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Timing Of Primary Surgery for cleft palate (TOPS): Protocol for a randomised trial of palate surgery at 6 months versus 12 months of age

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Timing Of Primary Surgery for cleft palate (TOPS): Protocol for a randomised trial of palate surgery at 6 months versus 12 months of age

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ABSTRACT

Introduction: Cleft palate is amongst the most common birth abnormalities. The success of primary surgery in the early months of life is crucial for successful feeding, speech, hearing, dental development and facial growth. Over recent decades, age at palatal surgery in infancy has reduced. This has led to palatal closure in one-stage procedures being carried out around the age of 12 months, but in some cases as early as 6 months. The primary objective of the TOPS trial is to determine whether surgery for cleft palate performed at 6 or 12 months of age is most beneficial for speech outcomes.

Methods and analysis: Infants with a diagnosis of non-syndromic isolated cleft palate will be randomised to receive standardised primary surgery (Sommerlad technique) for closure of the cleft at either 6 months or 12 months, corrected for gestational age. The primary outcome will be perceived insufficient velopharyngeal function at 5 years of age. Secondary outcomes measured across 12 months, 3 and 5 years will include growth, safety of the procedure, dentofacial development, speech, hearing level and middle ear function. Video and audio recordings of speech will be collected in a standardised age-appropriate manner and analysed independently by multiple speech and language therapists (SLTs). The trial aims to recruit and follow up 300 participants per arm. Data will be analysed according to the intention to treat principle using a 5% significance level. All analyses will be pre-specified within a full and detailed statistical analysis plan.

Ethics and dissemination: Ethical approval has been sought in each participating country according to country specific procedures. Trial results will be presented at conferences, published in peer-reviewed journals and disseminated through relevant patient support groups.

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Keywords: unilateral cleft palate, randomised clinical trial, TOPS, palatal surgery, velopharyngeal function, syllable inventory, Sommerlad technique

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Strengths and limitations of the study

- International trial covering speech development in children across Scandinavia, the UK, and Brazil
- Surgical repair was calibrated across surgeons who were all trained in the Sommerlad technique.
- Longitudinal speech assessments at 12 months, 3 and 5 years will be independently analysed by multiple speech and language therapists whose ratings will be calibrated on practice recordings.
- Standardised assessments of additional outcomes include postoperative complications, hearing levels, middle ear function and dentofacial development.
- The study excludes co-existing conditions such as syndromic cleft palate or severe developmental delays that are known to adversely affect speech development or its assessment

INTRODUCTION

Clefts of the lip and/or palate, occurring with an incidence of about 1 per 600 births, are among the most common birth anomalies. This trial will focus on isolated clefts of the palate, which occur with a global incidence of 4.5 per 10,000 births (1). Depending on geographic location, the prevalence of isolated clefts of the palate ranges from 1.8 to 14.6 per 10,000 (1).

The timing of palatal surgery has been a controversial issue since the 1930s (2). Traditionally, rationale for delaying hard palate surgery was partly based on the belief that postponing the trauma of palatal closure may reduce maxillary growth disturbance. However, there is little evidence that facial skeletal growth in individuals with isolated cleft palate is substantially affected by different surgical protocols, though maxillary arch form, especially transversely, may be affected (3-6).

Over recent decades, the age at which palatal surgery is carried out has reduced. This has led to one-stage palatal closure within 12 months of age at cleft units in Europe and the USA. Protagonists of early closure of the palatal cleft have proposed that since speech is a learned behaviour, the sooner an intact anatomy is created, the better (7-10). As yet however, there is no evidence that early surgery would lead to better speech development.

Rationale

The widespread uncertainty surrounding the timing of palatal closure was reflected in the diversity of protocols currently employed by the Scandcleft Research Group, a partnership of Scandinavian and UK cleft lip and palate centres (11-22). The Scandcleft Research Group, identified this uncertainty as a priority research question for a future trial. Its aim was to determine whether, in infants with cleft palate, repair at either age 6 or at 12 months (corrected for gestational age) would achieve better speech outcomes. The design of the trial was supported by a planning grant from the National Institute of Dental and Craniofacial Research (NIDCR), a substream of the US National Institute of Health, who subsequently funded the proposed trial.

Objectives

The aim of this project is to determine whether, in infants with isolated cleft palate, it is better to perform primary surgery at age 6 or 12 months (corrected for gestational age). Gestational age will be assessed based upon the date of the last menstrual period and the infant's date of birth (full term

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defined as day 1 of the 40th week of pregnancy), thus taking account of prematurity. This research will investigate the effect of the timing of surgery by assessing and comparing speech development outcomes measured across 12 months, 3 years and 5 years. In addition, secondary outcomes include growth, perioperative complications, dentofacial development, hearing level and middle ear function.

METHODS AND ANALYSIS

Design

Timing Of Primary Surgery for cleft palate (TOPS) is an international, multi-site trial using a parallel arm design aiming to detect whether surgery at 6 months is superior to surgery at 12 months. Infants will be randomised to receive primary surgery for cleft palate using a standardised technique (the Sommerlad technique (23)) at either age 6 or age 12 months (corrected for gestational age). The study design of TOPS trial is illustrated in Figure 1.

Setting

The trial will be conducted by the cleft palate teams based in centres across the UK, Scandinavia and Brazil. Criteria for selection of sites is based primarily on ability to enrol a high volume of patients into the trial. A list of the TOPS trial sites is provided in Table 1. The cleft team at each centre generally includes cleft surgeon(s), nursing staff, cleft speech and language therapist(s), clinical geneticist(s)/paediatrician(s), audiologist(s), orthodontist(s) and psychologist(s)/social worker(s)

Table 1: TOPS trial clinical sites

Country	Sites
Brazil	University of São Paulo (HRAC Bauru)
Denmark	Copenhagen Cleft Palate Centre / Århus Speech and Hearing Institute
Norway	Oslo University Hospital
	Helse Bergen HF
Sweden	Malmö University Hospital
	Göteborg University
	Karolinska University Hospital (Stockholm)
	University of Linköping
	Umeå University
	Uppsala University
United Kingdom	Royal Manchester Children's Hospital
	Alder Hey Children's NHS Foundation Trust
	Royal Belfast Hospital for Sick Children
	Birmingham Children's Hospital
	Royal Victoria Infirmary, Newcastle
	University Hospitals Bristol NHS Foundation Trust
	Morriston Hospital, Abertawe Bro Morgannwg University Hospital Board, Swansea
	Leeds General Infirmary
	Royal Hospital for Sick Children, Glasgow
	Royal Hospital for Sick Children, Edinburgh
	Salisbury NHS Foundation Trust
	The Children's Hospital , John Radcliffe Hospital, Oxford

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Eligibility criteria

All infants referred to the participating specialised cleft lip and palate centres are eligible to enter the trial if they meet the following inclusion and none of the exclusion criteria:

a. isolated cleft palate;
b. medically fit for surgery at 6 months, corrected for gestational age;
c. Written informed proxy consent;
d. One parent/carer must be a native language speaker of the majority language in the country of residence.

Infants with any of the following will be excluded from the study:

a. Consent not obtained;
b. Infants with severe developmental delay (as measured on DENVER II)or syndromic cleft palate (except Van der Woude syndrome, which can be included if hearing is not affected) will be excluded;
c. Congenital sensorineural hearing loss or structural middle ear anomalies;
d. Sommerlad technique could not be performed due to variation in the anatomical presentation;
e. Infants presenting with submucous cleft palate (defined by the classical triad of signs, bifid uvula, bony defect of the hard palate, muscular diastasis, as described by Jensen et al. (24))
f. Where the language spoken at home by at least one parent is not the majority language in the country of residence.

Since not all syndromic disorders will present prior to recruitment, all participants will undergo genetic testing to exclude chromosome abnormalities at the time of surgery. If a chromosome abnormality or another genetic syndrome is identified later in the study the data for these participants will be analysed separately. The same will apply if the participant fails the DENVER II developmental test at 3 year follow up.

Consent

Informed consent will be sought from the infant's parent/guardian by a member of the local trial team, and families who decline to participate will receive surgery in line with the hospital's current practice together with the same level of care and support as families participating in the trial. Consent forms used in the TOPS trial in the UK are shown in Supplementary Materials Nos. 1, 2 and 3; these forms were adapted and translated for use in the other participating countries while maintaining key content. The final consent forms in Brazilian-Portuguese, Danish, Norwegian and Swedish were translated to English to check for accuracy and completeness. Participants can withdraw from the trial at any time without giving an explanation, and their child's care will not be affected.

To reduce potential burden to families, where possible, trial information will be collected at visits scheduled in line with routine visits made to the site as part of the infant's ongoing care.

Randomisation

Infants meeting the eligibility criteria will be randomised to 6 or 12 month surgery, corrected for gestational age, in a ratio 1:1 using a minimisation routine incorporating a random element to reduce predictability. Allocations will be delivered via a password protected web-based system.

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Every effort will be made to arrange surgery within one of week of the target date. However, surgery may take place up to two weeks before or four weeks after the target date. The estimated timing of surgery and the allowed time window for the surgery will be calculated by the online randomisation system and provided to the trial site at the time of randomisation.

Interventions

The Sommerlad surgical technique (23)] will be used in all participants at 6 months or 12 months corrected for gestational as determined by randomisation. This technique will be standardised across all surgeons, including those who already use the technique, by receiving direct instruction from Mr Brian Sommerlad in the operating theatre. Written descriptions and a video of the surgical procedure will also be provided.

Blinding

The nature of the interventions prevents this trial from being blind to participants or their carers. However, speech and audiometry outcome assessments, at age 3 and 5 years, will be conducted and rated blind to the randomly allocated group.

Outcome Measures

The primary endpoint for the TOPS trial is defined as a dichotomous outcome of whether the child has been perceived by the SLTs to have insufficient velopharyngeal function at age 5 years or not. Adequate velopharyngeal function is a prerequisite for normal speech production. In children born with cleft palate, speech outcomes are often reported for velopharyngeal function and articulation. In the presence of insufficient velopharyngeal function, speech will inevitably be affected by symptoms such as hypernasality and nasal air emission to different degrees. In children with isolated cleft palate, articulation disorders occur less frequently than in children with complete cleft lip and palate. Insufficient perceived velopharyngeal function was therefore chosen to be the primary outcome and articulation outcomes as secondary outcomes. Velopharyngeal insufficiency is measured by velopharyngeal (VPC) sum, which is an overall score on the scale 1-6 (25). Scores ≥4 on this scale will be considered insufficient.

The secondary endpoints are summarised in Box 1and Table 2 (Schedule of Assessments).

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Box 1: Secondary Endpoints

1. **Velopharyngeal function at age 5 years;**
   a. **Velopharyngeal composite score summary (VPC sum)**
   b. **Insufficient velopharyngeal function (VPC rate)**
2. **Velopharyngeal function at age 3 years;**
   a. **Insufficient velopharyngeal function (VPC rate)**
   b. **Velopharyngeal insufficiency symptoms**
3. **Canonical babbling at age 12 months:**
   a. **Canonical babbling present**
   b. **Canonical babbling ratio**
   c. **Consonant inventory**
4. **Articulation at age 3 years:**
   a. **Percent consonants correct (PCC)**
   b. **Percent correct placement (PCP)**
   c. **Percent correct manner (PCM)**
   d. **Non-oral consonant errors**
   e. **Oral consonant errors**
5. **Articulation at age 5 years:**
   a. **Percent consonants correct (PCC)**
   b. **Percent correct placement (PCP)**
   c. **Percent correct manner (PCM)**
   d. **Non-oral consonant errors**
   e. **Oral consonant errors**
6. **Postoperative/long term complications:**
   a. **Dehiscence**
   b. **Infection**
   c. **Evidence of fistula**
7. **Hearing level:**
   a. ***At 12 months***
      i. **Abnormal Transient Otoacoustic Emission (TEOAE)**
      ii. **Abnormal Soundfield audiometry**
   b. ***At 3 and 5 years***
      i. **Abnormal Puretone audiometry in at least one ear**
      ii. **Abnormal Puretone audiometry in both ears**
      iii. **Severity of better ear (normal, mild, moderate, severe, profound)**
8. **Middle ear function**
   a. **Flat line Tympanogram in at least one ear (12 months, 3 years, 5 years)**
   b. **Flat line Tympanogram in both ears (12 months, 3 years, 5 years)**
9. **Dentofacial development at age 5 years:**
   a. **Soft tissue ANB (the angle between soft tissue nasion, A point, and B point on a profile photograph)**
   b. **Maxillary arch constriction score (using modified Huddart/Bodenham scoring system)**
10. **Growth at 12 months:**
    a. **Nude weight**
    b. **Crown to heel length**
    c. **Occipitofrontal circumference**

Speech outcome assessments

To ensure quality of speech data, all sites will receive identical high quality recording equipment (video recorder JVC-GY-HM100 series, audio recorder H4n/H5 Handy recorder, and microphone Rode NT4/NT5) to be used at each follow-up recording according to a detailed standard operating

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procedure. Before data collection starts at each follow up age, all SLTs will participate in a three-day calibration meeting. Afterwards, a series of video-audio practice recordings will be completed and quality checked. When sufficient recording quality has been reached, the site receives approval that they can start the trial recordings. To train the SLTs who are going to perform blinded speech assessments, a specific procedure has been developed. This includes theoretical lectures on development of speech and language in children with cleft palate and methodological considerations on assessment/rating, and listener training with discussions and personal feedback. Before the assessments start, all SLTs need to pass a test with a specified level of intra- and inter-rater reliability. They also have to pass a hearing test.

At 12-months of age, assessments will be done cross-linguistically. At age 3 and 5, SLT rating will be confined to records of children sharing the SLT's native language.

Vocalisations of 12-month old children will be assessed with adjusted real time listening, as described by Ramsdell et al (26). The SLTs will listen to a 45 minutes video recording, of a play session between the child and carer, divided in two parts (22 minutes each). The SLT will register every syllable a child produces as canonical or not, in real time, using a software, TimeStamper, specifically developed for this study (27). At the end of each recording, the SLT indicates if the child babbled canonically or not, and lists the syllables the child produced with control. In this way, the variables canonical babbling present, canonical babbling ratio, and consonant inventory are obtained.

The methodology for the 5-year assessment of articulation and velopharyngeal function cross-linguistically was developed within the Scandcleft study (12, 18, 22) and will be extended to include Brazilian Portuguese. At the 5-year assessment, 36 target consonants from the TOPS single word test will be transcribed phonetically for assessment of articulation and VPI-symptoms. Target words include similar target sounds in the same position and with similar phonetic context across languages. Further, repetition of sentences and continuous speech are collected, as well as nasalance scores (Nasometer™), and parent-reported intelligibility estimates of how well their children's speech is understood by different listeners (Intelligibility in context scale (28)). The 3-year assessment will be based on 30 of the 36 words used in the 5-year assessment, and target consonants will be transcribed phonetically for assessment of articulation. Error types will be classified automatically by a predefined script that will also allow calculation of PCC, PCP, and PCM. The VPC-rate will be rated by SLTs from continuous speech both at age 3 and 5 years

Outcome Measures	**Assessment Schedule (age is corrected for gestational age)**					
	Assessments	**Post-surgery**		**12 months**	**3 years**	**5 years**
		48 hours	**30 days**			
Surgical Complications	Dehiscence	√	√			
	Infection	√	√			
	Evidence of Fistula		√		√	√

Table 2: Schedule of Assessments

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Growth	Nude Weight			√		
	Crown to heel length			√		
	Occipitofrontal Circumference			√		
Canonical Babbling	Canonical Babbling present[e]			√		
	Canonical Babbling ratio[e]			√		
	Consonant Inventory[e]			√		
Velopharyngeal Function	Velopharyngeal composite score summary (VPC-sum)					√[a,b]
	Insufficient Velopharyngeal function (VPC rate)				√[c]	√[d]
	Velopharyngeal insufficiency Symptoms				√[a]	
Articulation	Percent Consonant Correct (PCC)[a]				√	√
	Percent Correct Placement (PCP)[a]				√	√
	Percent Correct Manner (PCM)[a]				√	√
	Non-oral consonant errors[a]				√	√
	Oral Consonant errors[a]				√	√
Hearing Level	Abnormal Transient Otoacoustic Emission (TEOAE)			√		
	Abnormal Soundfield Audiometry			√		
	Abnormal Pure Tone Audiometry in at least one ear*				√	√
	Abnormal Pure tone Audiometry in both ears*				√	√
	Severity of better ear*				√	√
	Soundfield Audiometry*				√	√
Middle Ear Function	Flat Line Tympanogram in at least one ear			√	√	√
	Flat Line Tympanogram in both ear			√	√	√

Dentofacial Development	Soft Tissue ANB**					√
	Maxillary arch Constriction score***					√
Others	DENVER II Developmental Assessment****				√	
	Intelligibility in Context Scale Questionnaire for parents (ICS)					√
	Local site questionnaire*****				√	√

*: if puretone audiometry could not be performed then Soundfield audiometry will be performed

**: the angle between soft tissue nasion A point and B pint on a profile photograph

***: maxillary arch constriction score is determined using modified Huddart/Bodenham scoring system

****: DENVER II developmental Assessment is carried out at the time of surgery

*****: Local site questionnaire sent to local speech and language therapists outside TOPS research team to collect data on direct and indirect therapy given to the child in the intervals between assessment visits

Sources of speech assessments; a: TOPS picture naming test, b: nine word string, c: spontaneous speech, d: spontaneous speech (retelling of bus story) and e: video of play interaction.

Patient and Public Involvment

Parents of children with cleft palate were approached by their orthodontist / surgeons prior to enrolment. Patients and their parents were not initially involved in the design of the study. However, a representative from the Cleft Lip & Palate Association (the charity for Cleft Lip & Palate in the UK) is a member of the Trial Steering Committee. Therefore, providing ongoing insight from a parent perspective with regards to the execution of this study and the dissemination of results.

Data collection and management

Trial data will be recorded on Case Report Forms (CRFs) and identifiable only by randomisation number. The data from completed CRFs will be entered onto the trial specific MACRO database by the Data Manager or appropriately trained personnel at the Data Coordinating Centre.

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Video and audio recording

Once recorded, video and audio recordings will be saved onto encrypted USB drives. They will be posted to the Data Coordinating Centre where, upon receipt, they will be logged and stored onto the trial specific secure server. This server will be backed up once a day to ensure data is not lost once received. Recordings are quality checked by the Core Speech Group and/or the Trial Administrative Centre. A satisfactory recording is one that passes pre-specified quality checks on lighting, length and sound. Quality checks will be performed regularly and feedback to site will be provided on their suitability for assessment.

Maxillary arch impressions

Maxillary arch impressions will be obtained at the time of surgery to provide a mould for plaster casts, which are sent to the TOPS Administrative Centre at the University of Manchester.

In addition, impressions of the maxillary and mandibular dental arches will be obtained at the 5 year follow-up appointment. Impressions are taken by a designated member of staff (usually the orthodontist) using appropriate impression material. The occlusion will be registered with a wax wafer in the position of maximal intercuspation. The study models made from the impressions will be stored at the TOPS Administrative Centre.

Photographs

Intra-oral photographs will be taken at the time of surgery, and frontal and lateral photographs will be obtained at the 5-year visit. The photographs will be saved onto encrypted USBs, upon receipt by the Data Coordinating Centre they will be logged and stored onto trial specific secure hard drives.

Statistical analysis and sample size considerations

Proposed sample size

300 patients per arm will allow a reduction in insufficient velopharyngeal function at 5 years from 40% to 29% to be detected with 81% power using a chi-square test (2 sided significance test at 0.05 level). The estimate of 40% was obtained from a pilot trial in 50 five year of patients, collected during the planning period for this grant application (12). To allow an approximate drop out of 10%, 648 participants will be recruited. However to consider the potential impact of variability around the value of 40%, 300 patients per group would provide 80% power to detect a reduction from 30% to 20% and 76% power to detect a reduction from 20% to 12%.

The trial enrolment, allocation, follow up and analysis will be reported using the "Consolidated Standard of Reporting Trials" ("CONSORT") (29) and the International Conference on Harmonisation E9 guidelines (30). A full and detailed statistical analysis plan (31) will be developed prior to the final analysis of the trial. The main features of the statistical analysis plan are included here.

The primary analysis will be by intention-to-treat principle, as far as is practically possible using a 5% significance level throughout. Rather than adjust for multiplicity of secondary outcomes, relevant

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results from other studies already reported in the literature will be taken into account in the interpretation. The approach to formal analyses will be dependent on outcome type as follows:

- *Dichotomous outcome* will be compared between the two groups using a chi-squared test and the effect estimate will be reported in terms of the relative risk and 95% confidence interval.
- *Short ordinal outcomes* will be compared using a chi-squared test for trend.
- *Continuous and long ordinal outcomes* will be compared between the two groups using a two group t-test. The difference in means will be presented with a 95% confidence interval.

Baseline and operative characteristics and safety data will be presented using descriptive statistics only.

If the percentage of major protocol deviations exceeds 10% and the trial management group consider this analysis appropriate, a per protocol analysis in which pre-specified major protocol deviations indicate exclusion of a participant from the analysis set will be conducted.

Trial oversight and monitoring

The Trial Management Group (TMG), Trial Steering Committee (TSC) and Data Safety and Monitoring Board (DSMB) will provide ongoing oversight and will monitor accruing trial data. The roles, responsibilities and composition of each of these committees are provided in Supplementary Material No. 4. A risk assessment has been conducted and used to inform a trial specific monitoring plan agreed by the independent oversight committees.

Trial status and timeline

The overall programme commenced 13/07/2010. Applications for ethics approval were submitted 10/11/2009. Recruitment to the trial commenced 13/07/2010. Participants will be followed up until 30th July 2020.

This trial completed recruitment on 21st July 2015 and the last patient is due to attend their last visit until 30th of July 2020.

ETHICS

The trial will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996), the Office of Human Research Protections (OHRP) Common Rule, 45 CFR 46 and General Data Protection Regulations (GDPR), accompanied by UK Data Protection Act (2018).

Ethical approval has been sought in each participating country according to country specific procedures. The protocol has gained favourable opinion from the Multicentre Research Ethics Committee in the UK and from relevant ethics committees for each participating centre. TOPS Protocol Version 1.1 (of 02 November 2009) was approved by UK ethics on 8 January 2010, the Protocol Version 4.0 (of 26 August 2015) was approved by UK ethics on 01 October 2015 and the Protocol Version 5.0 (of 22 August 2018) was approved by UK ethics on 18 November 2018. A

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summary of substantial protocol amendments and relevant ethics committees is provided in Supplementary Material No. 5.

DISSEMINATION

Following completion of the study, the Principal Investigator is expected to publish the results of this research in a peer-reviewed scientific journal. According to the National Institute of Health (NIH) Public Access Policy, all journal articles arising from this NIH funded trial will be submitted to the digital archive PubMed Central. Trial investigators have the right and responsibility to communicate their findings to the scientific community and to the public. Findings of the trial will also be presented at National and International meetings of relevant professional bodies and research groups. Reports will also be posted on the WHO website (www.who.org) craniofacial section. Access to clinical data sets within speech, genetic, surgical and other fields will be available to others following the acceptance for publication of the main findings from the final dataset. Requests to access data will be subject to participant confidentiality concerns, and to contemporary NIH guidance on data-sharing plans.

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Contributors William Shaw, the Chief Investigator , and Gunvor Semb conceived the trial as an extension of the Scandcleft Trial and developed the first version of the protocol with Anette Lohmander, Elisabeth Willadsen, Christina Persson, Paula Williamson and Carrol Gamble. Jill Clayton-Smith developed the genetic aspects of the protocol and Inge Kiemle Trindade provided logistic advice for extension of the study to Brazil. Nicola Harman and Dieter Weichart contributed to coordination and implementation of the study, and revised and finalised the study protocol and Kevin J Munro and Elizabeth J Conroy participated in writing the protocol. All authors reviewed and approved this manuscript.

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Website WWW.tops.trial.org.uk

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Sponsorship

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Competing interests statement None declared.

Patient consent Obtained.

Provenance and peer review: Not commissioned; peer reviewed for ethical and funding approval.

Data sharing statement: All the data used in this project will be generated directly as a result of the project, without any pre-existing data being used. All data generated during the project will be made available.

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Word count: 3772

Figure 1: flow diagram of TOPS study design

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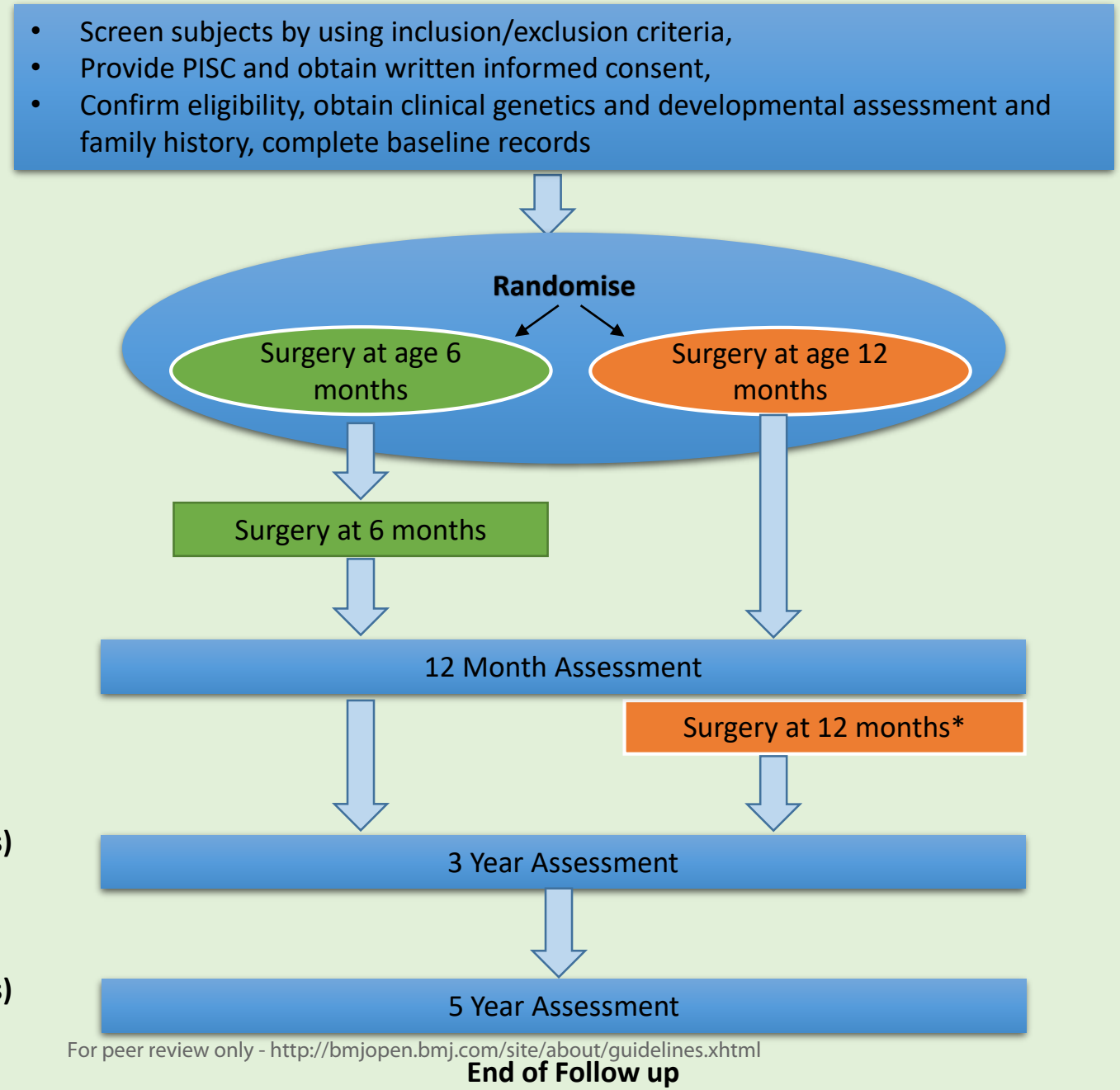
Figure 1: Flow diagram of the TOPS Trial study design



*Infants having surgery at 12 months will have their 12 month assessment prior to surgery

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Participant Randomisation Number								

INFORMATION FOR PARENTS

Research Trial Entitled: **Timing Of Primary Surgery For Cleft Palate (TOPS)**

This trial will assess the timing of primary surgery in children with cleft palate.

Recruiting Centre Name: <Centre Name>

Recruiting Centre ID number: <Centre ID>

Dear Parent,

We would like to invite your child to take part in a trial of treatment for cleft palate. Before you decide whether you would like your child to take part we would like to explain to you why the research is being done and what it would involve for you.

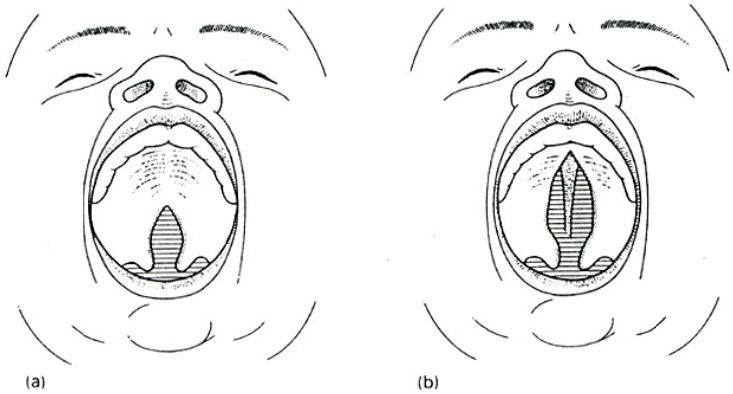
Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Talk to others about the trial if you wish.

Take time to decide whether or not you wish to take part.

Thank you for reading this information sheet.

1. What is the purpose of this trial?

The purpose of the trial is to find the best age at which to repair a cleft palate and give the child the best possible speech. Babies with cleft palate can have their surgery done at different times, usually before they are 18 months old.



The drawings above show (a) a cleft involving the soft palate and (b) a cleft involving the soft and hard palate.

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Some centres prefer to repair a cleft palate when the baby is around 6 months old, others when the baby is around 12 months. However as yet, there is no reliable evidence to help surgeons decide whether one timing is better than another. The only way to find out is to make a careful comparison of different timings.

Therefore an international partnership has been formed to carry out a trial that will provide clearer evidence for selecting the timing of surgery for future babies with cleft palate. A total of 650 babies will be included in the trial.

2. Why has my child been invited to take part?

The TOPS Trial team at <Centre Name> is inviting all infants with cleft palate to join the trial.

3. Does my child have to take part?

No, the research is voluntary. It is up to you to decide. We will describe the trial and go through this information sheet, which we will then give to you. You will be given time to think about the trial. Should you decide that you would like your child to participate we will ask you to sign a consent form. You are free to withdraw your child from the trial at any time, without giving a reason. This would not affect the standard of care your child receives.

If you decide that you do not want your child to participate in the TOPS trial the care they will receive will not be affected and will be the standard care provided at <Centre Name> with your child's surgery usually taking place at suitable time between the ages of 6 and 18months.

4. What will happen if I choose for my child to take part?

Babies with a cleft palate taking part in the trial will be divided into two groups. One group will have surgery at 6 months and one at 12 months. All will have surgery performed according to the same well-established technique and your cleft palate team will discuss the surgery with you at a routine clinic appointment. The age group that each baby goes in to will be decided by chance using a computer system, this is called randomisation and will ensure that there are equal numbers in each of the groups.

Before the operation a full physical examination will be done and a family history will be taken. During the operation a photograph and an impression of your child's mouth (called a maxillary arch impression) will be taken and a blood sample will be collected unless this has been taken previously. If a blood sample cannot be taken at surgery we will ask your permission to take it at another suitable time, for example, when your child is having a blood sample for another reason. The blood will be used to look for genetic markers which may be associated with cleft palate, these tests are routinely performed as part of your infants care and you will be informed of the results.

In all other respects the treatment and follow-up care for babies with cleft palate will be the same for those taking part in the trial and those who are not. The records used to make the comparison are the standard follow-up records and checks that all babies with cleft palate should have, although the appointments with the speech therapist at age 1, 3, and 5 years may take 20-30 minutes longer. We would also like to take a photograph of your child and make an impression of his/her teeth when they have their 5 year follow up visit.

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5. What will I have to do if my child takes part?

We would like you to keep all the usual appointments made to see the cleft palate team.

6. What are the alternatives for diagnosis or treatment?

As mentioned above, there are several different timings in use, but no evidence that one is better than another.

7. Are there any possible disadvantages and risks or side-effects of taking part?

The timing and techniques in the trial are standard practice, with no known differences in risk to your child.

8. What are the possible benefits of taking part?

The results we obtain from our trial of the surgical timing are unlikely to provide any direct benefit for your baby. However we hope that these results will help our team and other teams make the best possible decisions in providing treatment for future babies. The results of the genetic tests may help to identify a specific cause for the cleft palate in your family and if so we will be able to provide you with further information and offer testing to members of your extended family.

9. What will happen if something goes wrong?

In the event that something does go wrong due to negligence then you may have grounds for legal action for compensation against <Centre Name> but you may have to pay your legal costs.

If you have a concern about any aspect of the trial you should ask to speak to a member of the cleft team who will do their best to answer your questions (contact number below).

The normal complaints mechanisms in place at <Centre Name> will still be available to you. Details can be obtained from the hospital.

10. What happens if I want to withdraw my child from the trial?

You may withdraw your child from the trial at any time if you wish. If you withdraw your child from the trial your child's ongoing and future care will not be affected by your decision.

11. Will my child taking part in the trial be kept confidential?

All information that is collected about you and your child during the course of the trial will be kept strictly confidential, and any information that leaves <centre name> will have your child's name and address removed so that your child cannot be recognised. However, we would like to ask your permission for a copy of the consent form, which will have your and your child's name on it, to be sent to the Data Coordinating Centre at the University of Liverpool.

All legal requirements applying to research of this kind will be strictly adhered to.

12. What will happen to the blood sample?

This sample will be analysed to see whether there is any genetic condition that may be associated with the cleft. If changes are identified on the blood tests the findings will be discussed with you and you will be offered the opportunity to discuss them with a paediatrician or clinical geneticist, should you wish. These blood tests are part of the routine care offered by <centre name>.

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The blood samples will not be stored as part of the trial and we will not use them for any other tests.

13. What will happen to the results of the trial?

When the last patients in the trial reach age 5, and their speech has been assessed, we will analyse the results of the trial. No matter what the conclusions are, we will present the findings at professional meetings and in the appropriate medical journals so that as many future patients as possible will benefit. Naturally, no individual children will be identified in such reports. If you would like a copy of the final trial report you can indicate so on the consent letter.

14. Who is organising and funding the research?

The trial has been planned by an international collaboration of cleft specialists. The Administrative Centre for the trial is the University of Manchester, UK, the Data Coordinating Centre for the trial is the University of Liverpool, UK. The Administrative Centre will be responsible for the storage of your child's maxillary/dental impressions. The Data Coordinating Centre will store the information recorded, for the trial, by your child's cleft palate team, this data together with the impressions stored at Manchester will have your child's name removed. The trial is being funded by the National Institute of Dental and Craniofacial Research in the USA.

15. Who has reviewed the trial?

All research is looked at by an independent group of people called a research ethics committee to protect you and your child's safety, rights, wellbeing, and dignity. This trial has been reviewed and given a favourable opinion by Yorkshire and the Humber – Leeds East Research Ethics Committee

Contact for further information

If you would like more information about the trial please contact:

<Site Coordinator Name>

<Site coordinator Contact Number>

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Participant Randomisation Number								

CONSENT FORM

Research Trial Entitled: **Timing Of Primary Surgery For Cleft Palate (TOPS)**

Centre Name: <Centre Name/s>

Name of Researchers: <Names of all researches in involved centres>

		Initial box
1.	I confirm that I have read and understand the information sheet (version number 3.0, dated, 01-May-2013) for the above trial. I have had the opportunity to consider the information and ask questions and have had these answered satisfactorily.	☐
2.	I understand that the participation of my child's is voluntary and that I and my child are free to withdraw at any time, without giving any reason, without our medical care or legal rights being affected.	☐
3.	I understand that relevant sections of my child's medical notes and data collected during the trial may be looked at by individuals from the research team, representatives of the sponsor, from regulatory authorities or from the organization delivering healthcare, where it is relevant to my child participating in this research. I give permission for these individuals to have access to my child's records.	☐
4.	I agree to copies of my consent form to be sent to the Data Coordinating Centre at the University of Liverpool	☐
5.	I agree to photographs of my child being taken for the purposes of the trial.	☐
6.	I agree to audio and video recordings of my child being made for the assessment of speech development.	☐
7.	I agree to my child having impressions of their mouth and teeth (maxillary arch/dental impressions) for the purposes of the trial.	☐
8.	I agree to relevant information from routine genetic tests to be used by the trial team.	☐
9.	I agree to a small blood sample being taken during surgery, or at another appropriate time, for genetic tests if they have not already been performed.	☐
10.	I agree to be contacted by the cleft palate team using the information provided for myself and other relevant contacts or to be contacted using my NHS or national identification number where appropriate.	☐
11	I agree to my child's GP or local physician being informed about his/her participation in the trial where appropriate.	☐
12.	I agree to take part in the above trial and I also agree for my child to take part in the above trial.	☐
13.	I agree/do not agree (delete as appropriate) to be contacted by other researchers to participate in other ethically approved studies in cleft and lip palate.	☐
14.	I would like/ would not like (delete as appropriate) a copy of the final report.	☐

_____	_____	
Name of Child	Child's Date of Birth (dd-mm-yyyy)	
_____	_____	_____
Name of Parent/Guardian	Signature of Parent/Guardian	Date (dd-mm-yyyy)
_____	_____	_____
Name of Researcher	Signature of Researcher	Date (dd-mm-yyyy)

When completed, 2 copies need to be made, 1 for the participant, 1 for the investigator site file and the original must be kept in the medical notes. A copy of the consent form only should be faxed to the Data Coordinating Centre on +44 (0) 151 282 4721

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Participant identifier Number								

Timing Of Primary Surgery For Cleft Palate (TOPS)- Pilot study to develop methods for speech and language assessment

INFORMATION FOR PARENTS

Research Study Entitled: **Timing Of Primary Surgery For Cleft Palate (TOPS)-Pilot study to develop methods for speech and language assessment**

This study will assess how speech assessments of infants with cleft palate are made, the outcomes of this study will then inform data collection in another project that is exploring the timing of primary surgery in children with cleft palate.

Recruiting Centre Name: <Centre Name>

Recruiting Centre ID number: <Centre ID>

Dear Parent,

We would like to invite your child to take part in a study that is being carried out to help us find out the best way to assess speech in children with cleft palate. Before you decide whether you would like your child to take part we would like to explain to you why the research is being done and what it would involve for you.

Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Talk to others about the study if you wish.

Take time to decide whether or not you wish to take part.

Thank you for reading this information sheet.

1. What is the purpose of this study?

There are a number of ways that a child's speech can be recorded and assessed. The purpose of this study is to develop the method used to record and assess speech in children with a cleft palate. This method will then be used in another project (the TOPS trial) which aims to find out the best age at which to repair a cleft palate in order to give the child the best possible speech.

2. Why has my child been invited to take part?

The TOPS speech therapist at <Centre Name> is inviting all infants and children, aged between 10 and 14 months, 34 and 46 months and 58 and 70 months, to take part in this pilot study. Your child does not need to have a cleft palate for to take part.

3. Does my child have to take part?

No, the research is voluntary. It is up to you to decide whether you take part. We will describe the study and go through this information sheet with you. You will also be given a copy of this information to take home. Should you decide that you would like your child to participate we will ask you to sign a consent form. You are free to withdraw your child from the study at any time, without giving a reason.

If you decide that you do not want your child to participate in this study the care they will receive will not be affected and will be the standard care provided at <Centre Name>.

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Participant identifier Number								

4. What will happen if I choose for my child to take part?

If your child is aged 14 months or younger

Your speech therapist will make an audio and video recording of a play situation between you and your child. The purpose of this recording is to analyse the babbling of your child as it is known to be of importance for the language development.

If your child is aged 34 months or older

At the visit the speech therapist will ask your child to say a number of words (between 30 and 36) that have been carefully selected to allow assessment of all aspects of your child's speech. The speech therapist will make an audio and video recording of your child saying these words, and also a recording from spontaneous speech during a play session.

If your child is aged 58 months or older, your child will be asked to repeat sentences and retell a story. We will also ask your child to speak into a special microphone connected to a computer. This will assess how much nasal interference there is with your child's speech. You will also be asked to complete a very short questionnaire about how understandable your child's speech is to different people.

5. What happens to the video recording?

The audio/video recording of your child will be used as part of the training of your speech therapist. It will also be used to develop a training package for all of the speech and language therapists involved in the TOPS trial.

We are doing this so that all of the speech therapists in the TOPS trial follow the same method. We would also like to ask your permission to use this recording to help train speech therapists involved in future studies.

6. What will I have to do if my child takes part?

We would like you to keep the appointment made to see your child's speech therapist, in some cases this will be a usual visit or you may be asked to come for an additional appointment.

Your visit will last around 40-60 minutes.

7. Are there any possible disadvantages and risks or side-effects of taking part?

The speech assessment made by the speech therapist is standard practice with no known risk to your child. The audio and video recording has no known risk to your child.

8. What are the possible benefits of taking part?

Taking part in this study is unlikely to provide any direct benefit to your child. However, your child's recording will help to train speech and language therapists taking part in the TOPS trial which aims to find out if the timing of surgery for cleft palate repair influences a child's speech. The methods we develop for assessing speech may also help improve how we do future research and how speech is assessed in clinical practice.

9. What will happen if something goes wrong?

In the event that something does go wrong due to negligence then you may have grounds for legal action for compensation against <Centre Name> but you may have to pay your legal costs.

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Participant identifier Number								

If you have a concern about any aspect of the pilot study you should ask to speak to a member of the cleft team who will do their best to answer your questions (contact number below).

The normal complaints mechanisms in place at <Centre Name> will still be available to you. Details can be obtained from the hospital.

10. What happens if I want to withdraw my child from the study?

You may withdraw your child from the study at any time if you wish. If you withdraw your child from the study your child's ongoing and future care will not be affected by your decision. If you choose to withdraw your child from the study you may also choose for audio/video recordings already made to be destroyed.

11. Will my child taking part in the study be kept confidential?

All information that is collected about you and your child during the course of the study will be kept strictly confidential, and any information that leaves <centre name> will have your child's name and address removed.

We would like to ask your permission to use the audio and video recording for the training of speech and language therapists involved in the TOPS trial and also in future studies about cleft palate. To do this, a copy will be sent to the Data Coordinating Centre in Liverpool who will store the audio and video recording securely and identified by a unique number only. We would also like to ask your permission for a copy of the consent form, which will have your and your child's name on it, to be sent to the Data Coordinating Centre at the University of Liverpool.

All legal requirements applying to research of this kind will be strictly adhered to.

12. What will happen to the results of the study?

The results of the sample speech recordings made in this study will be used to standardise the method of speech sample collection across the TOPS trial. The TOPS trial will assess the effects of the timing of primary surgery for cleft palate on speech development. If you would like a copy of the final TOPS trial report you can indicate so on the consent form.

13. Who is organising and funding the research?

This study and the TOPS trial have been planned by an international collaboration of cleft specialists. The Administrative Centre for the projects is the University of Manchester, UK, and the Data Coordinating Centre for the projects is the University of Liverpool, UK. The study is funded by the National Institute of Dental and Craniofacial Research in the USA.

14. Who has reviewed the study?

All research is looked at by an independent group of people called a research ethics committee to protect you and your child's safety, rights, wellbeing, and dignity. This study has been reviewed and given a favourable opinion by Yorkshire and the Humber – Leeds East Research Ethics Committee.

Contact for further information

If you would like more information about the study please contact:

<Site Coordinator Name>

<Site coordinator Contact Number>

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Participant Identifier									

Timing Of Primary Surgery For Cleft Palate (TOPS)-
Pilot study to develop methods for speech and language assessment

CONSENT FORM FOR PARENTS

Research Study Entitled: **Timing Of Primary Surgery For Cleft Palate (TOPS) Pilot study to develop methods for speech and language assessment.**

Centre Name: <Centre Name/s>

Name of Researchers: <Names of all researches in involved centres>

To be filled in by the parent/guardian
Once you have read and understood each statement **please tick (✓) and initial**

Agreement to take part in the study

		Tick box (✓)	Initial
1.	I confirm that I have read and understand the information sheet (version number 3.0, dated, 01-May-2013) for the above study. I have had the opportunity to consider the information and ask questions and have had these answered satisfactorily.	☐	
2.	I understand that the participation of my child is voluntary and that I and my child are free to withdraw at any time, without giving any reason, without our medical care or legal rights being affected.	☐	
3.	I understand that data collected during the study may be looked at by individuals from the research team for training purposes, representatives of the sponsor, from regulatory authorities or from the organization delivering healthcare, where it is relevant to my child participating in this research. I give permission for these individuals to have access to my child's records.	☐	
4.	I agree to copies of my consent form to be sent to the Data Coordinating Centre at the University of Liverpool	☐	
5.	I agree for the recording to be sent to the University of Liverpool	☐	
6.	I agree to audio and video recordings of my child being made and used to train speech and language therapists participating in the TOPS trial.	☐	
7.	I agree to audio and video recording of my child being made and used to train speech and language therapists taking part in other cleft palate research.	☐	
8.	I agree to take part in the above study and I also agree for my child to take part in the above study.	☐	
9.	I would like/ would not like (delete as appropriate) a copy of the final report for the TOPS trial.	☐	

_____ _____
Name of Child Child's date of birth (dd-mm-yy)

_____ _____ _____
Name of Parent/Guardian Parent signature Date signed (dd-mm-yyyy)

_____ _____ _____
Name of Researcher Signature of Researcher Date signed (dd-mm-yyyy)

When completed, 2 copies need to be made, 1 for the participant, 1 for the investigator site file and the original must be kept in the medical notes. A copy of the consent form only should be faxed to the Data Coordinating Centre on +44 (0) 151 282 4721

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Centre Name		Centre ID		TOPS additional information and consent form V1.0 30-March-2015

Important changes to the TOPS trial

Dear Parent,

The TOPS trial that you and your child are taking part in will assess the timing of primary surgery in children with cleft palate. We have made some changes since you agreed to be in the trial and would like to let you know about these and to check you are happy with them. There are two changes aimed at improving the data we collect about your child's speech:

1. We would like to send a questionnaire to other therapists outside of <centre name> who have provided speech therapy for your child. This questionnaire will ask how many and what type of speech therapy sessions your child has had.

2. When you attend for your child's age 5 speech follow up we will ask you to complete a short questionnaire about how well your child is understood by others. The questionnaire has 7 questions and takes about 5 minutes to complete.

These changes have been looked at and approved by an independent group of people called a research ethics committee (The Yorkshire and the Humber– Leeds East Research Ethics Committee).

Please tell us if you are happy with each of these changes, or not, by completing the section below and returning this form in the addressed envelope provided. We have included a copy of the information for you to keep.

If you would like more information about these changes before you make a decision please contact:

<Site Coordinator Name>, <Site coordinator Contact Number>

Please tick ✓ and initial in the spaces below		
	Tick (✓)	**Initials**
I agree to my local speech therapist being contacted about my child's speech therapy sessions.	Yes ☐ No ☐	
I am happy with the changes made to the 5 year follow up visit and understand I will be asked to complete a short, 5 minute, questionnaire when I attend.	Yes ☐ No ☐	

Your name			
Your signature		**Today's Date**	
Your child's name		**Your child's date of birth**	

To be completed by the research team

Randomisation Number								

Date sent/given to parent	d	d	m	m	y	y	Sent by (Signature)	
Date received at site	d	d	m	m	y	y	Received by (Signature)	

When complete, 2 copies need to be made, 1 for the participant, 1 for the investigator site file and the original must be kept in the medical notes. A copy of the consent form only should be faxed to the Data Coordinating Centre on +44 (0) 151 282 4721

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Supplementary Material No. 4: TOPS Trial Committees

1.1 Trial Management Group (TMG)

The Trial Management Group (TMG) comprises members of the Administrative and Data Coordinating Centres and representatives of the core speech group and National Institute of Dental and Craniofacial Research. The Trial Management Group is responsible for the day-to-day running and management of the trial. The Trial Management Group will meet monthly in the first instance and a minimum of four times a year, attendance at Trial Management Group meetings will be by teleconference. Other meetings will be held by teleconference call as needed. Telephone and email will be a primary means of daily communication between members of the Trial Management Group.

1.2 Trial Steering Committee (TSC)

The Trial Steering Committee will be composed of the trial investigators, members of the trial team at the Administrative and Data Coordinating Centres in addition to an independent chairperson and independent experts in the field of cleft palate surgery, speech therapy and biostatistics.

The role of the Trial Steering Committee is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the Trial Steering Committee. The Trial Steering Committee will meet at least annually by teleconference. Other meetings will be held by bimonthly teleconference call as needed. E-mail will be a primary means of communication between members of the Trial Steering Committee. The Trial Steering Committee may also make recommendations to the Funder who may withdraw funding of the study.

1.3 Data and Safety Monitoring Board (DSMB)

The composition of the Data and Safety Monitoring Board will be decided by the National Institute of Health / National Institute of Dental and Craniofacial Research (NIH/NIDCR) and the initial committee meeting will be convened prior to the trial commencing.

The Data and Safety Monitoring Board is an independent (should not be involved with the trial in any other way or have some competing interest that could impact on the trial) multidisciplinary group consisting of at least one statistician and at least one clinician that,

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collectively, have experience in the management of children with cleft palate and in the conduct of randomised controlled trials.

The Data and Safety Monitoring Board will be responsible for reviewing and assessing recruitment, interim monitoring of safety, trial conduct and external data.

The full terms of reference and roles of the Data and Safety Monitoring Board are detailed in the Data and Safety Monitoring Board Charter and a copy of the open minutes from each DSMB meeting will be provided to the Program Official at National Institute of Dental and Craniofacial Research.

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Supplementary Material No. 5:

Ethics Approval and Summary of substantial protocol amendments

Research Ethics Committees Approval

In the UK, the TOPS Protocol version 1.1 and accompanying consent forms and their amendments have been approved by the Multicentre Research Ethics Committee in the UK (Yorkshire and the Humber – Leeds East) on 008 January 2010.

In Brazil, approvals were gained from the Ethics in Research on Human Beings Commission (Comitê de Ética em Pesquisa em Seres Humanos) of the Hospital for Rehabilitation of Craniofacial Anomalies (Hospital de Reabilitação de Anomalias Craniofaciais Universidade da São Paulo, HRAC-USP), and from the National Ethics in Research Commission (Comissão Nacional de Ética em Pesquisa, CONEP from the Conselho Nacional de Saúde).

In Denmark, approvals were received from the Institutional Review Board for the Central Denmark Region (De Videnskabsetiske Komiteer For Region Midtjylland).

In Sweden, the ethics committee approving the TOPS Protocol was the Regional Ethical Review Board in Stockholm (Regionala Etikprövningsnämnden i Stockholm)

In Norway, the regional committee for medical and health care research ethics in South-east Norway (Regional komité for medisinsk forskningsetikk sør-øst Norge, REK sør-øst B) gave ethical approval for the TOPS project. Table 1 summarises the international approval for the TOPS protocol and subsequent amendments.

Table 1: International approval of the TOPS protocol and subsequent amendments by the national and local Research Ethics Committees

Protocol		**Approval Dates**				
Version No	**Version Date**	**UK**	**Sweden**	**Denmark**	**Norway**	**Brazil**
1.1	02/11/2009	08/01/2010				
2	10/03/2010	26/05/2010				
2.1	06/09/2010	28/09/2010	18/11/2010	04/07/2011	20/09/2011	11/03/2011, 27/04/2011, 10/05/2011 *
3	01/05/2013	27/06/2013	11/02/2014	09/05/2014	18/12/2013	26/08/2014
4	26/08/2015	01/10/2015	22/12/2015	09/11/2016	12/08/2016	06/11/2016
5	22/08/2018	16/11/2018	03/01/2019	21/03/2019	TBC	30/04/2019

* Local REC approval followed by the national REC approval in Brazil

TBC: to be confirmed

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TOPS Protocol Version 2.0 (10 Mar 2010)

There were major amendments from version 1.0 to version 2.0, as summarised below.

The secondary outcomes of the trial have been amended to include growth at age 12 months, which will be assessed by heel to crown length, nude weight and occipitofrontal circumference.

In addition, total speech and language intervention together with total speech therapy will be assessed at age 3 and age 5 years.

The wording of the postoperative complications outcome has been amended to "Postoperative/long term complications: infection, wound dehiscence and fistula".

The TOPS protocol has been amended to include a pilot speech study, which will allow the training of speech therapists, involved in the TOPS trial, in the collection of a speech sample. The amendment requests that sample speech recordings are made in children with a cleft palate. Between 1 and 5 recordings will be made for each of the three age groups: 10-12 months, 34-38 months, 58-62 months. The number of recordings made will depend upon the experience of the speech therapists. A set of additional parent information sheets and consent forms have been included for parents and children who would like to participate in this pilot study.

TOPS Protocol Version 3.0 (01 May 2013)

There were major amendments to V3.0. Key changes are summarised below:

The timing of adverse event reporting was clarified so that adverse events taking place in the 30 day post-operative period only were reported. Unanticipated problems will continue to be reported throughout the full trial duration.

Changes were made into the audiology assessments. After discussion with the OM8-30 questionnaire, developer concerns were raised about the version control and validation of the questionnaire. The OM8-30 questionnaire for the assessment for glue ear will no longer be used.

The inclusion/exclusion criteria was amended. Participants may now be included in the trial if they have Van Der Woude syndrome, as this syndrome is not considered to have an impact on development or speech and language. The exclusion criteria now states:

Infants with syndromic cleft palate (except Van der Woude syndrome, which can be included if hearing is not affected) or severe developmental delay.

Initially it was planned for teams to make follow up phone calls with participants at age 2 and 4 years. However, patients are regularly seen in clinic and so this was no longer considered necessary.

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To help reduce the burden to sites data entry will now be completed centrally at the Data Coordinating Centre and this has been clarified in the protocol.

Other changes included amendments to the parent information sheets and consent forms (PISC) format to help ensure that the correct version (pilot study or main trial) was used. The PISC was also amended to reflect the changes to assessments and follow up telephone calls and to include an optional item for parents to consent to be contacted by other researchers regarding related research.

TOPS Protocol Version 4.0 (26 Aug 2015) The key changes introduced with major amendments from V3.0 to V4.0 were a very short questionnaire for the participants' parents (ICS (Intelligibility in context scale) questionnaire) and a new supplementary Parent Information and Consent form to arrange for consent to collect information using the ICS questionnaire. Furthermore, changes were made to the Pilot Parent Information and Consent form and there were also modifications to the secondary outcome measures. Finally, changes were made to the section of the protocol covering indemnity. Please see a brief summary of the changes listed below:

1. Intelligibility in context scale (ICS) questionnaire added to the speech assessments at 5 years
2. New supplementary Parent Information and Consent form, asking for consent to collect data using ICS and from local speech therapists
3. Pilot Parent Information and Consent form was amended, it now also covers collection of data using ICS and nasometer at 5 years, and includes an additional consent clause #5, stating that recordings will be sent to the Data Coordinating Centre in Liverpool.
4. Changes to secondary outcomes summarised:
    i. Change of secondary outcome "Velopharyngeal composite score summary at age 3 years and 5 years", to "Velopharyngeal composite score summary at 5 years", as VPC-sum at 3 years is no longer possible (because this measure was recently found not to be reliable with 3year olds).
    ii. Addition of detail to definition of secondary outcome measures No. 38: the details added now show the components of the outcome measures; The provision of detail made it necessary to split the outcome measure "Articulation" into two outcome measures: "Articulation at age 3 years" and "Articulation at age 5 years", as these are assessed in different ways; Also, the outcome measure "Audiological assessment (audiometry and tympanometry)" has now been split into "Hearing level" and "Middle ear function". While this addition of detail results in an increase of the number of secondary outcome measures listed, the actual outcome measures No. 3-8 have not changed since the last version of the protocol;
    iii. Removal of the two secondary outcome measures "Total speech and language therapist intervention at age 3 and age 5 years" and "Total speech therapy sessions at age 3 and age 5 years" as these are recorded as background data, and do no longer constitute secondary outcome measures.

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5. Section 14, Indemnity (page 77 in protocol): Section had initially described University of Manchester as a "cosponsor for international sites" – this has been corrected and clarified in detail: the University of Manchester is the sole Sponsor for the TOPS trial. For sites in the United Kingdom, the University of Manchester as Sponsor will provide Indemnity for the trial protocol. For all other trial sites, the University of Manchester will ensure that appropriate indemnity is in place at the trial site via the contractual agreements in place. The roles and responsibilities of the Administrative Centre, Data Coordinating Centre and the trial sites involved in the TOPS trial will be defined in a Division of Responsibilities document, which will form part of any signed contractual agreements.

TOPS Protocol Version 5.0 (22 August 2018)

The key change in this substantial amendment was introduction of additional outcome measures to enable the trial team to make the best use of the existing data collected. The amendment included the addition of nasalance score to the TOPS Statistical Analysis Plan, as an exploratory analysis but not as a standalone outcome. This is to compare consistency between Speech and Language Therapist's assessment of hypernasality and nasalance score. The additional outcome measures added to the protocol version 5.0 are summarised below along with the rational for the changes:

1. VPC-rate was added because it is important to assess velopharyngeal function not only on single words but also on spontaneous speech at age 5, the most common communication condition; this is the same outcome measure as for the 3 year follow up assessment.

2. Velopharyngeal insufficiency symptoms from single words will support the overall assessment of velopharyngeal function assessed from spontaneous speech at age 3.

3. Assessment of oral consonant errors contributes to a better understanding of the speech errors made by children with Cleft Palate; this is the same outcome measure as for the 5 year assessment. This change will make it possible to follow the prevalence longitudinally.

The above changes to the outcome measures will not affect site activity nor require any additional data to be collected from patients or affect their safety.

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Timing Of Primary Surgery for cleft palate (TOPS): Protocol for a randomised trial of palate surgery at 6 months versus 12 months of age

Reporting checklist for protocol of a clinical trial

▪

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	12
Protocol version	#3	Date and version identifier	1 & Supplementary files
Funding	#4	Sources and types of financial, material, and other support	1 and 13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12-13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they	13 and Supplementary material No 4

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		will have ultimate authority over any of these activities	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11 and Supplementary material No 4
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1 and 2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	1 and 2
Objectives	#7	Specific objectives or hypotheses	2
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5

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Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	4, 7 and 8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5-7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9 & Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	3&10

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Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4-5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA/ speech assessments are carried out under blinded conditions
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10

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Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10 and Text box 1
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11 and 12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11 and 12
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12 and Supplementary material No 1
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12 and Supplementary Material No 1

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Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8, 12 and Supplementary Material No 1
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11 and Supplementary Material No 4
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1, 1 and Supplementary Material No 5
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	Supplementary Material No 5
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4 and supplementary Materials No 1, 2 and 3
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Supplementary Materials 2 and 3
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12 &Supplementary Materials No 1 and 2
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12-13

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Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Materials No 1, 2 and 3
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	4, 10 and Supplementary materials No 1

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