Evidence-based Practice Center Systematic Review Protocol

Project Title: Ankyloglossia

I. Background and Objectives for the Systematic Review

Background

Ankyloglossia is a congenital condition characterized by an abnormally short, thickened, or tight lingual frenulum that restricts mobility of the tongue. While it can be associated with other craniofacial abnormalities, it is most often an isolated anomaly.[1] It variably causes reduced tongue mobility and has been associated with functional limitations in breastfeeding, swallowing, articulation, orthodontic problems including malocclusion, open bite, and separation of lower incisors, mechanical problems related to oral clearance, and psychological stress. Reported rates range from 2.1 – 10.7 percent,[2] but definitive incidence and prevalence statistics are elusive due to an absence of a criterion standard or clinically practical diagnostic criteria. The significance of this anomaly and the best method of management have been controversial for more than 50 years.[3]

Anterior ankyloglossia is defined as tongue ties with a prominent lingual frenulum and/or restricted tongue protrusion with tongue tip tethering. The diagnosis of posterior ankyloglossia is considered when the lingual frenulum was not very prominent on inspection but is thought to be tight on manual palpation or is found to be abnormally prominent, short, thick, or fibrous cord-like with the use of the grooved director. Although treatment is similar in anterior and posterior cases, posterior ankyloglossia is more subtle in presentation. Usually, clinicians recognize the anterior frenulum as the cause of ankyloglossia; however, an infant can have ankyloglossia even if that is not prominent. Anterior ankyloglossia was more common in males and posterior ankyloglossia in females in one series.[4] Posterior ankyloglossia is more likely to require revision surgery due to the relative difficulty of accurate diagnosis and treatment. In essence, posterior ankyloglossia is under-recognized compared to the anterior variant.

Recognition of potential benefits of breastfeeding in recent years has resulted in a renewed interest in the functional sequelae of ankyloglossia. Of infants with anterior or posterior ankyloglossia, there is a 25 to 80 percent incidence of breastfeeding difficulties including failure to thrive, maternal nipple damage, maternal breast pain, poor milk supply, maternal breast engorgement, and refusing the breast.[3] Ineffective latch is hypothesized to underlie these problems. Mechanistically, infants with restrictive ankyloglossia cannot extend their tongues over the lower gum line to form a proper seal and therefore use their jaws to keep the breast in the mouth. Adequate tongue mobility is required, and infants with ankyloglossia often cannot overcome their deficiency with conservative measures such as positioning and latching techniques, thereby requiring surgical correction.[3]

Despite these studies, consensus on ankyloglossia's role in breastfeeding difficulties is lacking. A minority of surveyed pediatricians (10%) and otolaryngologists (30%) believe it commonly affects feeding, while 69 percent of lactation consultants feel that it frequently causes

breastfeeding problems.[5] Therefore, depending on the audience, enthusiasm for its treatment varies. Currently, the National Health Service (NHS) and the Canadian Paediatric Society (CPS) recommend treatment only if it interferes with breastfeeding.[7] Unfortunately, a standard definition of "interference" with breastfeeding is not provided, leaving room for interpretation and variation in treatment thresholds. Uncertainty is further promulgated by absence of data on the natural history of untreated ankyloglossia. Some propose that a short frenulum elongates spontaneously due to progressive stretching and thinning of the frenulum with age and use.[1] However, there are no prospective longitudinal data on the fate of the congenitally short lingual frenulum. Without this information it is difficult to fully inform parents about the long-term implications of ankyloglossia, thereby complicating the decision making process.

Perhaps the best available evidence to date is provided by a recent systematic review that found frenotomy to be a well-tolerated and simple procedure that provides objective and subjective benefits in breastfeeding.[7] Specifically, this review reported that frenotomy facilitated breastfeeding, enhanced milk transfer to the infant, and contributed to protecting maternal nipple and breast health. However, reviews to date have not considered swallowing and psychosocial consequences related to ankyloglossia, particularly as children age. These omissions are critical because it is clear that not all infants with ankyloglossia have breastfeeding difficulties, dysphagia, or cause maternal breast discomfort, and many adapt and respond to conservative therapy. Maxillary tight labial frenulum (lip-tie) is often overlooked when an infant presents with breastfeeding difficulties. It can be present in conjunction with ankyloglossia, and it is important to evaluate for this condition as a cause for poor latching.[8]

Three systematic reviews addressing ankyloglossia have also been published recently. While each contributes to an understanding of ankyloglossia treatments, each has important limitations. In a review focused solely on frenotomy and breastfeeding, Segal and colleagues (2007) assessed diagnostic criteria, prevalence, and effectiveness of the procedure.[3] In the five prevalence studies identified, rates of ankyloglossia ranged from 4.2 to 10.7 percent. Diagnostic criteria for ankyloglossia, addressed in 12 studies, varied considerably (Appendix A), which likely accounts for the range in prevalence estimates. The authors rated most of the seven studies evaluating frenotomy as poor quality (mean score of 24.4, range 9-40 on a 47-point scale). Studies included one RCT, and all used different outcome-measures to assess effects of frenotomy. Outcomes (breastfeeding mechanics, nipple pain, rate of breastfeeding, sucking, weight gain) all improved post-procedure, and no studies reported significant adverse effects.

In a 2009 review addressing diagnosis and treatment, Suter and colleagues similarly noted multiple diagnostic criteria for ankyloglossia, and prevalence rates for the condition ranged from 0.1 to 10.7 percent.[2] In 10 studies assessing effects of treatment on breastfeeding outcomes, breastfeeding mechanics and related outcomes typically improved. Four studies of tongue mobility and three of speech problems also reported improvement. The review notes insufficient evidence related to choice of procedure, timing of procedure, or surgical versus conservative management; however, the investigators did not include any quality metrics for included studies.

The most recent systematic review, published in 2013, assessed outcomes related to breastfeeding and speech. The 20 included studies typically reported improvements in nipple

pain, milk intake and feeding, and weight gain. Outcomes in four studies addressing speech articulation reported few definitive improvements following treatment. This review did not evaluate non-surgical management or broader outcomes.

Clarity is needed to help guide clinical and family decision-making about whether, when and how to intervene to address ankyloglossia, in particular in light of controversies about the topic and the limitations of the existing systematic reviews.

Objectives
This systematic review will provide a comprehensive review of both potential benefits of treatments (surgical and nonsurgical) as well as harms associated with those therapies in individuals with ankyloglossia and tight labial frenulum (lip-tie) concomitant to ankyloglossia. We will assess outcomes beyond the impact of ankyloglossia on breastfeeding and address those related to tongue tie in later life (e.g., orthodontic and dental issues, speech, self-esteem). These factors should be understood and discussed when counseling parents about ankyloglossia and treatment options. For example, indications predicting the success and failure of conservative measures should be a priority to prevent unnecessary procedures and optimize short- and long-term maternal and patient outcomes.

II. The Key Questions

Key Questions (KQ) were developed in consultation with Key Informants and the Task Order Officer.

While we received numerous comments from the public posting, modifications to the Key Questions were not required. Comments typically focused on treatment issues or limitations of the evidence base, including:

- Attempting conservative nonsurgical treatments prior to undertaking surgical interventions
- Immediate breastfeeding benefits of surgical interventions
- Differentiating full and partial frenulum fusion and the type of surgery required for each
- Lack of diagnostic criteria
- Lack of validated assessment tool for tight labial frenulum (lip-tie)
- Potential harms (e.g., bleeding, pain, infection) from surgical interventions
- Need for studies reporting outcomes over time

Our Key Questions address the following areas. Key Question 1 is focused on breastfeeding outcomes in infants treated for ankyloglossia. Key Question 2 addresses feeding, speech, orthodontic and other concerns related to treatment in infants and children. Key Question 3 addresses social concerns, and Key Question 4 addresses ankyloglossia with concomitant tight labial frenulum (lip-tie).

Key Question 1 (KQ1)
What are the benefits and harms of various treatments in breastfeeding newborns and infants with ankyloglossia intended to improve breastfeeding outcomes? Surgical treatments include

frenotomy (anterior and/or posterior), frenuloplasty (transverse to vertical frenuloplasty), laser frenulectomy/frenulotomy, and z-plasty repair. Nonsurgical treatments include complementary and alternative medicine (CAM) therapies (e.g. craniosacral therapy, myofascial release, and other chiropractic therapies), lactation intervention, physical therapy, oral motor therapy, and stretching exercises/therapy.

Key Question 2a + b (KQ2)

KQ 2a What are the benefits and harms of various treatments* in newborns, infants, and children with ankyloglossia intended to prevent, mitigate, or remedy attributable medium and longterm *feeding* sequelae including trouble bottle feeding, spilling and dribbling, difficulty moving food boluses in the mouth and deglutition?

KQ 2b What are the benefits and harms of various treatments* in infants and children with ankyloglossia intended to prevent, mitigate, or remedy attributable medium and longterm *other* sequelae including articulation disorders, poor oral hygiene, oral and oropharyngeal dysphagia, sleep disordered breathing, orthodontic issues including malocclusion,open bite due to reverse swallowing, lingual tipping of the lower central incisors, separation of upper central incisors, crowding, narrow palatal arch, and dental caries?

*Surgical treatments include frenotomy (anterior and/or posterior), frenuloplasty (transverse to vertical frenuloplasty), laser frenulectomy, and z-plasty repair. Nonsurgical treatments include complementary and alternative medicine (CAM) therapies (e.g. craniosacral therapy, myofascial release, and other chiropractic therapies), lactation intervention, and speech therapy (for children ages 2-18 years) and physical therapy, oral motor therapy, and stretching exercises/therapy.

Key Question 3 (KQ3)
What are the benefits and harms of various treatments for ankyloglossia in children up to 18 years of age intended to prevent or address social concerns related to tongue mobility (i.e., speech, oral hygiene, excessive salivation, kissing, spitting while talking, and self-esteem)?

Key Question 4 (KQ4)
What are the benefits and harms of simultaneously treating ankyloglossia and concomitant tight labial frenulum (lip-tie) in infants and children up to age 18 intended to improve or remedy breastfeeding, articulation, orthodontic and dental, and other feeding outcomes? What are the relative benefits or harms of treating only ankyloglossia when tight labial frenulum (lip-tie) is also diagnosed?

Table 1 outlines the PICOTS (**p**opulation, **i**ntervention, **c**omparators, **o**utcomes, **t**iming, and **s**etting) for each KQ.

Table 1. PICOTS

PICOTS	Criteria
Population	• KQ1: Breastfeeding newborns with ankyloglossia • KQ2 and KQ3: Infants and children with ankyloglossia • KQ4: Infants and children (newborns up to 18 years of age) with ankyloglossia and

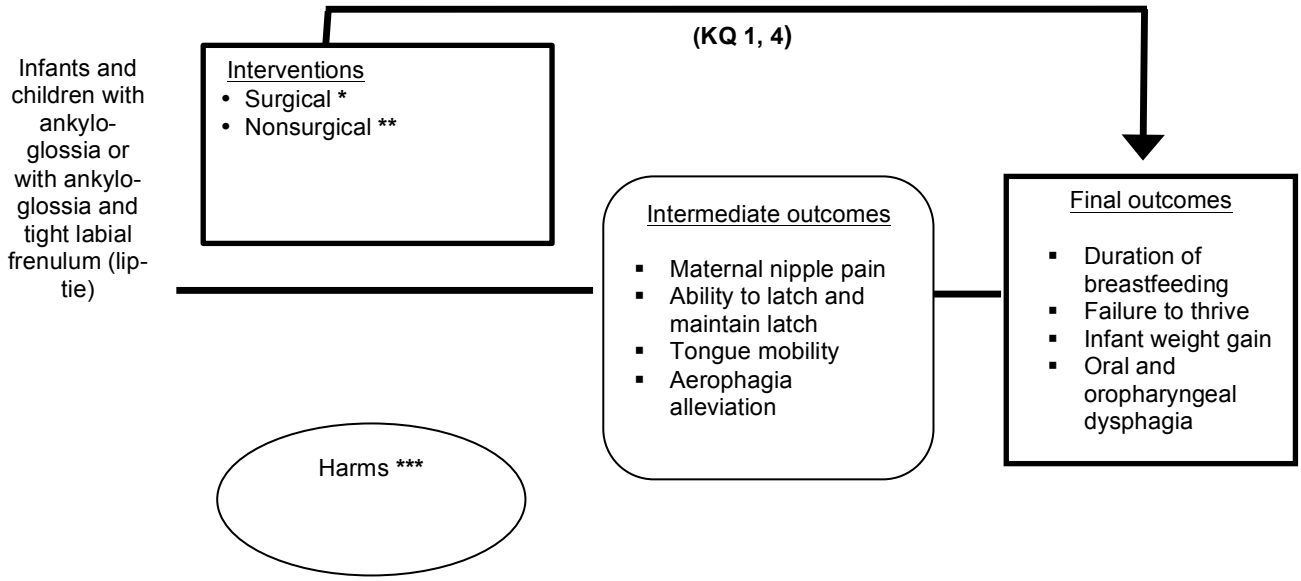
PICOTS	Criteria
	concomitant tight labial frenulum (lip-tie)
Intervention(s)	• Surgical interventions, including frenotomy (anterior or posterior), frenuloplasty, laser frenulectomy and z-plasty repair • Nonsurgical treatments include complementary and alternative medicine (CAM) therapies (e.g. craniosacral therapy, myofascial release, and other chiropractic therapies), lactation intervention, and speech therapy (for children ages 2 to 18 years), physical therapy, oral motor therapy, and stretching exercises/therapy
Comparator	• Other surgical approach • Non-surgical interventions including lactation intervention, speech therapy physical therapy oral motor therapy, and stretching exercises/therapy • Watchful waiting • Complementary and alternative medicine (CAM) therapies (e.g. craniosacral therapy, myofascial release, and other chiropractic therapies) • Placebo (sham therapy)
Outcomes	• Breastfeeding, including latch, nipple pain, nipple excoriations, nipple infections (mastitis), weight gain, aerophagia, swallowing function, failure to thrive, milk transfer, low milk supply, breastfeeding cessation • Other feeding issues, including difficulty bottle feeding, moving food boluses in the mouth, deglutition,spilling and dribbling, reflux • Articulation • Speech (e.g. speech fluency, effort with speech, speech intelligibility) • Sleep disordered breathing (sleep apnea) • Oral hygiene • Excessive salivation • Orthodontic problems, including malocclusion, open bite due to reverse swallowing, lingual tipping of lower central incisors, separation of upper central incisors, crowding, and narrow palatal arch, dental caries • Psychological (e.g., self-esteem) • Harms, including excessive bleeding, airway obstruction, pain, transient poor feeding secondary to discomfort, dysphagia, complications related to dysphagia such as aspiration pneumonia, surgical site infection, nerve damage, salivary gland damage, ranulae, scarring, soft tissue damage, oral aversion, readherence, and need for further surgery
Timing	• Short-term (breastfeeding) • Long-term (feeding) speech, psychological, oral hygiene
Setting	• Inpatient or outpatient pediatric care, operating room, newborn nursery or NICU, ENT clinic, primary care outpatient, dental office, breastfeeding medicine clinic

Abbreviations: PICOTS=Population, Intervention, Comparator, Outcomes, Timing, Setting, CAM= Complementary and alternative medicine, NICU= Neonatal intensive care unit, ENT= ear, nose and throat, KQ= Key Question

III. Analytic Framework

Figure 1 depicts Key Questions 1 and 4 within the context of the PICOTS described in the document. In general, the figure examines surgical and nonsurgical treatments in infants to improve breastfeeding outcomes. Intermediate outcomes include maternal nipple pain, ability to latch and maintain latch, tongue mobility, and aerophagia. Final outcomes include duration of breastfeeding, failure to thrive, infant weight gain and oral . and oropharyngeal dysphagia. Harms may occur at any point after the intervention is received.

Figure 1. Analytic Framework for Ankyloglossia in younger children



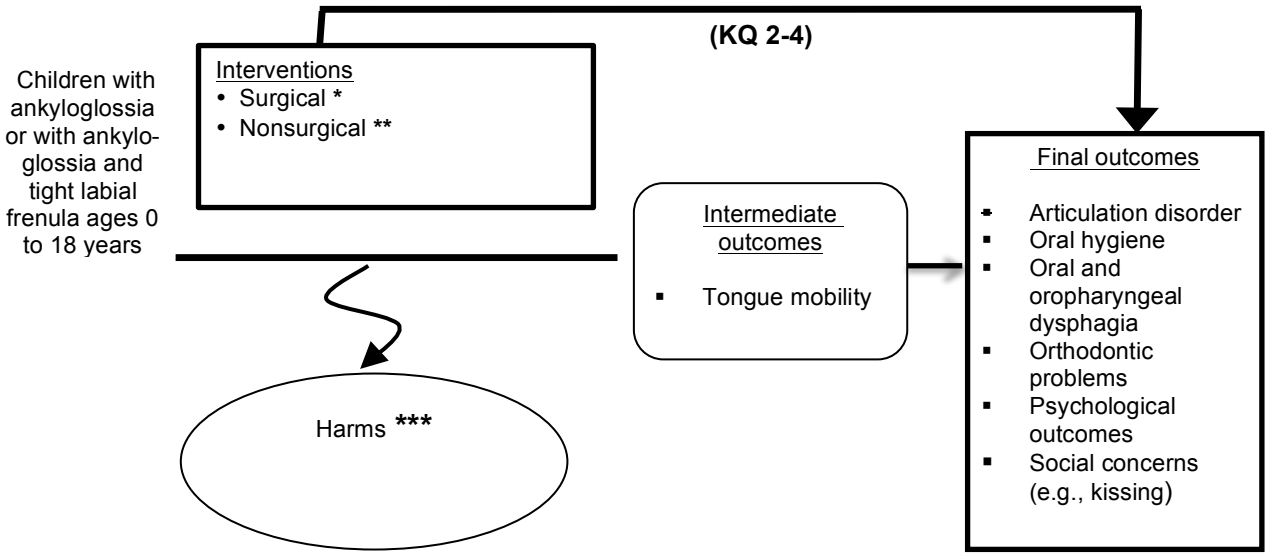
* **Surgical treatments** such as frenotomy, frenuloplasty, laser frenulectomy, and z-plasty repair

** **Nonsurgical treatments** include complementary and alternative medicine (CAM) therapies (e.g. craniosacral therapy, myofascial release, and other chiropractic therapies), lactation intervention, speech therapy, physical therapy, oral motor therapy and stretching exercises/therapy

*** **Harms** such as excessive bleeding, airway obstruction, pain, transient poor feeding secondary to discomfort, dysphagia, complications related to dysphasia such as aspiration pneumonia, surgical site infection, nerve damage, salivary gland damage, ranulae, scarring, soft tissue damage, oral aversion, readherence, and need for further surgery

Figure 2 depicts Key Questions 2, 3, and 4 within the context of the PICOTS described in the document. In general, the figure examines surgical and nonsurgical treatments in infants and children with ankyloglossia or ankyloglossia with concomitant tight labial frenulum (lip-tie). The intermediate outcome is tongue mobility and final health outcomes include articulation disorder, oral hygiene, oral and oropharyngeal dysphagia, orthodontic problems, psychological outcomes and social concerns including kissing. Harms may occur at any point after the intervention is received.

Figure 2. Analytic Framework for Ankyloglossia in infants and children up to 18 years of age



* **Surgical treatments** such as frenotomy, frenuloplasty, laser frenulectomy, and z-plasty repair

** **Nonsurgical treatments** include complementary and alternative medicine (CAM) therapies (e.g. craniosacral therapy, myofascial release, and other chiropractic therapies), lactation intervention, speech therapy, physical therapy, oral motor therapy and stretching exercises/therapy

*** **Harms** such as excessive bleeding, airway obstruction, pain, transient poor feeding secondary to discomfort, dysphagia, complications related to dysphasia such as aspiration pneumonia, surgical site infection, nerve damage, salivary gland damage, ranulae, scarring, soft tissue damage, oral aversion, readherence, and need for further surgery

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

We outline the inclusion/exclusion criteria selected based on our understanding of the literature, input from the topic refinement phase and content experts, and established principles of methodological quality in Table 2. Literature searches will not be restricted to a year range (i.e., searches will be from inception of the database to the present) given the need to capture variations in practice patterns and trends in breastfeeding over time. We will include studies published in English only. Two team members independently reviewed the titles and abstracts of the non-English language literature located via our MEDLINE search and not restricted to a year range. We determined that of 520 non-English references identified in MEDLINE (search conducted in February 2014), 502 would be clearly excluded based on our criteria. Of the 18 potential includes, six appeared, from the information in the abstract and/or title to be eligible for inclusion; 12 did not include abstracts or sufficient information from the title to make an inclusion decision. Two of these appeared to be case reports and neither gave clear indications on whether harms of surgical interventions were addressed. Given the high percentage of non-eligible items in this scan (97%), we feel that excluding non-English studies will not introduce significant bias into the review. We will, however, re-assess non-English studies as we update our MEDLINE search. The team will evaluate any additional non-English studies that appear relevant to determine how or if these studies should be addressed in the review (e.g., appendix providing relevant information gleaned from abstract).

Table 2. Inclusion criteria

Category	Criteria
Study population	Children ages 0-18 with ankyloglossia or ankyloglossia with concomitant tight labial frenulum (lip-tie); studies with participants with Van der Waude syndrome, Pierre Robin syndrome, Down syndrome, or craniofacial abnormalities will be excluded as will premature babies (<37 weeks of gestation)*
Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs RCTs, prospective and retrospective cohort studies, nonrandomized controlled trials, prospective and retrospective case series, and cross over studies Case reports will be used to assess harms Other criteria Original research studies providing sufficient detail regarding methods and results to enable use and aggregation of the data and results Studies must address one or more of the following: • Surgical interventions (simple anterior frenectomy, laser frenulectomy, posterior frenulectomy, z-plasty repair) • Nonsurgical treatments include complementary and alternative medicine (CAM) therapies (e.g. craniosacral therapy, myofascial release, and other chiropractic therapies), lactation intervention , speech therapy, physical therapy, oral motor therapy and stretching exercises/therapy • Baseline and outcome data (including harms) related to interventions for ankyloglossia Relevant outcomes must be able to be abstracted from data in the papers

Data must be presented in the aggregate (vs. individual participant data)

* *Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (NIH),Department of Health & Human Services (DHHS). Preterm Labor and Birth: Condition Information [Internet].Bethesda, MD: National Institute of Child Health and Human Development, National Institutes of Health, 2014. http://www.nichd.nih.gov/health/topics/preterm/conditioninfo/Pages/default.aspx. Accessed May 8, 2014*

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions Databases. To ensure comprehensive retrieval of relevant studies of therapies for children with ankyloglossia or ankyloglossia with concomitant tight labial frenulum (lip-tie), we will use four key databases: the MEDLINE® medical literature database via the PubMed® interface, the PsycINFO® psychology and psychiatry database, the Cumulative Index of Nursing and Allied Health Literature (CINAHL®) and EMBASE (Excerpta Medica Database), an international biomedical and pharmacological literature database via the Ovid® interface. Search strategies for each of these databases will focus specifically on terms related to ankyloglossia and its treatment, including keywords, subject headings, and a combination of subject headings and/or keywords (e.g. mouth abnormalities, frenum, z-plasty, craniosacral therapy). Literature searches will not be restricted to a year range (i.e., searches will be from inception of the database to the present) given the need to capture variations in practice patterns and trends in breastfeeding over time. All searches will be created by an expert librarian and reviewed by a second expert librarian. See Appendix B for search strategies.

Search updates. We will update the search when the draft report is submitted and will add relevant studies as needed while the draft report is undergoing peer review. We will also incorporate studies that meet our inclusion criteria or are relevant as background material that may be identified by both public and peer reviewers.

Hand searching. We will carry out hand searches of the reference lists of recent systematic reviews or meta-analyses of therapies for ankyloglossia; the investigative team will also scan the reference lists of articles that are included after the full-text review phase for studies that potentially could meet our inclusion criteria.

Grey literature. As we will not be reviewing medications or devices, we will not request Scientific Information Packets or regulatory information. We will review abstracts presented at annual meetings of key scientific societies including American Association of Pediatrics (AAP), Pediatric Academic Societies (PAS), Academy of Breastfeeding Medicine (ABM), American Academy of Pediatric Dentistry (AAPD), American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS), American Speech-Language-Hearing Association (ASHA), the International Lactation Consultant Association (ILCA), Lactation Consultants of Australia and New Zealand (LCANZ), the College of Lactation Consultants of Western Australia (CLCWA), the American Orthodontic Society (AOS) and the American Association of Orthodontists (AAO). We will identify relevant theses and dissertations through ProQuest Dissertations and Theses (PQDT), formerly known as Dissertation Abstracts.

C. Data Abstraction and Data Management

Data-screening and extraction forms. The forms used for the abstract review will contain questions about the primary exclusion and inclusion criteria. The forms used for the full-text review are more detailed and are intended to assist in (a) identifying studies that meet inclusion criteria and (b) initially sorting the studies according to the KQs. We will conduct data extraction for evidence and summary tables using the Systematic Review Data Repository (SRDR) system. We will extract those data necessary to inform our analyses of the evidence and perform data synthesis. We anticipate that these data will include those related to baseline participant characteristics (age, diagnosis, symptom severity, etc.), intervention characteristics, and outcomes.

Initial review of abstracts. We will review all the titles and abstracts identified through our searches against our inclusion/exclusion criteria. Each abstract will be reviewed by at least two members of the investigative team. When differences between the reviewers arise, we will err on the side of inclusion. For studies without adequate information to make the determination, we will retrieve the full-text articles and review them against the inclusion/exclusion criteria.

Retrieving and reviewing articles. We will retrieve and review all articles that meet our predetermined inclusion criteria or for which we have insufficient information to make a decision about eligibility. Each article will be reviewed by at least two members of the investigative team. Differences between the reviewers will be adjudicated by a senior team member.

Deciding which outcomes are to be extracted. We identified outcomes based on our clinical expertise and our initial scan of the literature. Our final list of outcomes includes the following: breastfeeding (including latch, nipple pain, nipple excoriations, nipple infections (mastitis),weight gain, aerophagia, swallowing function, failure to thrive, milk transfer, low milk supply, breastfeeding cessation), other feeding issues (including difficulty bottle feeding, moving food boluses in the mouth, deglutition), articulation, speech (including speech fluency, effort with speech, speech intelligibility), sleep disordered breathing (sleep apnea), oral hygiene, excessive salivation, orthodontic problems (including malocclusion, open bite due to reverse swallowing, lingual tipping of lower central incisors, separation of upper central incisors, crowding, and narrow palatal arch), psychological (e.g., self-esteem), harms (including excessive bleeding, airway obstruction, pain, transient poor feeding secondary to discomfort, dysphagia, complications related to dysphagia such as aspiration pneumonia, surgical site infection, nerve damage, salivary gland damage, ranulae, scarring, soft tissue damage, oral aversion, readherence, and need for further surgery).

We anticipate variation in reporting of the degree of ankyloglossia. Additionally, patient populations may not be well characterized in terms of severity. This is a particular challenge because decisions about where (e.g., in the newborn nursery or an alternative surgical environment) and by whom (e.g., primary care pediatrician or ENT specialist) treatment is administered are likely driven by severity. Thus, direct comparisons of outcomes between

settings and providers are likely to be confounded by indication. Outcome measures will vary among studies, as will definitions of clinically significant ankyloglossia. We anticipate the need to extract data as reported and consider possibilities for stratification to determine how best to deal with this heterogeneity.

For studies that meet the conditions of the second round assessment, the extractors will extract key data and risk of bias elements from the article(s) and enter them into the SRDR. As noted above, we anticipate that these elements will include population and intervention characteristics such as age, intervention approach, and outcomes. A second reviewer will review the initial data extraction against the original articles for quality control. Differences in data coding between the extractor and the reviewer will be resolved by consensus.

We will develop a simple categorization scheme for coding the reasons that articles at full review are excluded. We will then record those codes in an EndNote® (Thomson Reuters, New York, NY) bibliographic database so that we can later compile a listing of excluded articles and the reasons for such exclusions.

D. Assessment of Methodological Risk of Bias of Individual Studies

We will assess risk of bias by using the following established tools:

- *Cochrane risk of bias tool for randomized controlled trials*
- *Newcastle-Ottawa Scale for cohort studies*
- *EPC tool for case series*
- *McMaster Quality Assessment Scale of Harms (McHarm) for harms outcomes*

Two senior investigators will independently assess each included study with disagreements between assessors resolved through discussion to reach consensus.

E. Data Synthesis

Preparing summary tables. We will prepare summary tables to address each Key Question. The dimensions (i.e., areas of special focus, or the columns) of each table may vary by KQ as appropriate, but the tables will contain some common elements, such as author, year of publication, study location (e.g., country, city, state) and time period, population description, sample size, and study type (e.g., randomized controlled trial, prospective observational study).

Synthesizing results. We anticipate a small number of included studies and significant differences in populations, interventions, and outcomes measured in the ankyloglossia literature. We will work with our statistician to determine whether a quantitative analysis can be performed but we anticipate that this will be unlikely. We will provide a qualitative synthesis of studies meeting our review criteria.

Presentation of results. Within each KQ, we will organize results by study design and outcome, with a focus on those designs less subject to bias (i.e., randomized controlled trials,

controlled trials), those studies rated as having higher quality in our quality assessment process, and those employing comparison groups.

F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes.
We will use explicit criteria for rating the overall strength of the evidence for each key intervention-outcome pair for which the overall risk of bias is not overwhelmingly high. We will use established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending-sample sizes), the quality of evidence (from the quality ratings on individual articles), and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge.

The strength of evidence evaluation will be that stipulated in the Effective Health Care Program's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews,*[9] and in the updated strength of evidence guide[10] which emphasizes the following five major domains: study limitations (low, medium, high level of limitation), consistency (inconsistency not present, inconsistency present, unknown or not applicable), directness (direct, indirect), and precision (precise, imprecise), and reporting bias. Risk of bias is derived from the quality assessment of the individual studies that addressed the KQ and specific outcome under consideration. Each key outcome for each comparison of interest will be given an overall evidence grade based on the ratings for the individual domains.

The overall strength of evidence will be graded as:

Strength of evidence grades and definitions[10]

Grade	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome**. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Two senior staff will independently grade the body of evidence; disagreements will be resolved as needed through discussion or third-party adjudication. We will record strength of evidence assessments in tables, summarizing results for each outcome.

G. Assessing Applicability.
We will assess the applicability of findings reported in the included literature to the general population of children with ankyloglossia by determining the population, intervention, comparator, and setting in each study and developing an overview of these elements for each

intervention category. We anticipate that areas in which applicability will be especially important to describe will include the severity of ankyloglossia in the study population, the age range of the participants and the setting in which the intervention took place. We will also attempt to capture information about the clinical provider including specialty and training. We will describe any needs related to the setting, including anesthesia, surgical environment, materials for non-surgical interventions, etc.

V. References

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VI. Definition of Terms

AAP: American Academy of Pediatrics
AAPD: American Academy of Pediatric Dentistry
AAO: American Association of Orthodontists
AAO-HNS: American Academy of Otolaryngology – Head and Neck Surgery
ABM: Academy of Breastfeeding Medicine
AF: Analytic framework
AHRQ: Agency for Healthcare Research and Quality
AOS: American Orthodontic Society
ASHA: American Speech-Language-Hearing Association
CAM: Complementary and alternative medicine
CINAHL: Cumulative index of nursing and allied health literature
CLCWA: College of Lactation Consultants of Western Australia
CPS: Canadian Paediatric Society
ENT: Ear, Nose & Throat
EMBASE: Excerpta Medica Database
EPC: Evidence-based Practice Center
ILCA: International Lactation Consultant Association
KI: Key Informant
KQ: Key Question
LCANZ: Lactation Consultants of Australia and New Zealand
NHS: National Health Service
NICU: Neonatal intensive care unit
PAS: Pediatric Academic Societies
PICOTS: Population, Intervention, Comparator, Outcomes, Timing, Setting
PQDT: ProQuest Dissertations & Theses
RCT: Randomized controlled trial
SRDR: Systematic Review Data Repository

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as "because the AE/TOO/TEP/Peer reviewer told us to" but explain what the change hopes to accomplish.

VIII. Review of Key Questions

AHRQ posted the Key Questions on the Effective Health Care Website for public comment. The EPC refined and finalized the Key Questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the Key Questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA 290-2012-00009-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A. Criteria for diagnosing ankyloglossia (adapted from Suter 2009, Segal 2007)

Table A-1. Ankyloglossia diagnostic criteria

Author, Year	Criteria
Hogan et al. 2005[1]	Frenulum extending along 25-100% of tongues' total length
Ricke et al. 2005[2]	Hazelbaker's assessment tool for lingual frenulum function
Ruffoli et al. 2005[3]	Length of frenulum Normal: ≥2 cm Mild: 1.6 to 1.9 cm Moderate: 0.8 to 1.5 cm Severe: ≤0.7 cm Distance between incisal margin of upper central and lower homolateral incisor Normal: ≥2.3 cm Mild: 1.7 to 2.2 cm Moderate: 0.4 to 1.6 cm Severe: ≤0.3 cm
Griffiths 2004[4]	Frenulum thick Tongue heart-shaped when protruded
Ballard et al. 2002[5]	Hazelbaker's assessment tool for lingual frenulum function
Garcia Pola et al. 2002[6]	Level 1: Lingual mobility 51 to 100% Level 2: Lingual mobility 31 to 50% Level 3: Lingual mobility <30% Lingual mobility= mouth opening when tip of tongue touches palatal papilla/ maximum mouth opening
Messner et al. 2000[7]	Frenulum abnormally short
Messner and Lalakea 2000[8]	Frenulum abnormally short; decreased mobility of tongue tip
Kotlow 1999[9]	Normal: >16 mm Mild (class 1): 12 to 16 mm Moderate (class 2): 8 to 11 mm Severe (class 3): 3 to 7 mm Complete (class 4): <3 mm All measurements are length of tongue from insertion of lingual frenum in base of tongue to tip
Masaitis and Kaempf 1996[10]	Tongue heart-shaped when protruded Inability to bring tongue over lower gum ridge Abnormally short, thick frenulum Maternal nipple trauma
Harris et al. 1992[11]	Frenulum short, thick, and fibrous; frenulum extends to the papillated surface of tongue
Marmet et al. 1990[12]	Inability to bring tongue over lower gum ridge; normal breastfeeding sucking motion inhibited; tongue heart-shaped when protruded
Notestine 1990[13]	Frenulum <1 cm in length; tongue heart-shaped when protruded; tight feeling when finger placed under tongue along midline; tongue cannot reach gum line when protruded
Fleiss et al. 1990[14]	Tongue tip cannot reach top of gums Tongue tip cannot swing from one corner of mouth to the other Tongue displays notching when protruded Tongue cannot be protruded beyond lower gum
Jorgenson et al.1982[15]	Frenulum prevents protrusion of tongue; frenulum extends to papillated surface of tongue Frenulum fissures tongue tip during normal movements
Horton et al. 1969[16]	Mild: mucous membrane band Moderate: frenulum and genioglossus muscle are markedly fibrosed Complete: tongue fused to the floor of the mouth

References for Table A-1. Ankyloglossia diagnostic criteria

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Appendix B. Database Search Statements

Table 1. PubMed search strategies (PubMed web interface) (February 11, 2014)

Search terms		Search results
#1	("Mouth Abnormalities"[Mesh:noexp] OR "Tongue Diseases/congenital"[Mesh:noexp] OR "Tongue/abnormalities"[Mesh] OR "Lingual Frenum"[Mesh] OR "Lip Diseases/congenital"[Mesh:noexp] OR "Lip/abnormalities"[Mesh] OR "Labial Frenum"[Mesh] OR "Ankyloglossia"[Supplementary Concept] OR "ankyloglossia"[tiab] OR (("tongue"[tiab] OR "lip"[tiab] OR "lingual"[tiab] OR "linguae"[tiab] OR "labial"[tiab] OR "maxillary"[tiab]) AND ("frenum"[tiab] OR "fraenum"[tiab] OR "frenulum"[tiab] OR "frena"[tiab] OR "frenula"[tiab])) OR (("tongue"[tiab] OR "lip"[tiab] OR "maxillary"[tiab]) AND ("tie"[tiab] OR "tied"[tiab]))))	3501
#2	("Therapeutics"[Mesh] OR "therapy"[Subheading] OR "Treatment Outcome"[Mesh] OR "therapy"[tiab] OR "therapies"[tiab] OR "therapeutic"[tiab] OR "therapeutics"[tiab] OR "outcome"[tiab] OR "outcomes"[tiab] OR "Oral Surgical Procedures"[Mesh] OR "surgical"[tiab] OR "surgery"[Subheading] OR "surgery"[tiab] OR "frenulotomy"[tiab] OR "frenulectomy"[tiab] OR "frenotomy"[tiab] OR "frenectomy"[tiab] OR "frenuloplasty"[tiab] OR "z-plasty"[tiab] OR "h-plasty"[tiab] OR "laser"[tiab] OR "Rehabilitation of Speech and Language Disorders"[Mesh] OR "Speech Disorders "[Mesh] OR "Language Development Disorders "[Mesh] OR "speech therapy"[tiab] OR "speech therapies"[tiab] OR "language therapy"[tiab] OR "language therapies"[tiab] OR "oral motor therapy"[tiab] OR "oral motor therapies"[tiab] OR "Complementary Therapies"[Mesh] OR cam[sb] OR "complementary medicine"[tiab] OR "complementary therapy"[tiab] OR "complementary therapies"[tiab] OR "alternative medicine"[tiab] OR "alternative therapy"[tiab] OR "alternative therapies"[tiab] OR "cam"[tiab] OR "craniosacral therapy"[tiab] OR "cranial sacral therapy"[tiab] OR "myofascial release"[tiab] OR "myofascial therapy"[tiab] OR "rolfing"[tiab]) OR ("unsafe"[tiab] OR "safety"[tiab] OR "harm"[tiab] OR "harms"[tiab] OR "harmful"[tiab] OR "complication"[tiab] OR "complications"[tiab] OR "risk"[tiab] OR "risks"[tiab] OR "side-effect"[tiab] OR "side-effects" [tiab]OR ((undesirable OR adverse) AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))OR" sequelae" [tiab] OR "sequela" [tiab] OR ((postoperative OR surgical OR "post operative" OR "post surgical") AND (complication OR complications)) OR "adverse effects"[Subheading] OR "complications"[Subheading] OR "contraindications"[Subheading])	10219702
#3	#1 AND #2	2065
#4	#3 AND eng[la]	1496
#5	#4 NOT (editorial[pt] OR letter[pt] OR comment[pt] OR review[pt] OR news[pt] OR historical article[pt] OR practice guideline[pt] OR meta-analysis[pt])	1252

Key: [Mesh: noexp] exact medical subject heading, not including the terms nested beneath it; [MeSH] medical subject heading; [Supplmentary Concept] indexing terms for chemicals, substances and rare diseases; [tiab] keyword in title or abstract; [sh] subheading; [la] language; [pt] publication type.

Table 2: CINAHL search strategies (EBSCO Host interface) (February 11, 2014)

	Search terms	Search results
S1	((MH "Mouth Abnormalities") OR (MH "Tongue Diseases") OR (MH "Tongue /AB") OR (MH "Lip Diseases") OR (MH "Lip/AB") OR (MH "Frenum (Oral)") OR (MH "Ankyloglossia") OR "ankyloglossia" OR (("tongue" OR "lip" OR "lingual" OR "linguae" OR "labial" OR "maxillary") AND ("frenum" OR "fraenum" OR "frenulum" OR "frena" OR "frenula")) OR (("tongue" OR "lip" OR "maxillary") AND ("tie" OR "tied")))	864
S2	((MH "Therapeutics+") OR (MH "Treatment Outcomes+") OR "therapy" OR "therapies" OR "therapeutic" OR "therapeutics" OR "outcome" OR "outcomes" OR (MH "Surgery, Oral+") OR "frenulotomy" OR "frenulectomy" OR "frenotomy" OR "frenectomy" OR "frenuloplasty" OR "z-plasty" OR "h-plasty" OR "laser" OR "surgery" OR "surgical" OR (MW "su") OR (MH "Speech Disorders+") OR (MH "Communicative Disorders+") OR (MH "Language Disorders+") OR (MH "Rehabilitation, Speech and Language+") OR "speech therapy" OR "speech therapies" OR "language therapy" OR "language therapies" OR "oral motor therapy" OR "oral motor therapies" OR (MH "Alternative Therapies+") OR "complementary medicine" OR "complementary therapy" OR "complementary therapies" OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "cam" OR "craniosacral therapy" OR "cranial sacral therapy" OR "myofascial release" OR "myofascial therapy" OR "rolfing")	1269326
S3	S1 AND S2	497
S4	S3 AND limiters: English language	495
S5	S4 AND limiters: Exclude MEDLINE records	96

Key: MH CINAHL medical subject heading; MW CINAHL subheading

Table 3: PsycINFO search strategies (ProQuest interface) (February 11, 2014)

	Search terms	Search results
#1	(SU.EXACT.EXPLODE("Mouth (Anatomy)") OR SU.EXACT.EXPLODE("Tongue") OR SU.EXACT.EXPLODE("Lips (Face)") OR IF("ankyloglossia" OR (("tongue" OR "lip" OR "lingual" OR "linguae" OR "labial" OR "maxillary") AND ("frenum" OR "frenum" OR "fraenum" OR "frenulum" OR "frena" OR "frenula")) OR (("tongue" OR "lip" OR "maxillary") AND ("tie" OR "tied"))))	2022
#2	(SU.EXACT.EXPLODE("Treatment") OR (IF("therapy" OR "therapies" OR "therapeutic" OR "therapeutics" OR "outcome" OR "outcomes" OR "frenulotomy" OR "frenulectomy" OR "frenotomy" OR "frenectomy" OR "frenuloplasty" OR "z-plasty" OR "h-plasty" OR "laser" OR "surgery" OR "surgical" OR "speech therapy" OR "speech therapies" OR "language therapy" OR "language therapies" OR "oral motor therapy" OR "oral motor therapies" OR "complementary medicine" OR "complementary therapy" OR "complementary therapies" OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "cam" OR "craniosacral therapy" OR "cranial sacral therapy" OR "myofascial release" OR "myofascial therapy" OR "rolfing")))	684785
#3	#1 AND #2	235
#4	#3 AND LA(English)	220
#5	#4 with peer reviewed and scholarly journals selected	207

Key: SU.EXACT.EXPLODE subject term

Table 4. EMBASE search strategies (OvidSP interface) (May 23, 2014)

Search terms		Search results
#1	tongue disease/cn or tongue disease*.tw. or tongue abnormalit*.tw. or ankyloglossia/ or ankyloglossia.tw. or lip malformation/cn or lip malformation*.tw. or lip disease/cn or lip disease*.tw. or ((tongue/ or tongue.tw. or lip/ or lip*.tw. or labial.tw. or lingual.tw.) and (frenum.tw. or fraenum.tw. or frena.tw. or frenulum.tw. or frenula.tw.)) or ((tongue.tw. or lip/ or maxillary.tw.) and (tie.tw. or tied.tw. or ties.tw.))	1229
#2	th.fs. or therapy/ or therapy.tw. or therapies.tw. or therapeutic*.tw. or treatment outcome/ or treatment outcome*.tw. or outcome*.tw. or oral surgery/ or oral surger*.tw. or surgical.tw. or su.fs. or surgery.tw. or frenulotom*.tw. or frenulectom*.tw. or frenotom*.tw. or frenectom*.tw. or frenuloplast*.tw. or z plasty/ or z plasty.tw. or h plasty.tw. or laser surgery/ or speech rehabilitation/ or speech rehabilitation.tw. or speech disorder/ or speech disorder*.tw. or developmental language disorder/ or language development disorder*.tw. or speech therapy/ or speech therap*.tw. or language therap*.tw. or oral motor therap*.tw. or complementary therap*.tw. or cam.tw. or complementary medicine*.tw. or alternative medicine/ or alternative medicine*.tw. or alternative therap*.tw. or craniosacral therapy/ or craniosacral therap*.tw. or myofascial therap*.tw. or myofascial release.tw. or manipulative medicine/ or rolfing/ or rolfing.tw. or (Unsafe.tw. or safety/ or safety.tw. or harm.tw. or harms.tw. or harmful.tw. or complication/ or complication*.tw. or risk/ or risk*.tw. or side effect/ or side effect*.tw. or contraindication*.tw. or ((undesirable.tw. or adverse.tw.) and (effect.tw. or effects.tw. or reaction.tw. or reactions.tw. or event.tw. or events.tw. or outcome.tw. or outcomes.tw.)) or sequelae.tw. or sequela.tw. or ((postoperative.tw. or surgical.tw. or post operative.tw. or post surgical.tw.) and (event.tw. or events.tw. or outcome.tw. or outcomes.tw.)) or si.fs. or co.fs.)	8617400
#3	1 AND 2	730
#4	Limit 3 to English	585
#5	Limit 4 to human	541
#6	5 not (review.pt. or editorial.pt. or letter.pt. or note.pt. or short survey.pt. or conference paper.pt. or meta analysis/ or practice guideline/ or systematic review/)	431
#7	5 Exclude MEDLINE journals	25

Key: / Emtree heading; .tw. abstract, title and drug trade name; /cn congenital; .fs. subheading; si.fs. side effects subheading; th.fs. therapy subheading; su.fs. surgery subheading; co.fs. complications subheading; p.t. publication type