ (2027) 28 or/18-27 (46191) 29 17 and 28 (364) 30 6 or 7 or 8 (3) 31 29 and 30 (3) 32 Maxilla/ or Maxilla*.ti,ab. (60013) 33 31 and 32 (3) 34 29 and 32 (239) – 238 unique	371
Embase (Elsevier)	'cleft lip'/exp/mj OR 'cleft palate'/exp/mj OR ((gnatho* OR cheilo* OR palato) NEAR/10 schisis):ab,ti OR (alveolar NEAR/3 cleft*):ab,ti OR (orofacial NEAR/3 cleft*):ab,ti OR (cleft NEAR/3 lip*):ab,ti OR (cleft NEAR/3 palate*):ab,ti OR (cleft NEAR/3 maxilla*):ab,ti OR (oral NEAR/3 cleft):ab,ti AND ('malocclusion'/exp/mj OR 'maxilla'/exp/mj OR 'maxillofacial development'/exp/mj OR 'retrognathia'/exp/mj OR malocclusion:ab,ti OR retrognathia:ab,ti OR ('class iii':ab,ti AND (angle*:ab,ti OR malocclusion*:ab,ti OR bite*:ab,ti)) OR underbite*:ab,ti OR 'under bite':ab,ti OR 'reverse bite':ab,ti OR prognath*:ab,ti) AND ('orthodontics'/exp OR 'orthodontic device'/exp OR ((growth NEAR/3 modif*):ab,ti AND (jaw:ab,ti OR maxilla*:ab,ti)) OR ('fixed appliance':ab,ti OR brace*:ab,ti AND orthodontic*:ab,ti) OR (extraoral:ab,ti OR 'extra oral':ab,ti OR maxillary:ab,ti AND (traction:ab,ti OR protraction:ab,ti)) OR (chin NEAR/1 cap*):ab,ti OR (facemask*:ab,ti OR 'face mask':ab,ti OR 'reverse head-gear':ab,ti OR 'reverse headgear':ab,ti AND orthodontic*:ab,ti) OR (orthopedic*:ab,ti OR orthopaedic*:ab,ti AND (dental:ab,ti OR orthodontic*:ab,ti OR facial:ab,ti))) AND ('maxilla'/exp/mj OR maxilla*:ab,ti) AND [embase]/lim 95 references, 65 unique	

Cinahl (Ebso)	S18	S3 AND S16 AND S17	95 , 68 uniek		
	S17	S10 OR S11 OR S12 OR S13 OR S14 OR S15	4,828		
	S16	(S4 OR S5 OR S6 OR S7 OR S8 OR S9)	19,467		
	S15	(MH "Orthodontics+")	4,176		
	S14	TI ((chin N1 cap*) OR (facemask* OR 'face mask' OR 'reverse head-gear' OR 'reverse headgear' AND orthodontic*)) OR AB ((chin N1 cap*) OR (facemask* OR 'face mask' OR 'reverse head-gear' OR 'reverse headgear' AND orthodontic*))	429		
	S13	TI ((chin N1 cap*) OR (facemask* OR 'face mask' OR 'reverse head-gear' OR 'reverse headgear' AND orthodontic*)) OR AB ((chin N1 cap*) OR (facemask* OR 'face mask' OR 'reverse head-gear' OR 'reverse headgear' AND orthodontic*))	429		
	S12	TI ((extraoral OR 'extra oral' OR maxillary AND (traction OR protraction))) OR AB ((extraoral OR 'extra oral' OR maxillary AND (traction OR protraction)))	287		
	S11	TI ('fixed appliance' OR brace*) AND orthodontic*) OR AB ('fixed appliance' OR brace*) AND orthodontic*)	49		
	S10	TI (((growth N3 modif*) AND (jaw* OR maxilla*))) OR AB (((growth N3 modif*) AND (jaw* OR maxilla*)))	3		
	S9	TI (angle* OR malocclusion* OR bite* OR underbite* OR 'under bite' OR 'reverse bite' OR prognath*) OR AB (angle* OR malocclusion* OR bite* OR underbite* OR 'under bite' OR 'reverse bite' OR prognath*)	11,849		
	S8	TI ((malocclusion OR retrognathia or 'class iii' or maxilla*)) OR AB ((malocclusion OR retrognathia or 'class iii' or maxilla*))	6,312		
	S7	(MH "Retrognathism")	159		
	S6	(MH "Maxillofacial Development")	277		
	S5	(MH "Maxilla")	2,769		
	S4	(MH "Malocclusion")	2,279		
	S3	(S1 OR S2)	2,381		

	S2	TI (((gnatho* OR cheilo* OR palato) N10 schisis) OR (alveolar N3 cleft*) OR (orofacial N3 cleft*) OR (cleft N3 lip*) OR (cleft N3 palate*) OR (cleft N3 maxilla*) OR (oral N3 cleft)) OR AB (((gnatho* OR cheilo* OR palato) N10 schisis) OR (alveolar N3 cleft*) OR (orofacial N3 cleft*) OR (cleft N3 lip*) OR (cleft N3 palate*) OR (cleft N3 maxilla*) OR (oral N3 cleft))	1,909		
	S1	(MH "Cleft Palate") OR (MH "Cleft Lip")	2,135		

Module: Retention

Database	Search terms	Total
Medline (OVID) Inception-Jan. 2015	1 cleft lip/ (11854) 2 Cleft Palate/ (16734) 3 ((gnatho* or cheilo* or palato) adj10 schisis).ti,ab. (9) 4 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (17733) 5 1 or 2 or 3 or 4 (23847) 6 exp Orthodontic Appliances, Functional/ (2495) 7 exp Orthodontic Appliances, Removable/ (4329) 8 exp Orthodontics/ (44247) 9 ("growth modif*" and (jaw or maxilla* or mandible)).ti,ab. (48) 10 (("fixed appliance*" or brace*) and orthodontic*).ti,ab. (1047) 11 ((extraoral or extra-oral or maxillary) and (traction or protraction)).ti,ab. (699) 12 "chin cap*".ti,ab. (67) 13 ((facemask* or face-mask* or "reverse head-gear" or "reverse headgear") and orthodontic*).ti,ab. (63) 14 ((orthopedic* or orthopaedic*) and (dental or orthodontic* or facial)).ti,ab. (2238) 15 "Palatal Expansion Technique"/ or "Palatal Expansion Technique".ti,ab. (2037) 16 "Orthodontic Space Closure".ti,ab. (102) 17 or/6-16 (46010) 20 "Orthodontic Retainers"/ (783) 21 recurrence/ (147731) 22 "Tooth Migration"/ (889) 23 (retention or retain* or stabili* or stabili* or recurrence* or relapse*).ti,ab. (976228) 24 ((Tooth or teeth) adj3 (Migrat or mobility)).ti,ab. (968) 25 20 or 21 or 22 or 23 or 24 (1070705) 26 5 and 17 and 25 (143)	178

<table>
<tr><td>Embase (Elsevier)</td><td>'cleft lip'/exp/mj OR 'cleft palate'/exp/mj OR ((gnatho* OR cheilo* OR palato) NEAR/10 schisis):ab,ti OR (alveolar NEAR/3 cleft*):ab,ti OR (orofacial NEAR/3 cleft*):ab,ti OR (cleft NEAR/3 lip*):ab,ti OR (cleft NEAR/3 palate*):ab,ti OR (cleft NEAR/3 maxilla*):ab,ti OR (oral NEAR/3 cleft):ab,ti AND ('orthodontics'/exp OR 'orthodontic device'/exp OR ((growth NEAR/3 modif*):ab,ti AND (jaw:ab,ti OR maxilla*:ab,ti)) OR ('fixed appliance':ab,ti OR brace*:ab,ti AND orthodontic*:ab,ti) OR (extraoral:ab,ti OR 'extra oral':ab,ti OR maxillary:ab,ti AND (traction:ab,ti OR protraction:ab,ti)) OR (chin NEAR/1 cap*):ab,ti OR (facemask*:ab,ti OR 'face mask':ab,ti OR 'reverse head-gear':ab,ti OR 'reverse headgear':ab,ti AND orthodontic*:ab,ti) OR (orthopedic*:ab,ti OR orthopaedic*:ab,ti AND (dental:ab,ti OR orthodontic*:ab,ti OR facial:ab,ti)) AND ('maxilla'/exp/mj OR maxilla*:ab,ti) OR 'palatal expansion technique':ab,ti OR 'orthodontic space closure':ab,ti) AND ('dental retainer'/de OR 'recurrent disease'/de OR retention:ab,ti OR retain*:ab,ti OR stabili*:ab,ti OR recurrence*:ab,ti OR relapse*:ab,ti) AND [embase]/lim (55) – 31 unique</td><td></td></tr>
<tr><td>Cinahl (Ebsco)</td><td>
<table>
<tr><th>#</th><th>Query</th><th>Results</th><th>Action</th></tr>
<tr><td>S27</td><td>(S18 AND S26)</td><td>18 – 4 uniek</td><td></td></tr>
<tr><td>S26</td><td>(S23 OR S24 OR S25)</td><td>68,856</td><td></td></tr>
<tr><td>S25</td><td>TI (retention or retain* or stabili* or stabili* or recurrence* or relapse*).) OR AB (retention or retain* or stabili* or stabili* or recurrence* or relapse*).)</td><td>56,966</td><td></td></tr>
<tr><td>S24</td><td>TI "Tooth Migration" OR AB "Tooth Migration"</td><td>12</td><td></td></tr>
<tr><td>S23</td><td>(MH "Recurrence")</td><td>17,569</td><td></td></tr>
<tr><td>S22</td><td>(S3 AND S21)</td><td>138</td><td></td></tr>
<tr><td>S21</td><td>(S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S19 OR S20)</td><td>4,897</td><td></td></tr>
<tr><td>S20</td><td>TI "Palatal Expansion Technique" OR AB "Palatal Expansion Technique"</td><td>1</td><td></td></tr>
<tr><td>S19</td><td>TI "Orthodontic Space Closure" OR AB "Orthodontic Space Closure"</td><td>10</td><td></td></tr>
<tr><td>S18</td><td>S3 AND S17</td><td>138</td><td></td></tr>
<tr><td>S17</td><td>S10 OR S11 OR S12 OR S13 OR S14 OR S15</td><td>Display</td><td></td></tr>
<tr><td>S16</td><td>(S4 OR S5 OR S6 OR S7 OR S8 OR S9)</td><td>Display</td><td></td></tr>
<tr><td>S15</td><td>(MH "Orthodontics+")</td><td>Display</td><td></td></tr>
<tr><td>S14</td><td>TI ((chin N1 cap*) OR (facemask* OR 'face mask' OR</td><td>Display</td><td></td></tr>
</table>
</td><td></td></tr>
</table>

	'reverse head-gear' OR 'reverse headgear' AND orthodontic*)) OR AB ((chin N1 cap*) OR (facemask* OR 'face mask' OR 'reverse head-gear' OR 'reverse headgear' AND orthodontic*))		
S13	TI ((chin N1 cap*) OR (facemask* OR 'face mask' OR 'reverse head-gear' OR 'reverse headgear' AND orthodontic*)) OR AB ((chin N1 cap*) OR (facemask* OR 'face mask' OR 'reverse head-gear' OR 'reverse headgear' AND orthodontic*))	Display	
S12	TI ((extraoral OR 'extra oral' OR maxillary AND (traction OR protraction))) OR AB ((extraoral OR 'extra oral' OR maxillary AND (traction OR protraction)))	Display	
S11	TI ('fixed appliance' OR brace*) AND orthodontic*) OR AB ('fixed appliance' OR brace*) AND orthodontic*)	Display	
S10	TI (((growth N3 modif*) AND (jaw* OR maxilla*))) OR AB (((growth N3 modif*) AND (jaw* OR maxilla*)))	Display	
S9	TI (angle* OR malocclusion* OR bite* OR underbite* OR 'under bite' OR 'reverse bite' OR prognath*) OR AB (angle* OR malocclusion* OR bite* OR underbite* OR 'under bite' OR 'reverse bite' OR prognath*)	Display	
S8	TI ((malocclusion OR retrognathia or 'class iii' or maxilla*)) OR AB ((malocclusion OR retrognathia or 'class iii' or maxilla*))	Display	
S7	(MH "Retrognathism")	Display	
S6	(MH "Maxillofacial Development")	Display	
S5	(MH "Maxilla")	Display	
S4	(MH "Malocclusion")	Display	
S3	(S1 OR S2)	Display	

	S2	TI (((gnatho* OR cheilo* OR palato) N10 schisis) OR (alveolar N3 cleft*) OR (orofacial N3 cleft*) OR (cleft N3 lip*) OR (cleft N3 palate*) OR (cleft N3 maxilla*) OR (oral N3 cleft)) OR AB (((gnatho* OR cheilo* OR palato) N10 schisis) OR (alveolar N3 cleft*) OR (orofacial N3 cleft*) OR (cleft N3 lip*) OR (cleft N3 palate*) OR (cleft N3 maxilla*) OR (oral N3 cleft))	Display		
	S1	(MH "Cleft Palate") OR (MH "Cleft Lip")	Display		

Chapter 11 Rhinoplasty in patients with clefts of the lip and palate

Database	Search terms	Total
	1 cleft lip/ (11582) 2 (cheilo* adj10 schisis).ti,ab. (8) 3 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (oral adj3 cleft)).ti,ab. (10673) 4 (harelip* or "hare lip*" or hare-lip*).ti,ab. (473) 5 1 or 2 or 3 or 4 (14647) 6 Nose/ (17775) 7 Nose/ab [Abnormalities] (2333) 8 ((nasal or nose) adj3 deformit*).ti,ab. (1384) 9 7 or 8 (3320) 10 Reconstructive Surgical Procedures/ (28552) 11 9 and 10 (194) 12 Rhinoplasty/ (6580) 13 rhinoplasty.ti,ab. (3397) 14 12 or 13 (7356) 15 11 or 14 (7475) 16 5 and 15 (615) 17 limit 16 to english language (473) 18 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (204267) 19 17 and 18 (4) 20 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1347553) 21 17 and 20 (13) 22 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or prospective.tw. or Cross sectional.tw. or Cross-sectional studies/ [Exp cohort studies also include longitudinal, prospective and retrospective studies] (1958420) 23 17 and 22 (129) 24 *Time Factors/ or Age Factors/ or (secondary or primary or tertiary).ti. or (eruption adj4 (canine* or cuspid*)).ti,ab. or Cuspid/ or (timing or age).ti. or (late or early or delayed).ti. (1047161) 25 17 and 24 (158) 26 19 or 21 or 23 (139) 27 25 and 26 (64) 28 25 not 27 (94) 92 unique 29 23 not 30 (122)	369
	'cleft lip nose'/exp OR 'cleft lip nose':ab,ti OR ('cleft lip'/exp/mj OR (cheilo* NEAR/10 schisis):ab,ti OR (alveolar NEAR/3 cleft*):ab,ti OR (orofacial NEAR/3 cleft*):ab,ti OR (cleft NEAR/3 lip*):ab,ti OR (cleft NEAR/3 maxilla*):ab,ti OR (oral NEAR/3 cleft):ab,ti OR harelip*:ab,ti OR 'hare lip':ab,ti AND ('nose malformation'/mj OR ((nasal OR nose) NEAR/3 deformit*):ab,ti)) AND [english]/lim AND [embase]/lim 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/ OR 'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR	

	'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti NOT 'conference abstract':it)) (32), 23 unique 'major clinical study'/exp (88) 68 unique ('chronology'/exp/mj OR 'chronosequence'/exp/mj OR 'canine tooth'/exp/mj OR secondary:ti OR primary:ti OR tertiary:ti OR (eruption NEAR/4 (canine* OR cuspid*)):ti OR timing:ti OR age:ti OR late:ti OR early:ti OR delayed:ti) (110) 47 unique	

Chapter 12 Psychosocial guidance for patients with clefts of the lip and palate

Database	Search terms	Total
Medline (OVID) 2000-Dec. 2014 English, Dutch	1 cleft lip/ (12859) 2 Cleft Palate/ (17842) 3 ((gnatho* or cheilo* or palato) adj10 schisis).ti,ab. (9) 4 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (18981) 5 1 or 2 or 3 or 4 (25502) 6 exp Parents/ed, px or exp Family/ed, px or exp Psychotherapy/ or exp Family Therapy/ or exp Counseling/ or exp Parent-Child Relations/ (284763) 7 (Psychosocial or "patient education" or counse*ling).ti,ab. (138030) 8 (The psychosocial effects of cleft lip and palate: a systematic review).m_titl. (1) 9 6 or 7 (394410) 10 5 and 9 (869) 11 limit 10 to (yr="2000 -Current" and (dutch or english)) (412) 12 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (233236) 13 11 and 12 (18) 14 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1469288) 15 11 and 14 (38) 16 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or prospective.tw. or Cross sectional.tw. or Cross-sectional studies/ [Exp cohort studies also include longitudinal, prospective and retrospective studies] (2147759) 17 11 and 16 (154) 18 13 or 15 (53) 20 17 not 18 (129)	213
PsychInfo	1 cleft lip/ (0) 2 Cleft Palate/ (297) 3 ((gnatho* or cheilo* or palato) adj10 schisis).ti,ab. (0) 4 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (384) 5 1 or 2 or 3 or 4 (413) 6 exp psychotherapy/ or exp family therapy/ or exp Counseling/ (166519) 7 parent child communication/ or parent child relations/ or attachment behavior/ or attachment disorders/ or attachment theory/ or authoritarian parenting/ or authoritative parenting/ or exp childrearing practices/ or exp parent child communication/ or parent training/ or exp parental characteristics/ or parental expectations/ or parental investment/ or parental involvement/ or parental role/ or parenting skills/ or exp parenting style/ or permissive parenting/ (69468) 8 (Psychosocial or "patient education" or counse*ling).ti,ab. (101711) 9 exp Social Adjustment/ or exp Adaptation, Psychological/ or exp Health Knowledge, Attitudes, Practice/ (5990) 10 (coping or "social behavio?r").ti,ab. (60353) 11 (The psychosocial effects of cleft lip and palate: a systematic review).m_titl. (0) 12 6 or 7 or 8 or 9 or 10 (353832) 13 5 and 12 (82) 14 limit 13 to ((dutch or english) and yr="2000 -Current") (40) – 39 unique	

Medline (PubMed) publisher[sb]	((cleft palate or cleft lip) and (psychosocial or psycho-social or counsel*)) (18) – 16 unique	

Database	Search terms	Total
Medline (OVID) English, Dutch 2000-March 2015	14 cleft lip/ (11909) 15 Cleft Palate/ (16805) 16 schisis.ti,ab. (333) 17 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (17895) 18 14 or 15 or 16 or 17 (24324) 20 "Self Concept"/ or "Social Behavior"/ or "Interpersonal Relations"/ or "Depression"/ or Anxiety/ or Cleft Palate/px or Cleft Lip/px (235398) 21 ("Self Concept" or "Social Behavio?r" or "Interpersonal Relations" or Depressi* or Anxiety).ti,ab. (338430) 22 anxiety, separation/ or exp "attention deficit and disruptive behavior disorders"/ or child behavior disorders/ or exp child development disorders, pervasive/ or exp communication disorders/ or developmental disabilities/ or exp learning disorders/ or intellectual disability/ or reactive attachment disorder/ (163943) 23 exp Intelligence/ or Intelligence.ti,ab. (98900) 24 ((development* or learning or emotional or mood or psychosocial or psycho-social) adj3 (disorder* or disabilit*)).ti,ab. (43724) 25 ((learning or emotional or mood or psychosocial or psycho-social) adj3 development).ti,ab. (4876) 26 or/20-25 (722857) 27 18 and 26 (2489) 28 limit 27 to (yr="2000 -Current" and (dutch or english)) (910) 29 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (229168) 30 28 and 29 (30) 31 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or prospective.tw. or Cross sectional.tw. or Cross-sectional studies/ [Exp cohort studies also include longitudinal, prospective and retrospective studies] (2094003) 32 28 and 31 (300) 33 32 not 30 (296) – 294 unique	376

PsycINFO	1 Cleft Palate/ (302) 2 schisis.ti,ab. (1) 3 ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (391) 4 1 or 2 or 3 (421) 10 social behavior/ (11379) 11 exp interpersonal interaction/ (211438) 12 exp interpersonal relationships/ (103394) 13 "depression (emotion)"/ or exp major depression/ or sadness/ or exp separation reactions/ (107625) 14 anxiety/ or performance anxiety/ or social anxiety/ or speech anxiety/ (39220) 15 separation anxiety/ or attachment behavior/ or attachment disorders/ or school phobia/ (17586) 16 exp childhood development/ (64533) 17 exp intelligence/ (13662) 18 Intelligence.ti,ab. (34146) 19 ((learning or emotional or mood or psychosocial or psycho-social) adj3 development).ti,ab. (11476) 20 ((development* or learning or emotional or mood or psychosocial or psycho-social) adj3 (disorder* or disabilit*)).ti,ab. (49435) 21 ("Self Concept" or "Social Behavio?r" or "Interpersonal Relations" or Depressi* or Anxiety).ti,ab. (268402) 22 or/9-21 (695065) 23 4 and 22 (144) 25 meta-analysis/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or (selection criteria or data extraction).ab. (66790) 28 limit 23 to yr="2000 -Current" (94) 29 limit 28 to (dutch or english) (84) 30 25 and 29 (3) – 1 uniek 31 limit 28 to (dutch or english) (84) 32 (Case control or (cohort adj (study or studies)) or Cohort analy$ or (Follow up adj (study or studies)) or (observational adj (study or studies)) or Longitudinal or Retrospective or prospective or Cross sectional).tw. (175184) 33 31 and 32 (19) 34 Peer Reviewed Journal.pt. (2182089) 35 31 and 34 (68) 36 33 or 35 (71) 37 36 not 30 (68) – 51 unique	

Appendix 9 Overview of declaration of interests

Table with declaration of interests

Guideline task force member	*Position*	*Other positions*	*Personal financial interests*	*Personal relationships*	*Reputation management*	*Externally funded research*	*Knowledge valorisation*	*Other interests*
Admiraal	Physician	none	no	no	no	no	no	no
Bierenbroodspot	member of the guideline task force on behalf of the NVMKA	no	no	no	no	no	no	no
Bitterman	paediatrician in Wilhelmina Children's Hospital Utrecht. Currently head of the Paediatric Dentistry Outpatients' Clinic of the Wilhelmina Children's Hospital Utrecht	works as a dentist in general practice	no	no	no	no	no	no
De Wilde	speech therapist Wilhelmina Children's Hospital Utrecht	Post-graduate course in Orofacial cleft	no	no	no	no	no	no
Dijkstra-Putkamer	cleft team speech therapist (8 hours p/w) physician assistant ENT (32 hours p/w)	chair of the guideline task force cleft team speech therapists The Netherlands, unpaid. Board member of the Schisis Friesland foundation, unpaid. Board member NVSCA, unpaid	no	no	no	no	no	no
Kuipers-Jagtman	Professor of orthodontics; 1.0 fte until 01-Mar-2014; thereafter 0.6 fte	Editor-in-Chief Orthodontics and Craniofacial Research, a scientific impact-factor journal in the field of orthodontics and craniofacial research; 0.2 fte, paid Deputy Professor, Universitas Indonesia, Jakarta (Indonesia), education and research in the field of orthodontics and orofacial clefts; unpaid Member Cochrane Oral Health Expert Group, evaluation and prioritisation of topics for Cochrane Systematic Reviews, evaluation of Cochrane protocols in the field of Oral Health, which includes orofacial clefts; unpaid Councillor World Federation of Orthodontics, professional world organisation to advance the art and science of orthodontics throughout the world; unpaid Chair of the Sumbing Bibir Foundation for the treatment of and research into orofacial clefts in Indonesia; unpaid	no	no	Until 01-Jan-2014, I was head of the Centre for Orofacial Clefts and Craniofacial Abnormalities of the Radboudumc.	no	no	no
Mink van der Molen	50% UMCU, 50% St. Antonius Hospital, Nieuwegein	no	no	no	no	no	no	no
Moues	Guideline task force member Plastic surgeon in Leeuwarden	no	no	no	no	no	no	no

Guideline task force member	*Position*	*Other positions*	*Personal financial interests*	*Personal relationships*	*Reputation management*	*Externally funded research*	*Knowledge valorisation*	*Other interests*
Swanenburg de Veye	Clinical psychologist	none	no	no	no	no	no	no
Van Adrichem	Plastic surgeon, Erasmus MC Rotterdam (Sophia Children's Hospital), sector head Plastic surgeon, Velthuis Clinic (via AZR/SFG plastic surgery partnership) Educator Plastic Surgery Erasmus MC/SFG; interim head of department Erasmus MC plastic surgery	Advisor Medirisk/VVAA (paid via Partnership) Vice-chairman of the paediatric surgery group (unpaid, SKZ) Secretary of concilium plastico chirurgicum (unpaid, nvpc) BBC NVPC advisor on-call (unpaid) Focus group Erasmus MC New Building (unpaid) Project group structure theme Dijkzigt (unpaid) Chairman of the Erasmus MC cleft team (unpaid) Chairman of the national "Knowledge Centres on Skull Deformities"	no	no	no	no	no	no
Van den Boogaard	clinical geneticist	no	no	no	no	no	no	no
Van Gemert – Schriks	Paediatric dentist - Coordinator post-initial training in paediatric dentistry (ACTA) - Paediatric dentist at CBT Rijnmond		none	none	none	N/A	N/A	no
Van Tol-Verbeek	treatment coordinator Kentalis early treatment - 0.8 FTE	member of LZMG network and the NVO (unpaid)	no	no	no	no	no	no
Vermeij – Keers	registration leader NVSCA orofacial clefts and craniofacial abnormalities (unpaid)	scientific researcher Erasmus MC; retired with guest privileges (unpaid)	no	no	no	no	no	no

Table with declaration of interests asked in 2018

Surname of task force member	*Main position*	*Other activities*	*Personal financial interests*	*Personal relationships*	*Externally financed research*	*Intellectual interests and reputation*	*Other interests*	*Signed on*
Bittermann	*- University staff member UMC Utrecht department Special dentistry (paediatric dentistry) in the W.K.Z.* *- General practicing dentist in Giessenburg* *- Work division 50-50%*	*Board member (secretary) European Cleft organisation. Tasks include organising ECPCA conference in June 2019 (unpaid)*	*None*	*No*	*None*	*I am a member of the Cleft Team in the WKZ*	*No*	*14-2-2018*

Adrichem, van	*- Plastic Surgeon UMC Utrecht, 0.6 fte* *- Plastic Surgeon Van Adrichem Medical B.V. 0.4 fte, activities primarily in the Velthuis Clinic Rotterdam*	*Membership of boards & scientific steering groups (all unpaid)* ** 2018-present: member Professional Interests Committee NVPC* ** 2017-present: chairman of the task force Capacity Estimates* ** 2017: member of the task force Appointment Aios (Bols)* ** 2017-present: cluster head F UMC Utrecht: representative of all surgical specialisms division of Surgical Specialisms in the WKZ* ** 2017: member of the task force "Transparancy of uninsured care" NZA"* ** 2016-present: member of the task force development of a care standard "craniofacial surgery"* ** 2016-present: chairman task force and editor "Revision national training plan plch POWER"* ** 2016-present: chairman Medical Council Equipe Care Companies* ** 2016-present: design and maintenance of procedures thesaurus (DHD-NVPC)* ** 2015-present: chairman of Concilium Plastico Chirurgicum NVPC* ** 2015-present: member of the Training Council FMS as NVPC representative* ** 2014-present member of the sounding board group "vrest"* ** 2014-present: design and*	*None*	*No*	*No*	*No*	*No*	*25-2-2018*

		maintenance of the diagnosis thesaurus (DHD-NVPC) **** 2014-present: member of the guideline committee "schisis"*** **** 2014-2017: member of the Professional Interests Council FMS as NVPC representative*** **** 2013-present: coordinator and designer of mathematical model "policy-rich assignment of national inflow of aios to plastic surgery***						

Bierenbroodspot	*Maxillo-facial surgeon Isala Zwolle*	*-*	*None*	*No*	*No*	*None*	*No*	*8-2-2018*
Janssen	*Maxillo-facial surgeon UMC Utrecht*	*-*	*None*	*No*	*N/A*	*None*	*No*	*26-2-2018*
Kuijpers-Jagtman	*Emeritus professor of Orthodontics RadboudUMC*	*- Member guideline Advisory Committee (RAC) of the KIMO (unpaid)* *- Chairman Taskforce Research Angle Society of Europe (unpaid)* *- Chairman Global Taskforce Cleft lip and Palate Research (unpaid)*	*None*	*None*	*None*	*None*	*None*	*11-1-2017*
Mink van der Molen	*Plastic surgeon in UMCU*	*N/A*	*N/A*	*N/A*	*N/A*	*No, N/A*	*Not known*	*8-3-2018*