TOPS
Timing **O**f **P**rimary **S**urgery for Cleft Palate.

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This protocol has been authorised by:

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Name	**(Lead Investigator Data Coordinating Centre)**	**Signature**	**Date**
Name	**(Lead Statistician)**	**Signature**	**Date**
Name	**(Sponsor)**	**Signature**	**Date**

General Information

This document describes the Timing of Primary Surgery for Cleft Palate (TOPS) trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, and centres entering patients for the first time will be provided with the most up to date version. In the event of uncertainty of the protocol version in use centres are advised to contact the Data Coordinating Centre (DCC) [Liverpool Clinical Trials Centre(LCTC), University of Liverpool] to confirm they have the most up to date version.

Statement of Compliance

This trial will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975, 2000), Venice (1983), Hong Kong (1989), South Africa (1996) amendments and will be conducted in compliance with the protocol, DCC Standard Operating Procedures, Good Clinical Practice outlined in the EU Directive 2005/28/EC and with the requirements of the Office of Human Research Protections" (OHRP) Common Rule, 45 CFR 46.

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Glossary

AC	Administrative Centre
AE	Adverse Event
CI	Chief Investigator
CF	Consent Form
CGH	Comparative Genomic Hybridization
CFR	US Code of Federal Regulations
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DCC	Data Co-ordinating Centre
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
GCP	Good Clinical Practice
ISRCTN	International Standard Randomised Controlled Trial Number
ICS	Intelligibility in Context Scale questionnaire for parents
IEC	Independent Ethical Committee
LREC	Local Research Ethics Committee
MCRN	Medicines for Children Research Network
MLPA	Multiplex Ligation-Dependent Probe Amplification
MREC	Main Research Ethics Committee
NIH	National Institutes of Health
NIDCR	National Institute of Dental and Craniofacial Research
NRES	National Research Ethics Service
OCP	Occipitofrontal Circumference
OHRP	Office of Human Research Protections, United States
PI	Principal Investigator
PISC	Patient Information Sheet and Consent Form
PM	Project Manager
RCT	Randomised Controlled Trial
R&D	Research & Development
SAE	Serious Adverse Event
SC	Site Coordinator
SOP	Standard Operating Procedure
TC	Trial Coordinator
TMF	Trial Master File
TMG	Trial Management Group
TOPS	Timing of Primary Surgery for Cleft Palate
TSC	Trial Steering Committee
UCLP	Unilateral Cleft Lip And Palate
UCP	Unilateral Cleft Palate
UPR	Unanticipated Problem Involving Risks to Human Subjects

1 PROTOCOL SUMMARY

Title: Timing of Primary Surgery for Cleft Palate (TOPS)
A randomised trial of palate surgery at age 6 months versus age 12 months.

Population: 648 infants with a diagnosis of cleft palate who are considered medically fit for operation at 6 months, corrected for gestational age, will be included in the trial. Infants will be excluded if there is cleft lip, an associated syndrome or developmental delay, congenital sensorineural hearing loss or middle ear abnormalities, variation in anatomical presentation which would exclude the Sommerlad technique, submucous cleft palate or where neither parent is a native language speaker.

Number of Sites: Research sites in the UK, Scandinavia and Brazil listed in the Declaration of Trial Centres (supplementary trial-specific document #1).

Trial Duration: 5 year follow-up per participant.

Description of Intervention Infants with a diagnosis of cleft palate will be randomised to receive primary surgery for cleft palate using the Sommerlad technique at either age 6 months or age 12 months (corrected for gestational age).

Objectives:

The main research objective is to determine whether surgery for cleft palate, using the Sommerlad technique, at age 6 months, when compared to the surgery using the Sommerlad technique at age 12 months, improves velopharyngeal function at age 5 years.

The primary endpoint for the TOPS trial is insufficient velopharyngeal function at 5 years of age.

Secondary research objectives are to determine whether surgery for cleft palate, using the Sommerlad technique, at age 6 months, when compared to surgery at age 12 months using the Sommerlad technique, improves any of the following outcome measures;

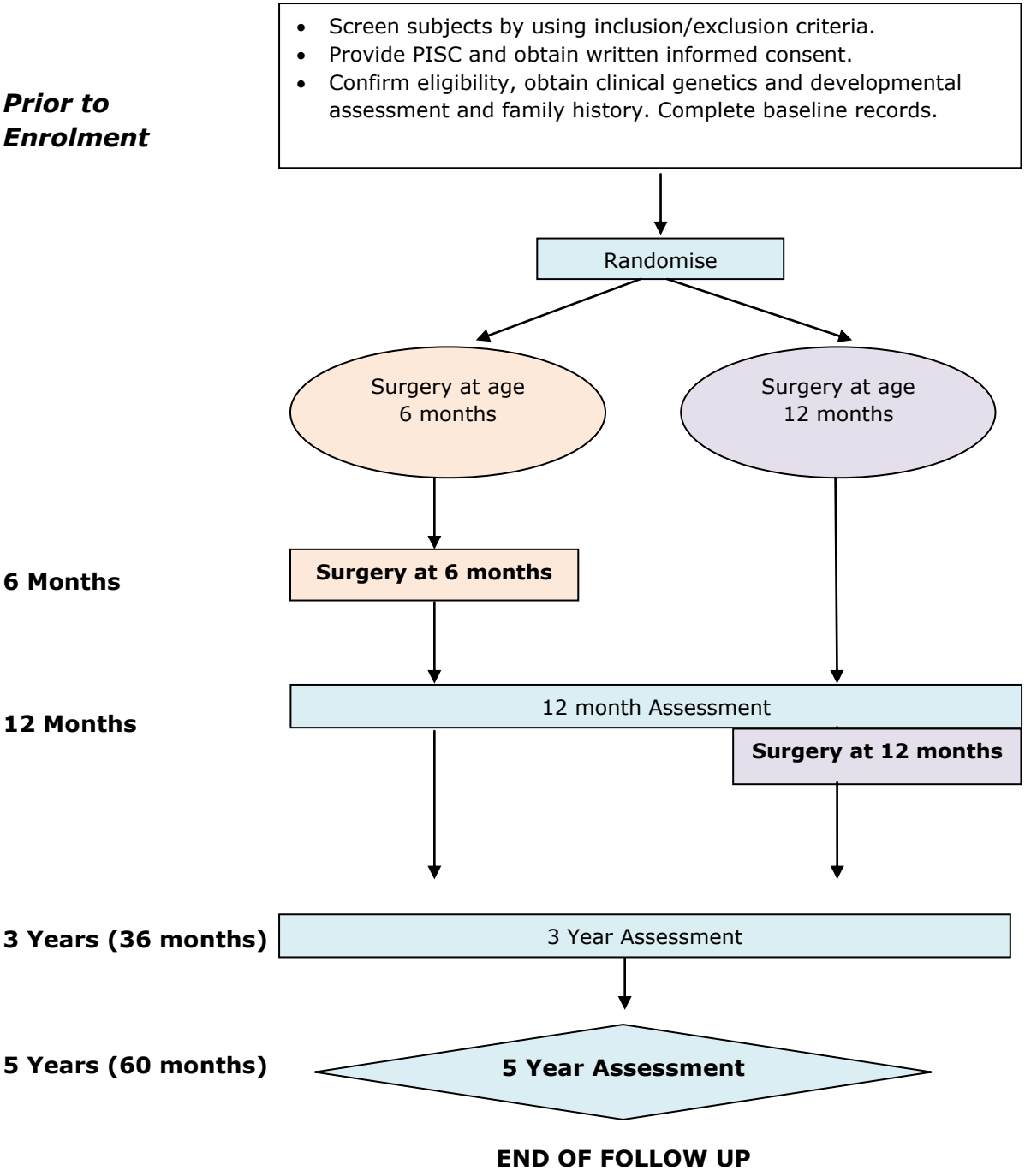
1. Velopharyngeal function at age 5 years:
    a. Velopharyngeal composite score summary (VPC sum)
    b. Insufficient velopharyngeal function (VPC rate)
2. Velopharyngeal function at age 3 years:
    a. Insufficient velopharyngeal function (VPC rate)
    b. Velopharyngeal insufficiency symptoms
3. Canonical 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 [55])
    b. Maxillary arch constriction score (using modified Huddart/Bodenham scoring system [56])
10. Growth at 12 months:
    a. Nude weight
    b. Crown to heel length
    c. Occipitofrontal circumference

Protocol Summary - continued

Schematic of Trial Design:



2 BACKGROUND INFORMATION

2.1 Introduction

2.1.1 The evidence base in cleft care

Clefts of the lip and/or palate, occurring with an incidence of about 1 per 600 births, are among the commonest birth anomalies. A drawing of unilateral cleft lip and palate (UCLP) is shown in Figure 1. The anatomical location of the defect creates problems in feeding, speech, hearing, dental development and facial growth. Furthermore, the associated communication disability and the distorted facial appearance represent serious barriers to social integration. The success of primary surgery in the early months of life is crucial in determining outcome for the above functions, and the subsequent cost of secondary surgery and remedial care. Previous research indicates that unsuccessful primary surgery may lead to a tenfold increase in unfavourable sequelae [1].

This trial focuses on isolated clefts of the palate which occurs with a prevalence from 1.35 to 25.31 per 10,000, depending on geographic location (WHO, 2003). A drawing of isolated cleft palate (CP) is shown in Figure 2. This is a relatively heterogeneous group of conditions varying in size and shape, and in the level of association with other anomalies[2-7].

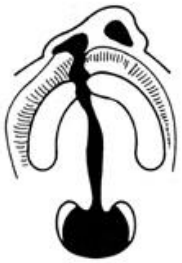


Figure 1. Unilateral cleft lip and palate (UCLP).



Figure 2. Isolated cleft palate (CP).

2.1.2 Prevailing beliefs and uncertainties in the timing of palate surgery

Timing of palatal surgery in patients with cleft palate has been a controversial issue since the 1930s, reflecting in part, inadequacies in trial design with numerous confounding factors, and a lack of objective and standardised speech data in earlier reports.[8]

Over the years, the age of palatal surgery has tended to reduce, related perhaps to improved pediatric postoperative care. One stage palatal repair around the age of 12 months or earlier has been common practice at many cleft units in Europe and the USA for some time. Protagonists of early closure of the palatal cleft also argue that since speech is a learned behavior, the sooner an intact anatomy is created, the better.[9]

However, it is unclear just how early palatal surgery should be performed. In a randomised trial of primary surgery in unilateral cleft lip and palate, in 76 infants, at USP-HRAC (described in more detail below) comparison of complete palatal surgery at 9-12 months or at 15-18 months revealed no significant difference in velopharyngeal function.[10]

On the other hand, differences were observed in one small randomised controlled trial undertaken in Mexico, where patients with unilateral cleft lip and palate were operated on either at 6 months or at age 12 months.[11] The trial groups consisted of 41 participants operated on at 12 months and 35 participants operated on at 6 months. Though there was no statistically significant difference in velopharyngeal function, phonological development was described as significantly better in patients operated at six months of age than in patients with palatal closure at 12 months of age. Further, none of the patients operated at six months of age developed compensatory articulation. However, these results were reported on the basis of direct listening in the absence of speech recording. Thus inter- and intra-rater reliability could not be determined. Also one investigation of infants with isolated clefts of the soft palate who underwent repair at 6 months found that their velopharyngeal function and articulation at age 5 were comparable to non-cleft controls.[12]

In studies of non-cleft children it has been established that there is a link between the phonetic repertoire of babbling and the basic sound system of a child's language, whatever that language might be.[13,14] It has been shown that this relationship is also evident in the cleft population and, therefore, that the early speech patterns of children with cleft palate are related to their babbling patterns.[15,16, 53, 54]

Thus an association between the characteristics of babbling and early word acquisition has been observed in normally developing non-cleft children.[17] Stoel-

Gammon (2002)[18] and, Vihman and Greenlee (1987)[19] found that a diverse consonant production in canonical syllables was related to early acquisition of 10 meaningful words, and phonological ease at 3 years of age.

Recently the acquisition of canonical babbling has also been studied in children with clefts that involve the palate. Chapman et al. (2001)[20] found that only 57% (n=30) of American children with an unoperated cleft palate had reached the canonical babbling stage by age 9 months, and this was significantly fewer than for a non-cleft group of children where 93% (n=15) had acquired canonical babbling. In contrast, Willadsen and Albrechtsen (2006)[21] reported that 92% (n=38) of Danish children with unilateral cleft lip and palate with soft palate repair at around 4 months of age (the hard palate cleft still unrepaired) had reached the canonical babbling stage at 11 months. This corresponded well with their non-cleft control group where 94% (n=36) had reached canonical babbling at 11 months leading Willadsen and Albrechtsen to suggest that the performance of the cleft group may be attributable to their early soft palate repair. O'Gara and Logemann, (1988)[22] noted that earlier palatoplasty may facilitate normal speech sound acquisition and may have facilitated the higher frequency of occurrence of high intraoral pressure consonant constrictions**.**

Despite the possible gains from early soft palate repair noted by Willadsen and Albrechtsen (2006)[21], two stage palate closure with delay in hard palate closure may have some drawbacks in addition to a second visit to the operating theatre.

Several investigations have found a lower frequency of oral stops in pre-speech vocalisations of children with early soft palate closure (around 4-6 months) than in non-cleft controls.[21, 23, 24] However, the same finding has been consistently reported for children with unrepaired clefts – even though the magnitude of oral stop productions seem to be higher in children with early soft palate closure. The drawback of delaying closure of the hard palate may become evident after 12 months of age when the child begins to develop his/her phonological system. By age 3 years children with delayed hard palate closure have a higher frequency of retracted/backed articulation than children who had the entire palate closed around 12 months of age. However, children with delayed hard palate closure do seem to develop fewer compensatory articulations than children receiving one-stage palatal closure around 12 months of age.[23,25] Surgical technique for soft palate closure appears to be an important issue with disparity between reported results. For example, some studies have reported an extremely high frequency of compensatory articulations in children having followed a delayed hard palate closure paradigm.[26, 27, 28]

The rationale for delaying hard palate surgery arose from the belief that postponing the trauma of hard palate repair would reduce maxillary growth disturbance. However, some data suggests that facial skeletal growth in individuals with isolated

cleft palate is not substantially affected by different surgical protocols, though maxillary arch form, especially transversely, may be affected. [29-32]

Peterson-Falzone's comprehensive literature review (2006)[8] notes that the increased knowledge gained in the 1980's and 1990's regarding the effects of early structural constraints on pre-speech vocalisations and on later speech development in children with clefts could constitute a "very good reason" to perform palatal closure early, e.g., before the child reaches the milestone of producing his first meaningful words. In her 2013 update, Peterson-Falzone argues that the question regarding optimal age for palatoplasty to facilitate normal speech development is still relevant, and concludes "there is no question that normal speech depends upon velopharyngeal closure being provided when it is needed" (p 799), that is, as or before a child's pre-speech develops.[33]

Kemp-Fincham et al. (1990)[34], reviewing the literature on the development of speech motor control and phonetic development in infants, concluded that there is a particularly sensitive period or state of readiness between the ages of 4 and 6 months. While these authors identified some disadvantages for early repair, such as surgical disruption to a baby's maturation processes, on balance they argued that surgical palatal closure before or during this time frame may be important "if we are to avoid the development of the maladaptive compensatory articulations that are so devastating to a child's early communication attempts." (Table 1).

Table 1. Relationship between phonetic, anatomic-physiologic, and motor development in the first year of life (Kemp-Fincham et al., 1990)[34]

Age (months)	Phonologic Development	Anatomic-Physiologic Development	Motor Development
0-2	Quasi-resonant nuclei, vegetative sounds, glottal attack	Engaged larynx and nasopharynx. Tongue fills the oral cavity, moving along the anterior-posterior plane	Primitive reflexes
2-4	Quasi-resonant nuclei, velar and uvular or pharyngeal constrictions; cooing, gooing, and laughter	Change in oral cavity shape. Increased mobility of the tongue, but tongue is still restricted by larynx-nasopharynx engagement	Increased head control. Sits supported. Onset of rhythmic stereotypes using legs, torso, and arms.
4-6 "expansion phase"	Fully resonant nuclei. Yelling, growling, squealing, prolonged vocalizations, raspberries, trills, repetition of vowels, marginal babbling, whispering, shouting	Onset of disengagement of the larynx and nasopharynx. Better coordination of the respiratory system and the larynx	Sits without support. Onset of rocking on hands and knees
6-9	Reduplicated or canonical babbling. Cyclicity or rhythmicity of repeated utterances		Crawls, pulls him/herself to standing position. Peak in rhythmic movements of limbs and torso
9-12	Variegated babbling, first words		Decline in rhythmic movements. Walks without support

There has also been speculation on the possible influence of early palate repair on hearing. The prevalence of otitis media with effusion (OME) has been reported to approach 100 percent in the population of children with unrepaired palatal clefts, attributed to impaired Eustachian tube function.[35,36] A moderately fluctuating conductive hearing loss is a complication of OME and has a potential adverse effect on the child's educational, linguistic, and psychosocial development. [33]

In an NIDR funded trial, Doyle et al. (1986)[38] assessed Eustachian tube function before and after palate repair in a group of 24 children. They found improved passive functioning of the Eustachian tube following surgery, attributable to repositioning of the levator palati muscle. The trend towards earlier palate repair has increased interest in its potentially positive effect on Eustachian tube function, but this has yet to be investigated.[39]

On the basis of the above, we believe that there is a good case for testing the influence of one stage palatal closure at age 6 months rather than 12 months, especially with regard to speech development, but also in respect of auditory health and the development of the maxillary arch.

2.2 Rationale

To develop the rationale for the trial, two focus groups were convened by the TOPS research team: a speech focus group and a surgical focus group. Both groups included clinicians (surgeons and speech therapists) and researchers who had participated in the Scandcleft trials. Discussions were concluded at a two day meeting where the timing and type of surgery were considered together with the outcome measures.

The speech focus group reached a view that the most important question concerning surgery for isolated cleft palate was whether single stage repair around 6 months would secure better speech outcomes. Although there has been little in the way of reliable comparative studies, the speech group concluded that the studies of early acquisition of speech in non-cleft children and in children with cleft palate pointed to the desirability of normalising the palato-pharyngeal anatomy as or before pre-speech develops.

The surgical focus group debated the practicality and safety of bringing forward the timing of surgery from the more traditional age of 12 months or later. It was acknowledged that the tradition of later repair had arisen from earlier concepts postulating that at 12 months, palate repair might be easier and safer since the infant is bigger, some spontaneous reduction in cleft size may have occurred, and postoperative airway management for a more mature infant would be more straightforward. On the other hand, many surgeons (including several among the applicants – see Table 2 below and those involved in the surgical focus group)

already worked in teams who had been persuaded, by the possibility of better speech outcomes, to close the palate at 6 months. In addition none of the teams who performed palate repair at 6 months had observed a higher frequency of difficulties in the post operative period. Furthermore in the Scandcleft trials of primary surgery for unilateral cleft lip and palate, the participating surgeons had experienced early palatal surgery as half of the infants had soft palate (though not hard palate) repair at 3-4 months. There was, in conclusion, equipoise throughout the participating teams for randomisation to surgery at 6 months or at 12 months.

Table 2. Timing of primary surgery for cleft palate at the time of grant application (2007)

COUNTRY/CENTRE	TIMING OF PRIMARY SURGERY (months)
Brazil	
Bauru	12-18m
Denmark	14m
Finland	
Helsinki	9m
Norway	
Bergen	12m
Oslo	12m
Sweden	
Göteborg	6m
Linköping	12m
Malmö	12m
Stockholm	12m
Umeå	6m
Uppsala	6m
UK	
Northern Ireland	6m
North-East England	6m
North-West England	9-10m
Midlands	6-7m
South-West England	6-9m

Focusing the investigation on surgical timing was also seen as especially valuable, since any recommendations for, a change in timing would require only a revision of service organisation, rather than the acquisition of new technical skills. Recommendations on timing would also have a reasonable prospect of successful transfer to other orofacial clefts where the palate is involved.

It was agreed that, as in the Scandcleft Trials, the age for operation would be adjusted for gestational age, thus taking account of prematurity.

2.2.1 Selection of a single surgical method to use throughout the trial

To simplify trial design only one surgical technique will be used by all surgeons, at all centres, for all types of palatal clefts. Following discussion, adoption of the Sommerlad technique was unanimously agreed as the method of choice, principally because the majority of participating surgeons are already familiar with it. Closure of the nasal layer and palatal mucosa are performed with long established procedures, the distinctive feature being the extent of muscle dissection from the nasal mucosa, palatal mucosa, and posterior edge of hard palate. Mr Sommerlad will act as lead surgeon for surgical calibration.

3 OBJECTIVES

The aim of this research is to determine whether, in infants with cleft palate, it is better to perform primary surgery at age 6 or 12 months (corrected for gestational age).

Thus, this research will investigate the effect of the timing of surgery by assessing and comparing speech outcomes, including velopharyngeal function, canonical babbling, articulation, dentofacial development and peri-operative complications, in infants over a 5 year follow up period.

3.1 Potential Risks and Benefits

3.1.1 Potential risks

There is no evidence to suggest any additional risk or side effects to participants other than those associated with routine cleft palate surgery. Risk associated with routine surgery may include complications relating to:

a. Anaesthetic
b. Airway
c. Bleeding
d. Wound dehiscence
e. Infection

DNA sampling is routinely carried out in patients suspected of having a syndrome as part of the patients care and poses no physical risk to the participant.

3.1.2 Known potential benefits

Participation in the TOPS trial is unlikely to provide any direct benefit to the participant as there is currently no evidence to suggest that one timing of surgery is better than another in its effects on speech development. The results of the genetic tests may help to identify a specific cause for the cleft palate and if so further information and counselling, if desired, will be provided to families together with the offer of testing to members of the extended family.

4 SELECTION OF CENTRES/CLINICIANS

4.1 Centre/Clinician Inclusion Criteria

This trial will be carried out by cleft palate teams based in centres across the UK, Scandinavia and Brazil (Declaration of Centres, Trial Supplementary Document #1). Criteria for selection are based on a high volume of patients and/or the ability to enrol patients into a clinical trial as demonstrated by past experience. The cleft team at each centre will usually comprise: Cleft surgeon(s), nursing staff, cleft speech and language therapist(s), clinical geneticist/paediatrician, audiologist(s), orthodontists, social worker. Collaboration and recruitment is already agreed with the trial teams listed in the Declaration of Centres, Trial Supplementary Document #1.

The TOPS Trial Coordinator at the Data Coordinating Centre will send out a Site Specific Information (SSI) pack to each participating site (translated as appropriate; translation processes are described in supplementary trial-specific document #12) which will contain all of the information required to obtain ethical approval (and any other local approvals required for the conduct of clinical research).

Before any site can begin recruitment the green light process of the Data Coordinating Centre (DCC) will be fulfilled. A Principal Investigator, currently acting as healthcare professional at each centre will be identified together with other relevant personnel. The Principal Investigator will ensure that the following documents are received by the TOPS Data Coordinating Centre Trial Coordinator (see contact details at front of protocol):

Documents required for green light process (to be received prior to recruitment):

a. Positive ethics approval as outlined by country specific requirements;
b. Any other country specific approvals;
c. A completed 'Signature and Delegation Log';
d. Evidence of completion of Good Clinical Practice (GCP) training for all personnel listed on the signature and delegation log;
e. A Curriculum Vitae for all trial personnel listed on the signature and delegation log;
f. A signed Trial Agreement (Principal Investigator and Sponsor signature);
g. Evidence of surgical calibration as detailed on the surgical calibration log;
h. Completed contacts list of all site personnel working on the TOPS Trial;
i. Evidence of clinical genetics assessment calibration for appropriate trial personnel;
j. Evidence of a scheduled speech calibration for speech and language therapists to take place in good time prior to the 12 month visit.

The TOPS Data Coordinating Centre Trial Coordinator will ensure that the trial site receives:

a. A site visit where training on trial-specific procedures (excluding surgery) will be provided;
b. A trial pack containing all documents required to recruit a patient to the TOPS trial and to follow up that patient.

The TOPS Administrative Centre Project Manager will ensure that surgical calibration is arranged for all trial centres.

Upon fulfilling the green light process the centre will be activated by a confirmation letter sent to the Principal Investigator/Site Coordinator detailing that the centre is now ready to recruit patients into the trial. This letter should be filed in each centre's Investigator Site File.

To facilitate the day to day running of the trial, a Site Coordinator will be identified within each research team whose role will be to co-ordinate data collection.

4.1.1 Surgical calibration

Prior to starting the trial, a formal process of surgical standardisation will take place for all surgeons completing surgery as listed on the delegation log. The designated surgeon, Mr Sommerlad will act as lead surgeon for surgical calibration and will provide instruction via written text, video demonstrations and illustrated seminar and discussion sessions. This instruction will also include a calibration session in the operating room. Before commencing the trial surgeons will complete the TOPS Surgical Calibration Training Log; this log will be signed by Mr Sommerlad to confirm that the listed individuals have attended the calibration session.

4.1.2 Calibration for speech and genetic assessments

Calibration sessions will be held for designated speech and language therapists and clinical geneticists. Calibration sessions for clinical geneticists will take place prior to centre opening. Calibration sessions for speech language therapists will be scheduled prior to site initiation and will be completed in good time prior to the 12 month assessment of the first patient recruited to the trial on a whole trial and not centre basis; likewise for age 3 and age 5 assessments. All trial team members involved in speech or genetic assessments will be detailed on the delegation log and will be asked to complete the TOPS clinical genetics or speech and language therapist Calibration Training Log as appropriate.

4.1.2.1 Speech and Language Therapist Calibration Recordings

To enable the calibration of the speech and language therapists working on the TOPS trial it is necessary for a series of audio/video recordings of infants ideally with a cleft palate (not essential), to be completed prior to completing the audio and video recordings for trial participants.

A series of calibration recordings will be made by each speech and language therapist which reflect the timings of the TOPS follow up visits. Each speech and language therapist will make a minimum of 1 recording and a maximum of 5 recordings for each age group, depending on their experience to ensure that they are familiar with the prescribed standardised approach and that recordings are suitable (in quality and content) for analysis (section 9.1.4).

The age groups for which practice recordings will be made are:

- Infants aged 10-14 months
- Infants aged 34-46 months
- Infants aged 58-70 months

Consent for participation in pilot speech recordings

Before recordings are made the site coordinator or speech and language therapist will introduce the purpose of the recording to the infant's parent/legal guardian who will then be given ample time to read and understand the participant information sheet and consent form (PISC), for the pilot study, and to ask questions.

The parent/guardian(s) will be told that they are not obligated to participate, that there will be no penalty for declining to participate, and that treatment will not be compromised if patients do not participate or cease participation at any time.

If the parent/guardian would like their child to participate, consent will be sought for the audio/video recording to be made and for this to be used in the training/calibration of the TOPS speech and language therapists.

The consent forms should be signed by the parents/guardians and by the researcher taking consent.

In Sweden only the dates of consent signatures between parents and re-searchers may be different, due to the practicalities associated with patients being spread across a large geographical region. However, the researcher should satisfy themselves at a visit that the parent/legal guardian understands what is going to happen and how the data collected will be used.

Once completed, copies of the patient information sheet and consent form will be made and one given to the parents, one retained by the site coordinator and the

original kept in the patient's medical notes. A copy of the consent form only will also be sent to the Data Coordinating Centre by fax or other method agreed due to restrictions at site.
Where country specific regulations prevent the consent form being sent to the Data Coordinating Centre, the Site Coordinator will complete the TOPS consent form checklist and fax a copy of the completed checklist to the Data Coordinating Centre.

4.1.2.2 Video recording

Video recordings (with audio) will be completed at the cleft unit/department of the local site. The recording will be made using a video recorder and an external microphone.

A fixed set of age appropriate toys will be used by each site. The child's parent/guardian will then be asked to play with her/his child as naturally as possible and to try to elicit as much vocal activity from her/his child. Recordings should be made in the absence of siblings.
The speech and language therapist will not take part in the interaction with the child and will remain quiet for the duration of the recording.

The camera operator should not interact with the child but should ensure that the child's face is kept in focus and that there is no direct light on the face of the child and parent during the recording. Further details of the procedures for calibration (practice) recordings are described in supplementary trial-specific documents #24, #25, and #26.

4.1.2.3 Transfer of speech recordings.

Once a speech recording has been made a digital file will be sent to the Data Coordinating Centre.
Sites should ensure that they maintain their own copies of recordings before sending recordings to Data Coordinating Centre. The Data Coordinating Centre will track receipt of the recordings and forward these on for quality checks. The management of speech recordings at the Data coordinating Centre is described in supplementary trial-specific document #21.

4.1.2.4 Quality assessment of speech recordings

The speech recordings will be assessed for technical quality by the core speech group, or by a member of the trial team at the Administrative Centre, using predefined criteria. Quality checks of 12-month trial recordings at the Administrative Centre are described in supplementary trial-specific document #28, and quality checks of 3-year and 5-year trial recordings are described in supplementary trial-specific document #29.

The core speech group will provide individualised training on speech sample collection, if necessary, based on the video recordings. In addition speech samples will be used as part of the speech and language therapist training for linguistic analyses and phonetic transcription.

Digital files will be transferred to the data coordinating centre using a trial-specific USB flash drive that has been encrypted using appropriate software unless an alternative process is needed and agreed with site due to local restrictions. The procedures for securely transferring digital files are described in supplementary trial-specific documents #24, #25, and #26. Instructions on how to work with the encrypted drives can be found in supplementary document #27 – Using encrypted containers.

4.1.3 Local research personnel

During the site initiation visits, representatives from the trial teams at the Administrative and Data Coordinating Centres will provide training to local personnel. This training will encompass protocol and trial-specific procedure requirements, completion of case report forms (CRFs) and transfer to the Data Coordinating Centre (DCC), centralised data ntry onto MACRO and handling of data queries, maintaining document control, filing and archiving of essential documents. Discussions will also be held on the standardised recording and transfer of audio, video and digital images to the Data Coordinating Centre using encrypted USB devices or other method as agreed with the site**.** The transfer of maxillary arch and dental impressions to the Administrative Centre will also be reviewed.

A record of the trial initiation visit will be created and will document all participating personnel. Once created, copies of the trial initiation report will be filed in the Trial Master File held at the Data Coordinating Centre and in the Investigator Site File maintained at each site.

5 TRIAL DESIGN

5.1 Primary Endpoint

The primary endpoint for the TOPS trial is insufficient velopharyngeal function at 5 years of age.

This is a dichotomous outcome of whether the child has insufficient function or not. This is measured by velopharyngeal function (VPC) sum which is an overall score on the scale 0-6. Scores ≥4 on this scale will be considered insufficient.

5.2 Secondary Endpoint(s)

The secondary endpoints are as follows. Source of speech endpoints are indicated by a superscript and provided in the table below:

1. Velopharyngeal function at age 5 years;
    a. Velopharyngeal composite score summary (VPC sum) [a, b]
    b. Insufficient velopharyngeal function (VPC rate) [d]
2. Velopharyngeal function at age 3 years;
    a. Insufficient velopharyngeal function (VPC rate) [c]
    b. Velopharyngeal insufficiency symptoms [a]
3. Canonical babbling at age 12 months:
    a. Canonical babbling present [e]
    b. Canonical babbling ratio [e]
    c. Consonant inventory [e]
4. Articulation at age 3 years:
    a. Percent consonants correct (PCC) [a]
    b. Percent correct placement (PCP) [a]
    c. Percent correct manner (PCM) [a]
    d. Non-oral consonant errors [a]
    e. Oral consonant errors [a]
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

*c. At 3 and 5 years^*

iv. Abnormal Puretone audiometry in at least one ear

v. Abnormal Puretone audiometry in both ears

vi. 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 [55])
    b. Maxillary arch constriction score (using modified Huddart/Bodenham scoring system [56])
10. Growth at 12 months:
    a. Nude weight
    b. Crown to heel length
    c. Occipitofrontal circumference

All outcomes assessed at 12 months of age will be adjusted for gestational age. Speech outcomes will be assessed centrally. Due to emerging methodology in the way speech is assessed, the methods for evaluating all speech related outcomes will be finalised prior to central evaluation of the recordings at each key timepoint (12 months, 3 years and 5 years of age). If any changes are required due to emerging methodology then these outcomes will be updated in a protocol amendment.

*The methods involved in obtaining speech recordings vary according to the child's age. Importantly velopharyngeal function at 3 years uses an age appropriate alternative to the VPC sum used at 5 years

#The time frame for post-operative/long term complications is as follows:

- *Dehiscence:-* Dehiscence is assessed 48 hours and 30 days postoperatively. Secondary surgery with dehiscence as the reason for this is also assessed.
- *Infection:-* Infection is assessed 48 hours and 30 days postoperatively.
- *Fistula*:- Fistula is assessed 30 days post operatively and at the 3 and 5 year follow up.

^If Puretone audiometry could not be performed then Soundfield audiometry will be collected.

Sources of secondary speech endpoints

[a]	Pictures
[b]	9 word string
[c]	Spontaneous speech
[d]	Spontaneous speech/retelling of bus story
[e]	Video of play interaction

6 TRIAL POPULATION

6.1 Inclusion Criteria

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

6.2 Exclusion Criteria

a. Consent not obtained;
b. Infants with syndromic cleft palate (except Van der Woude syndrome, which can be included if hearing is not affected) or severe developmental delay;
c. Congenital sensorineural hearing loss or structural middle ear anomalies;
d. Variation in the anatomical presentation is such that the surgeon who will perform the procedure considers that one stage closure with the Sommerlad technique would be inappropriate;
e. 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 (1988)[43];
f. Where the language spoken at home is not the majority language in the country of residence.

6.3 Participant Withdrawal and Transfer

6.3.1 Participant withdrawal

In consenting to the trial, participants are consenting to trial intervention, follow-up and data collection.

Withdrawal from allocated timing of surgery

If a decision is made to withdraw from the allocated timing of surgery then the infant may have a different timing of surgery to that allocated but remain in the trial and have scheduled follow ups should the parent/legal guardian be happy to do so. Form W1 (Withdrawal) should only be completed if the parent/guardian does not wish to continue with follow-ups.

Withdrawal from follow-up

If parents/guardians indicate that they wish to withdraw from the trial, that wish will be honoured. The site coordinator will complete the withdrawal Case Report Form (Form W1) documenting:

- That date of patient withdrawal;
- The extent to which consent is withdrawn;
- The reason for withdrawal if provided by the parent/guardian.

A participant's parent/guardian can partially or totally withdraw consent, for example not wishing to provide dental casts made specifically for the trial.

If a participant's parent/guardian withdraws consent for follow-up no further data will be recorded for the trial but the data collected up to that point will be used in data analyses unless the parent/guardian explicitly states that this is not their wish. Please contact the TOPS trial team for advice if you are unsure about the level of withdrawal from TOPS.

6.3.1.1 Participant exclusions post randomisation – identification of a syndrome or severe developmental delay

The TOPS clinical genetics assessment will aim to identify all syndromic patients prior to randomisation. However, some syndromes may only be identified if new symptoms and signs arise with the passage of time or following genetic analysis of a blood sample. Blood samples will be collected in all children at the time of surgery (unless previously taken). Likewise the DENVER II assessment will be repeated at age 3 to aid the identification of a severe developmental delay that was not evident at the original baseline assessment.

If analysis of the blood sample identifies a definite syndrome or the DENVER II identifies a severe developmental delay, the patient may remain in the trial and as many follow up assessments should be completed as appropriate/possible and trial data collected.

6.3.1.2 Participant total withdrawal from trial

Data from infants whose parent/guardian wishes to withdraw him/her from the trial completely can be included in the trial if anonymised unless the parent/guardian requests that none of their child's data be used. If the parent/guardian explicitly states their wish not to contribute further data to the trial, the Data Coordinating Centre should be informed in writing by the responsible physician using a withdrawal Case Report Form – Form W1.

6.3.2 Participant follow up and missed appointments

Every effort will be made to maintain contact with each participant randomised in the trial. In Scandinavia this may be facilitated by a national identification number. In the UK and Brazil sites should ensure that contact details from families are maintained according to local policies.

Families with young children may miss their follow-up appointments for a number of reasons. The burden of visits will be minimised by collecting trial specific information during customary visits to the clinical team. However, more than one visit may be necessary to complete all evaluations. If evaluations are completed on different dates all evaluations should be completed within the timeframes specified below.

The site coordinator, tracking individual trial patients, may adopt a more proactive approach to encourage attendance:

- A pre-visit telephone call may be made to confirm that the family has received the appointment and will be able to attend.
- The clinical team in general will offer reasonable flexibility in accommodating families in social or geographic circumstances that make attendance at fixed times difficult.
- Special transport arrangements may be arranged for individual families on an *ad hoc* basis.
- If a follow-up appointment has not taken place within the times stated below the Principal Investigator, Site Coordinator and site trial team will discuss possible solutions to ensure future patients are seen within the appropriate timeframe.
    - +/-4 weeks of 12 month follow up visit for those allocated surgery at 6 months
    - -2 weeks/+4 weeks of the 12 month follow up visit for those allocated surgery at 12 months (follow up visit must take place prior to surgery)
    - +/-4 weeks of the 3 year and 5 year follow up visit.

For further details of scheduling follow-up visits, see section 9.1.4.

6.3.3 Transfer of participant to a different trial site

For participants moving from the area, every effort will be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient.

A copy of the participant Case Report Forms will be provided to the new site. The parent/legal representative of the patient will be asked to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the

original centre. The Data Coordinating Centre should be notified of patient transfers by the Site Coordinator or Principal Investigator, using Case Report Form 15 (Participant Transfers).

7 ENROLMENT AND RANDOMISATION

7.1 Pre-Surgical Assessment

Upon notification of the Cleft Team of the birth of an infant with cleft palate, local protocols for initial care including feeding, information and support will be followed. The Site Coordinator will be notified and will arrange for a screening assessment to take place at a pre-surgical assessment visit, usually at around age 3 months, to minimise the burden to families.

At the pre-surgical assessment medical status of the infant will be assessed to determine whether the infant would be fit for surgical admission for cleft repair at age 6 months, corrected for gestational age.

If it is not possible to be certain that the infant will be medically fit to undergo surgery at age 6 months, since other investigations are pending, the baby is failing to thrive, or there are social difficulties to resolve, it may be necessary to arrange a further pre-surgical assessment. Eventually these will determine if surgery at 6 months would be appropriate (if so assigned) and whether the infant is a potential participant for the trial or not. In all centres standard procedures will be followed that will assess the infants suitability for the surgical intervention.

7.2 Screening and Informed Consent

Screening will be completed by appropriately trained staff, as detailed on the delegation log, and will normally be scheduled to take place on the same day as the customary visit for pre-surgical assessment or at another routine visit scheduled prior to surgery. The Site Coordinator will be responsible for seeing that screening and enrolment is carried out according to the TOPS trial protocol.

Upon notification from the cleft team the Site Coordinator will complete the Screening Log (form S1). This form will be held by the participating centre as a record of all referred infants and will document eligibility, uptake of consent and enrolment into the trial including the randomisation number for those enrolled. The Screening Log (form S1) will hold no identifiable information.

To facilitate participant tracking and allocate a screening number trial sites will be provided with a patient tracking log. The patient tracking log will document the participant name, date of birth and allocate a screening number. The patient tracking log is for site use only and will not be returned to the Data Coordinating or Administrative Centres to ensure that identifiable information is not transferred out of the clinical site.

The surgeon or a designated member of the surgical team will be present. Inclusion and exclusion criteria (Sections 6.1 and 6.2) will be applied. At this point, it will have been deemed likely that the infant will be fit for surgery at age 6 months, if so randomised. An oral examination will be carried out first and the cleft classified.

If the pre-surgical assessment identifies a potential participant, the parents/guardian will be invited to receive information about the trial and about the process for considering the child's enrolment into the trial. A designated member of the trial team will discuss the nature of the trial, randomisation, trial procedures, the importance of compliance with trial procedures, potential risks and benefits, and the duration of the trial.

The parent or legal guardian will then be given ample time to read and understand the participant information sheet and consent form (PISC) and to ask questions. The parent/guardian(s) will be told that they are not obligated to participate, that there will be no penalty for declining to participate, and that treatment will not be compromised if patients do not participate or cease participation at any time.

In Sweden only dates of consent signatures between parents and researchers may be different, due to the practicalities associated with patients being spread across a large geographical region. However, the researcher should satisfy themselves at a visit that the parent/legal guardian understands what is going to happen and how the data collected will be used.

Once completed, copies of the patient information sheet and consent form will be made and one given to the parents, one retained by the site coordinator and the original kept in the patient's medical notes. A copy of the consent form only will also be sent to the Data Coordinating Centre (the consent form will not be sent to the DCC where country specific regulations prohibit the transfer of the consent form).

Where country specific regulations prevent the consent form being sent to the Data Coordinating Centre the Site coordinator will complete the TOPS consent form checklist and fax a copy of the completed checklist to the Data Coordinating Centre.

Following informed consent the TOPS trial team should schedule the clinical genetics assessment for the infant see 9.1.2.3. The clinical genetics assessment should take place following consent and prior to randomisation. Further details are described in the supplementary trial specific document #14 ("Screening, recruitment and randomisation").

Changes in TOPS procedures will always be reviewed by the Trial Management Group. Significant changes will require re-consent of the participant(s) in any instance where the new procedures contradict any information given in the

information sheet (PISC) used for initial consent, or where new tests are introduced which were not mentioned in the initial consent.

Re-consent should be sought from parents/legal guardians at the earliest opportunity and prior to further trial assessments taking place. The same procedures for consent, described above, should be applied to re-consent.

7.3 Randomisation

Upon receipt of informed consent and completion of participant screening the site coordinator will assess patient eligibility from the paper Case Report Form.

Participant data from paper Case Report Form will be entered on to the online form and eligible participants will be randomised using a secure online randomisation system. Access to the randomisation facility will be controlled by the Data Coordinating Centre.

The participant will be randomised to receive surgery either at 6 or 12 months of age corrected for gestation. Each patient will be assigned a unique randomisation number.

Two members of each trial team will be allocated a unique username and password for the online randomisation system. The TOPS randomisation system can be accessed at https://www.mcrnctu.org.uk/trials/tops/rand_TOPS/
Requests for randomisation usernames should be sent to – tops.trial@liv.ac.uk

8 TRIAL INTERVENTIONS

8.1 Introduction

All participants recruited to the trial will receive primary surgical repair of cleft palate surgery using the Sommerlad technique.

Each surgeon, including those who already use the Sommerlad technique, will be provided with written descriptions of the surgical procedures and a video prepared by Mr Sommerlad illustrating all steps to be followed in the surgery. Each surgeon will also attend surgical calibration where they will receive instruction by Mr Sommerlad. The written descriptions of the surgical technique have been reproduced from B.C. Sommerlad's publication "A technique for cleft palate repair" (2003)[40] and "Comprehensive Cleft Care" (2009)[41]. Each participating surgeon will receive a copy of these four weeks prior to calibration. The procedures are also described in supplementary trial specific document #15.

Participants will be randomised to either surgery at 6 months or surgery at 12 months of age (corrected for gestational age).

8.2 Surgical Admission Time Frame

The surgical admission will be scheduled for age 6 months or age 12 months corrected for gestational age.
Gestational age will be assessed based upon the date of the last period and the infants date of birth.

Teams will make every effort to arrange surgery within one week of the target date. However, surgery may take place up to 2 weeks before or 4 weeks after the target date and still be considered as receiving the intervention.

There are several reasons why the intended date of admission will not be achieved precisely: other pressures on the operating theatre, cancellation of operating lists due to sickness of the designated surgeon, cancellation due to sickness of the participant, vacation plans and so forth. Where surgery is not going to take place within target period, the Principal Investigator will be notified and reasons documented and reported to the Data Coordinating Centre.

8.3 Blinding

It is not possible to maintain blinding for the randomised interventions of timing assignment of surgery. However, emphasis has been given to the collection of durable records, so that outcomes that depend upon subjective appraisal can be

rated by blinded judges. These include the primary outcome, insufficient velopharyngeal function at age 5, and the secondary outcomes at the 5 year follow-up.

8.4 Co-enrolment Guidelines

Patients should not be enrolled on any other intervention trials whilst participating in the TOPS trial. In the case of a patient wishing to participate in another clinical study the trial centre may contact the Administrative or Data Coordinating Centre to discuss the nature of the proposed trial and the appropriateness of participant co-enrolment.

9 ASSESSMENTS AND PROCEDURES

9.1 Schedule for follow up

9.1.1 Pre-screening period

The cleft palate is usually diagnosed in the maternity hospital at birth, but occasionally is not suspected until difficulties in feeding are experienced. The cleft team becomes involved soon after diagnosis is made and advice and support are provided with regard to feeding, and information on long term management. Services differ between centres; all centres will be asked to continue with their current care pathway.

To aid the sites in scheduling appointments and tracking trial forms, the supplementary trial specific document #13 ("TOPS Overview of Key Tasks") captures all of the TOPS tasks on one page, from screening and surgery to follow-up.

9.1.2 Screening and enrolment

9.1.2.1 Screening

See section 7.2. and supplementary trial specific document #14 ("Screening, recruitment and randomisation").

9.1.2.2 Enrolment

Prior to enrolment into the trial the Site Coordinator together with a member of the surgical team will have evaluated the patients eligibility by applying the inclusion and exclusion criteria detailed in section 6. At this stage it will have been deemed likely that the infant will be fit for surgery at 6 months. An oral examination will be carried out to confirm the nature of the cleft palate. Submucous cleft palate or any extreme anatomical variations should now be evident and would lead to exclusion from the trial. Additionally the cleft will be defined according to the classification of Jensen et al (1988)[43] and this classification recorded on the screening assessment Case Report Form.

If eligibility is confirmed and the family wishes to consent to entering the trial, the consent form will be signed by the infant's parent/guardian and designated member of the research team. A clinical genetics assessment (9.1.2.3) and history and the Denver II Developmental test will be completed by appropriately trained site personnel. The infant's weight, crown-heel length and occipitofrontal circumference

(OFC) will also be measured as part of the clinical genetics assessment. Centres will be provided with a standardised set of scales, fibreglass tape measure and a measuring mat to assess crown-heel length.

9.1.2.3 Clinical genetic assessment

A clinical genetic assessment of patients with cleft palate will take place after enrolment to the trial, and prior to randomisation, to identify patients who may have a syndromic cause of cleft palate. A detailed family and clinical history will be taken using standard procedures together with baseline growth measurements (nude weight, crown heel length and occipitofrontal circumference). In addition a photograph of the infant may be taken using a digital camera to be used in the assessment of the presence of a syndrome in uncertain cases. Further details are to be found in supplementary trial specific document #14 ("Screening, recruitment and randomisation").

9.1.3 Surgical admission

Soon after the screening visit, completion of the clinical genetics assessment and confirmation of eligibility, consented infants will be randomised to receive surgical intervention at age 6 months or age 12 months and the family notified accordingly.

Surgery may take place up to 2 weeks before or 4 weeks after the target date and still be considered as receiving the intervention. If children are late or very late to receive their surgery, they will remain in the trial according to the principle of "intention to treat".

When the infant is anesthetised, the surgeon will record the extent of the defect. He or she will also confirm that there is no variation in the anatomic presentation that would require modified surgical management (e.g. a two-stage repair), and would therefore not be amenable to the standard protocol repair. However if this is the case the most appropriate treatment will be performed and the infant will continue to attend follow up visits in order to facilitate the intention to treat analysis.

A blood sample (if required for genetic analysis) and maxillary arch impression will be obtained and the operation carried out.

The surgery and perioperative care CRF (Form 2) should be completed by the surgeon and other relevant members of the trial team at the site.

9.1.3.1 Additional surgery

Additional surgeries during the follow up period that relate to palate repair are recorded on a dedicated Case Report Form (#12), to capture reasons for the secondary surgery and methods of re-repair, if applicable. Additional surgery for any of the following reasons should be recorded: Dehiscence, fistula, velopharyngeal insufficiency, other reasons resulting in further repair of the palate.

9.1.3.2 Maxillary Arch Impression and Photographs at Surgery

9.1.3.2.1 Maxillary arch impressions

Impressions will be taken in the operating theatre to provide a record of the palatal cleft prior to surgery. Impressions will be taken whilst the infant is anaesthetised and the airway is protected. Impressions will be taken by a designated member of the research team, usually the surgeon, using alginate impression material in an appropriately sized impression tray. The site coordinator will ensure that a selection of special trays is available.

The impression should be wrapped in moist gauze or tissue, placed in a polythene bag and sent to the dental laboratory at site labelled with the infant's trial specific randomisation number and the date the model was collected. Two copies of the model will be prepared in vacuum-mixed white stone, for example, Crystal R. One copy of the impression will be for trial purposes and identified only by the randomisation number and date of impression.

Maxillary impressions should be sent to the Administrative Centre together with the T1- sample transfer form. The impressions should be appropriately wrapped and packaged to allow safe transport, taking care to separate the upper and lower impression by using a layer of soft material. This can be achieved by wrapping the impressions in bubble wrap and/or soft foam, and placing them in a solid cardboard box.

Maxillary impressions at surgery should be sent to the Administrative Centre no later than six weeks after surgery.

Upon receipt of the maxillary arch impression the Administrative Centre will confirm receipt with the trial site. Any missing T1 forms will be immediately chased up by the Administrative Centre.

On the day of receipt, the T1 forms will be faxed from the AC to the DCC enabling receipt of the study models to be logged in the trial database. The completed T1 forms are retained at the AC.

Pre-surgical maxillary impressions will be scanned with a suitable state-of-the –art 3D surface laser scanner. Scanning and analysis of the scan will be completed at the Administrative Centre by suitably trained personnel; procedures are described in supplementary trial specific document #33.

9.1.3.2.2 Photographs

At surgery prior to repair of the cleft photographs will be taken to document the shape and size of the cleft palate. Photographs will be taken by medical illustration or other designated member of the team at the cleft centre using a digital camera set at high resolution.

Photographs should be transferred to the Data Coordinating Centre using an encrypted USB drive. Further details on procedures for taking these photographs and for transferring the image files to the Data Coordinating Centre are given in supplementary trial specific document #20; information on using encrypted containers is provided in supplementary trial specific document #27.

9.1.3.3 Genetic Laboratory Investigations

Where patients have had a karyotype and detailed analysis of the chromosome 22q11 region to rule out a 22q11 microdeletion consent will be sought to access results rather than repeating the test. Where routine karyotyping and exclusion of a 22q11 deletion has not been performed a blood sample will be taken during anaesthesia at the time of surgical repair and used to carry out karyotyping and 22q11 analysis. Some laboratories will use routine G-banding techniques and carry out FISH analysis to detect 22q11 microdeletions others routinely use molecular karyotyping involving DNA-based techniques such as multiplex ligation-dependent probe amplification (MLPA) and array comparative genomic hybridization (CGH).
All of these are acceptable techniques. We anticipate that array CGH which can detect smaller chromosome imbalances than routine karyotyping, will be used increasingly as a first line karyotype in some laboratories during the course of the study. Where array CGH has been carried out, results will be requested.

We considered it unreasonable to obtain blood samples on infants other than at the time of operation. However, if this is not possible and further blood samples need to be taken for genetic assessment then we will attempt to liaise with others involved in the child's care to obtain a suitable sample for the study whilst minimising the burden to the infant.

Blood samples will be stored in line with the routine practice of the lab and will not be stored for trial purposes. Samples will not be used for other measurements within the trial.

9.1.4 Follow up

Trial teams should aim to schedule appointments close to the expected visit date, and within the visit windows shown in Table 3. Follow up schedules will be sent to sites on a regular basis to provide the expected, earliest and latest dates of visits for each participant.

Table 3. Expected visit windows for follow-up

Trial Visit	**Expected timing of the follow-up visits**	
12 month follow up	**If surgery at 6 months:** -4 weeks/+4 weeks of estimated visit date. Estimated visit date is 52 weeks from the infant's date of birth corrected for gestational age (full term defined as day 1 of the 40th week of pregnancy)	**If surgery at 12 months:** Visit window the same as surgery, all assessments to take place prior to surgery: 52 weeks from the infant's date of birth corrected for gestational age (full term defined as day 1 of the 40th week of pregnancy)
3 year follow up	-4 weeks/+4 weeks of estimated visit date. Estimated visit date calculated as 156 weeks from the infant's date of birth	
5 year follow up	-4 weeks/+4 weeks of estimated visit date. Estimated visit date calculated as 260 weeks from the infant's date of birth	

There may be instances where participants are not seen during the visit window due to, for example, child illness or cancelled clinics. Where the follow up visit will take place after the latest visit date they should still be completed and data collected according to the following:

Speech and language assessments:

- 12 month recordings: For babies randomized to 6 month surgery (who have received their surgery, even if they have been operated late), it will be attempted to obtain the "12 month recording" up to 18 months. If this is not possible, the next recording will be made when they are 3 years old. Babies randomized to 12 month surgery but where the operation is cancelled, can still have their 12 months pre-operative speech assessment done, if they are well enough and are already at the hospital. However if that is not possible, the 12 month recording should be done just before surgery.

- 3 year recordings: If the protocol window is missed, it will be attempted 3 times to recall the patient for the recording up to age 3 years and 11 months.
- 5 year recordings: If the protocol window is missed, it will be attempted 3 times to recall patient for the recording up to age 5 years and 11 months.

Other assessments:
Similar time scales apply for the other follow-up assessments; the following table summarizes the time windows for additional relevant visits:

Table 4. Time scales for follow-up assessments in addition to speech

Follow-up visit	Attempt to recall patients up to
DENVER II at age 3 years	up to age 3 years and 11 months
Audiology at age 12 months	up to age 23 months
Audiology at age 3 years	up to age 3 years and 11 months
Audiology at age 5 years	up to age 5 years and 11 months
Fistula assessment at age 12 months	up to age 23 months
Fistula assessment at age 3 years	up to age 3 years and 11 months
Fistula assessment at age 5 years	up to age 5 years and 11 months

9.1.4.1 12 month assessment

At 12 months (corrected for gestational age), an age appropriate standardised speech sample and an audiological evaluation will be obtained. In addition the infant's weight, crown-heel length and occipitofrontal circumference (OFC) will be measured using the standardised equipment provided to centres.

To minimise the burden of visits, this visit will be one of the customary follow-up visits for infants who had surgery at 6 months. For the 12 month surgery group, the records will be taken following admission for surgery but before surgery is performed. The time frame between admission for surgery and the surgical procedure will follow the current practice of the centre.

9.1.4.2 Speech and Audiological assessment at age 12 months

Speech recordings at age 12 months will be made in designated speech therapy rooms by one speech therapist. High quality sound recording equipment will be used to collect the speech samples. A digital video camera recorder with an external, portable wireless microphone, attached to the lapel of a light vest, will be used for the video recordings. In parallel, backup audio will be recorded by means of a digital audio recorder. All centres will be provided with recording equipment (see supplementary trial specific document #16).

9.1.4.3 3 and 5 year assessment

At 3 and 5 years, age appropriate speech and audiological evaluation will be undertaken (see supplementary trial specific document #17 and #18). In addition

the DENVER II developmental assessment will be repeated by a suitably trained member of the trial team at age 3. Visits at age three and five should be scheduled based on the child's date of birth i.e. without correction for gestational age.

9.1.4.4 Speech assessments at age 3 and 5 years

Speech recordings at age 3 and age 5 years will be made in designated speech therapy rooms. High quality sound recording equipment will be used to collect the speech samples. A digital video camera recorder with an external microphone will be used for the video recordings. In parallel, backup audio will be recorded by means of a digital audio recorder. All centres will be provided with recording equipment.

If only an audio recording is made, due to video equipment failure, the audio recording should be submitted to the Data Coordinating Centre. In this case, no further visit by the parents is required to repeat the recording.

All 3 and 5 year assessments will be both digitally audio and video recorded by two designated speech and language therapists at each site. One speech and language therapist will sit opposite the child to elicit the speech sample. The camera will be positioned to point directly at the child's face. The second speech and language therapist, or other appropriately trained personnel, will operate the camera to keep the child's face in view.

Two microphones will be used and will be placed at a distance of 40 cm from the edge of the table in front of the child and on the same side as the camera (see Figure 3 below). A neutral backdrop will be used for the video recording in order that a clear image of the child's face is recorded with no visual distractions. The child's head and shoulders will be within the frame of the recording so that tongue and lip movements for the articulation of consonants will be visible and can be assessed. The pictures used for the naming test will be presented to the child in such a way that they will be looking forward straight at the camera with their head in a neutral position (the pictures should not be presented on the table as the child may lower their head and the articulators will not be visible on camera).

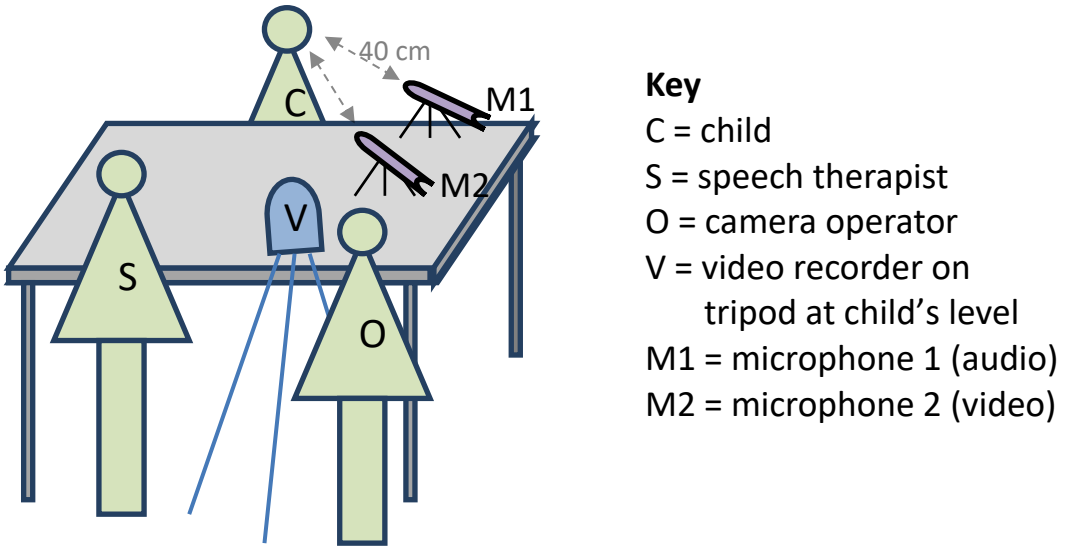


Figure 3. Setting for recording the speech sample

The speech assessment material will consist of age appropriate tests that are described in supplementary trial specific document #17 for 3 year speech assessments and supplementary trial specific document #18 for 5 year assessments.

As part of the 5 year assessments, the Intelligibility in Context Scale (ICS) questionnaire will be given to the parents to complete at the visit. For details, see supplementary trial specific document #18.

In addition, at the 5 year assessments, nasality in speech production (nasalance) will be determined using Nasometer™ II (Model 6450, KayPENTAX) instruments at all trial sites. The scores of nasalance readings will be recorded on Form 13 (5 Year Speech Assessment). Nasality recordings should be kept at site only; for further details see supplementary trial specific document #18.

9.1.4.5 Speech sample analysis

Analysis of the speech samples will be carried out by calibrated, trained speech and language therapists. To avoid bias the speech and language therapist carrying out the analysis will not have been involved in the treatment of the child. Prior to analysis, speech recordings will be edited following the processes described in supplementary trial specific document #29.

In the case of the 3 year and 5 year assessments, *with the exception of hypernasality,* the first language of the speech and language therapist analysing the speech samples needs to be the same as the child's, while for the analysis of 12-month recordings, this is not required.

Recorded speech samples will be presented in a random order and the rater will be blinded to the timing of palate repair. The analysis of speech samples is outlined in figure 4. Further details of analysis are described in supplementary trial specific document #30.

Participants' vocalizations at 12 months will be assessed using real time listening, as described by Ramsdell et al (2012)[52]. This methodology has also been shown to be reliable for assessment in a study using clinical data (Patten et al. 2014)[51]. In real time listening, the rater listens to recorded speech samples without pausing, fast forwarding or replaying and, while viewing, registers every syllable the baby produces and makes a judgement on whether or not the syllable is canonical. To limit the memory constraints of the listener the recordings are no longer than twenty minutes. At the end of the recording the rater lists, using broad transcription, the syllables which she/he finds by the baby is in control of, based on his/her overall impression from the video recording. Then she/he fills in if the child was found to be in the canonical babbling stage or not. In this way the following parameters are obtained: canonical babbling ratio, canonical babbling stage, number of canonical syllables and consonant inventory. As opposed to what has often been reported for phonetic transcription, real time listening has been found to have good reliability across listeners, it is time efficient, and has a better correspondence with parents' judgments of their child's syllable inventory than syllable inventory retrieved from phonetic transcription (Ramsdell et al., 2012)[52].

Canonical babbling ratio (CBR) is calculated as the number of canonical syllables divided by all syllables produced by a child. A ratio of at least 15% canonical syllables has to be produced in order for a child to be regarded as having acquired canonical babbling (Oller et al., 1994)[44]. One hundred consecutive utterances will be analyzed, and the CBR is calculated by the "TimeStamper" software program created at the University of Copenhagen for this purpose, as the number of canonical syllables divided by the total number of all syllables indicated by the listener during the real time listening procedure. An utterance may contain more than one syllable. Then the listeners give their judgement of which syllables the child commands.

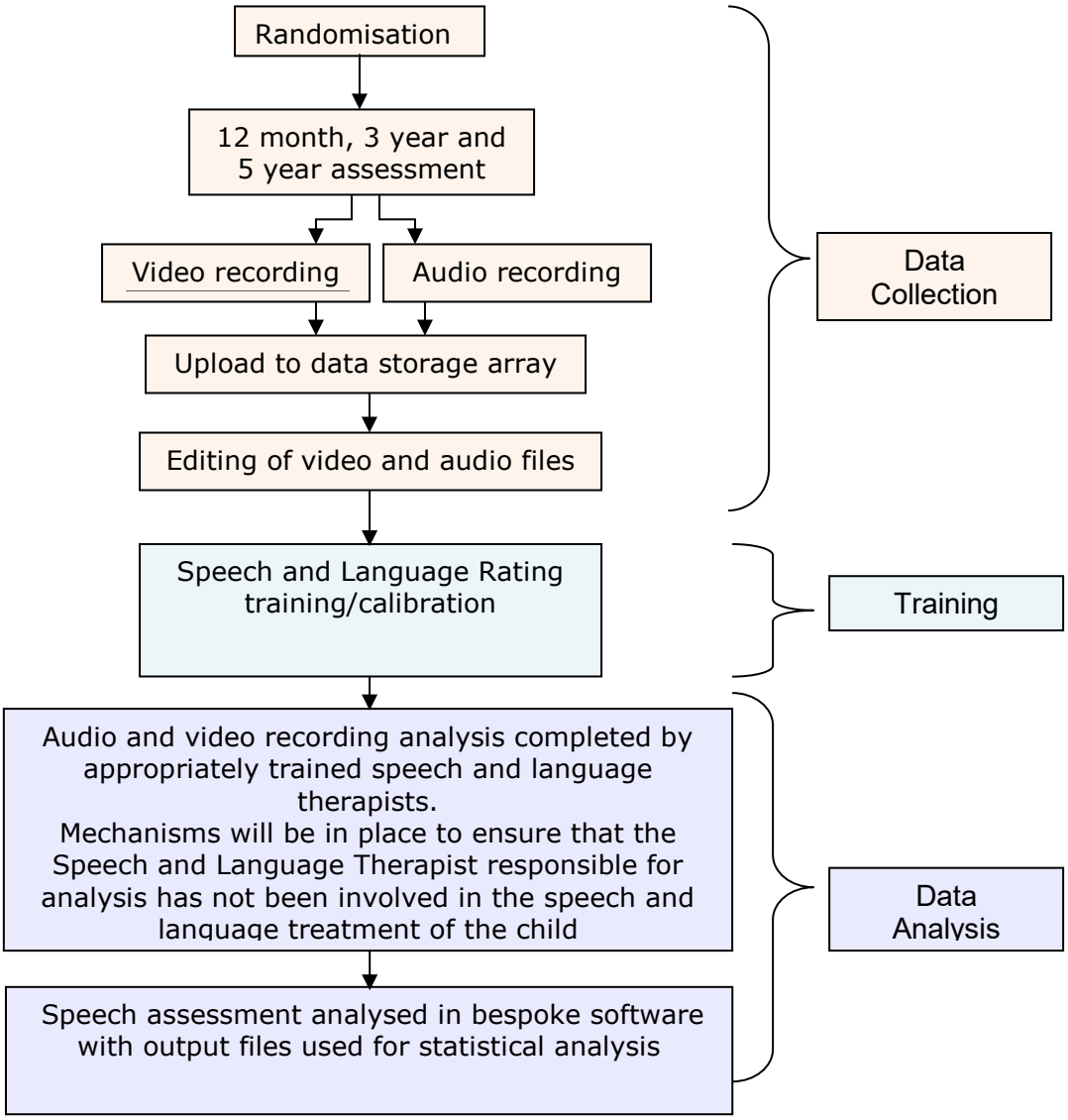


Figure 4 – Pathway of speech sample (audio and video) collection and analysis.

9.1.4.5.1 Velopharyngeal function

At age 3 an overall assessment will be performed, based on spontaneous speech, to determine whether velopharyngeal function is sufficient or not.

Insufficient velopharyngeal function at age 5 is determined by a score of 4 to 6 on the velopharyngeal composite summary score (VPC-sum). The VPC-sum score is based on the main speech characteristics of velopharyngeal impairment described for example by Trost (1981)[45]: hypernasal resonance, audible nasal air leakage accompanying oral pressure consonants (including nasal emission and nasal turbulence); weak production of oral pressure consonants; and active, non-oral articulation. Scores from these main speech characteristics combine to arrive at the final VPC-sum score. This composite score was first developed and described by Lohmander et al (2009)[42], and is similar to the procedure for cleft speech analysis described by John et al (2006)[46]. Since 2009 the VPC-sum was further

developed (Lohmander et al, 2013)[49]. The score for hypernasality is derived from a four point rating scale. The scores for the remaining parameters are based on narrow phonetic transcription, and audible nasal leakage and weak pressure consonants are combined to produce a score for velopharyngeal incompetence (VPI) symptoms.

The following transfer rules are used for calculation of the VPC-sum: Rating 0 on hypernasality gives a score zero, rating 1 a score 1, and rating 2-3 a score two in the first VPC-sum component (A). 0-2 active non-oral errors and VPI-symptoms respectively give a score zero, 3-5 errors a score one and 6 or more a score two in the VPC-sum components B and C:

Table 5. Transfer rules for VPC-sum

Variables	Transfer rules			VPC-sum component
A: Hypernasality	0 = **0**	1 = **1**	2-3 =**2**	**A [0-2]**
B: Active non-oral errors	0-2 =**0**	3-5 = **1**	≥6 = **2**	**B [0-2]**
C: VPI-symptoms	0-2 =**0**	3-5 = **1**	≥6 = **2**	**C [0-2]**

VPC-sum is then calculated by adding A, B and C: VPC-sum = A + B + C

9.1.4.5.2 Articulation

Each child will be assessed on how many target sounds they can produce correctly from the TOPS picture naming test at 3 and 5 years. Percentage of consonants correct (PCC) modified from Shriberg (Shriberg et al., 1997)[48] will be calculated by dividing the number of accurate consonants within the sample by the total consonants sampled. At 3 years production will be transcribed using broad phonetic transcription. At 5 years narrow phonetic transcription will be used and phonetic distortions, as well as non-target system substitutions will be treated as errors.

9.1.4.5.3 Intelligibility of Speech

Speech intelligibility at 5 years will be measured by the Intelligibility in Context Scale (ICS) (McLeod et al., 2012)[50]. The ICS is a parent-reported intelligibility measure which allows estimating the degree to which children's speech is understood by different listeners. Intelligibility of speech was identified by an international panel of speech and language pathology experts as an important universal parameter when reporting speech outcomes (Henningsson et al, 2008)[47]. However, to date few studies have reported on this key outcome for children born with cleft palate. The ICS is a recently developed measure of speech intelligibility which has been translated into 57 different languages, and has undergone initial reliability and validity testing (McLeod et al., 2012)[50].

9.1.4.6 Audiological assessment at age 12 months, 3 and 5 years

Audiologists will be experienced clinicians who already perform hearing tests and audiological assessments according to international standards.

All children will have their middle ear function determined at each of their three visits to the clinic. The test will be performed in a sound proofed room, and the sound field within the room will be calibrated annually. All equipment used will be calibrated annually. The hearing thresholds will be obtained using the standard test suitable to the children's developmental age, ear specific measurements will be determined if at all possible and all results recorded in decibel hearing level (dBHL). If, for any reason, the thresholds cannot be determined, tympanometry will be performed and the findings recorded.

The designated audiologist at each centre will receive instruction, if needed, in the completion of the data collection forms. Standardised protocols for the audiological tests will be documented

9.1.4.7 Photographs and dental impressions at 5 year assessment

Photographs

Frontal and lateral photographs of the face will be taken with a digital camera (Nikon S3 camera with a 105 mm focal length or equivalent). The camera should be set at a ratio of 1:8. Lighting should consist of two fill-in lights and the main light should synchronise with the camera. The background will be blue. Photographs will be taken by the orthodontist or other designated member of the team at the cleft centre. Further details on procedures for taking these photographs and for transferring the image files to the Data Coordinating Centre are given in supplementary trial specific document #20.

Once photographed the digital images are saved by the Site Coordinator with their file-names indicating the trial randomisation number and the date on which the image was captured. Digital images will be transferred to the data coordinating centre using a trial specific USB flash drive that has been encrypted using appropriate software unless an alternative method is agreed with a site due to local restrictions. Instructions on how to use the encrypted USB flash drives can be found in supplementary document #27 – Using encrypted containers. Procedures concerning the management of photographs at the data coordinating centre are described in supplementary trial-specific document #31.

Photographs will be assessed using profile analysis performed using a standardised angular analysis.

Dental impressions

Model impressions with orthodontic alginate will be obtained at the 5 year follow-up appointment. Patients who miss the five year appointment will be re-called so that impressions can be taken no later than 5.5 years.

The occlusion will be registered with a wax wafer in the position of maximal intercuspation. The impressions will be sent to the dental laboratory at site for casting and trimmed to the occlusion indicated by the wax bite.

Preparation and trimming of models will be performed according to WHO working party guidelines (WHO, 2002, page 147) so that the participant cannot be identified:

- Cast in vacuum-mixed white stone, for example, crystal R.
- Hand trimmed using a fine wheel to the standard angles shown in figure 5.
- Finished with wet and dry paper (not soaked).

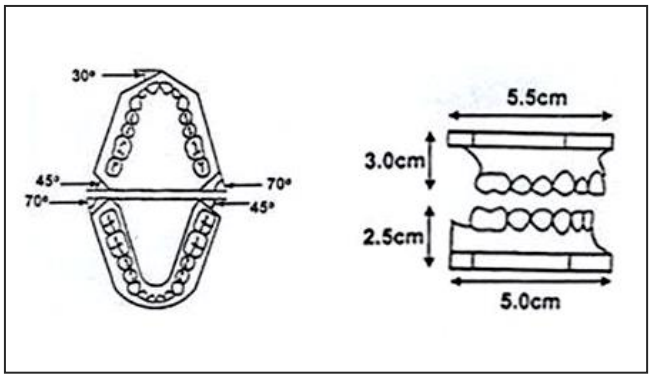


Figure 5. Trial model trimming

Dental impressions should be identified only by the randomisation number and date of impression and sent to the Administrative Centre together with the T1- sample transfer form. The impressions should be appropriately wrapped and packaged to allow safe transport, taking care to separate the upper and lower impression by using a layer of soft material. This can be achieved by wrapping the impressions in bubble wrap and/or soft foam, and placing them in a solid cardboard box.

Dental impressions at 5 years should be sent to the Administrative Centre within six weeks after the 5-year visit.

Upon receipt of the dental impression the Administrative Centre will confirm receipt with the trial site and the T1 form is faxed to the Data Coordinating Centre on the same day.

Further information on creation and transfer of dental impressions are given in supplementary trial specific document #20.

The Administrative Centre will be responsible for the analysis of the samples using a suitable state-of-the-art 3D surface scanner. Analysis of the scan and dental arch relationship will be completed after the five year follow up assessment. For further

details on analysis, please see supplementary document #33 ("Analysis of Dental Study Models").

9.1.4.8 Data collection from local Speech and Language therapists

Local Speech and Language Therapists outside the TOPS clinical site will be contacted to collect summary data on interventions during the period of the trial (until the participants are five years of age). These data will be collected via Case Report Form 11 (3 year local site speech therapy questionnaire) and Case Report Form 14 (5 year local site speech therapy questionnaire), and query the types of therapy (direct versus indirect), and the reasons for these interventions until the time points of 3 years and 5 years of age, respectively.

Where patients have not already consented for this data to be collected, suitable consent must be sought before the data are requested from local sites. Parents/legal guardians may choose to opt out of this additional data collection.

9.1.4.9 Annual Birthday cards

To aid participant retention and maintain interest in the trial, birthday cards may be sent to participants for the duration of the trial follow up. Birthday cards may be sent by the local research team and may include a reminder of a forthcoming follow up visit if necessary. Birthday cards will be supplied to sites**.**

		Visit				
Assessment/ Procedures	Form Number and Name	Screening and Randomisation	Surgical Visit	12 month follow up	3 year follow up	5 year follow up
Patient tracking log	Patient tracking log – FOR SITE USE ONLY	**X**				
Signed consent form	TOPS trial current PISC	**X**				
Screening and assessment of eligibility criteria	**S1:** Screening Log.	**X**				
	C1: Clinical genetics assessment	**X**				
	DENVER II: DENVER II developmental assessment	**X**			**X**	
	1: Screening and randomisation	**X**				
Trial Intervention – Surgery at age 6 or 12 months	**2:** Surgery and postoperative care form		**X**			
	C2: Blood sample for clinical genetics assessment (Sample request)		**X** (only if no results available at screening)			
	3: Late Complications form		**X** (complete 30 days post surgery)			
	Photograph of unrepaired palate		**X**			
Maxillary arch impression	**Form T1**: sample transfer		**X**			
12 month assessment	**4:** 12 month speech assessment*			**X**		
	5: 12 month growth assessment*			**X**		
	6: 12 month audiology data collection form*			**X**		
	7. Fistula Assessment			**X**	**X**	**X**
3 and 5 year follow up assessments	**8:** Audiology data collection form				**X**	**X**
	9: 3 year speech assessment form				**X**	
	10: 3 year DENVER II assessment report				**X**	
	11: 3 year speech local site questionnaire				**X**	
	13: 5 year speech assessment form					**X**
	14: 5 year speech local site questionnaire					**X**
	Intelligibility in Context Scale questionnaire for parents (ICS).					**X**
	Photographs as specified in supplementary document					**X**
Speech recordings and photographs	**T2 –** Speech recording and photograph transfer		**X**	**X**	**X**	**X**
Dental Impression	**Form T1:** sample transfer					**X**
Review of Serious Adverse Events	**A1:** Serious Adverse Event reporting form	**Complete for each Serious Adverse Event (including unanticipated problems)in the first 30 days following surgery**				
Review of concomitant medication	**M1:**Concurrent medication form	**Complete for each concurrent medication during surgery and for 30 days post surgery**				
Review of unanticipated problems	**U1:** Unanticipated Problem reporting form	**Complete for each Unanticipated Problem for the duration of the trial**				
Additional surgery	**12:** Additional surgery	**Complete for each participant receiving additional surgery during the trial**				
Transfer of participant	**15:_**Participant Transfer	**Complete for each participant transferred from one TOPS site to another TOPS site during the trial (does not apply to Bauru site)**				

Table 6. Schedule of visits and key tasks * Pre-operatively if randomised to surgery at 12 months -2 weeks/+4weeks of target date.

9.2 Trial Closure

The end of the trial is the date of database lock as defined in the Data Management Plan. At the time of database lock, data entry privileges are withdrawn from the trial database. However the trial may be closed prematurely. The Data and Safety Monitoring Board may make a recommendation to the Trial Steering Committee and the National Institute for Dental and Craniofacial Research regarding trial closure after data review. The funder may withdraw funding in the event of futility, study misconduct, or other unanticipated events.

10 STATISTICAL CONSIDERATIONS

10.1 Introduction

A separate and full Statistical Analysis Plan will be developed prior to the final analysis of the trial. The statistical analysis plan will be agreed by the Trial Steering Committee before being sent to the independent Data and Safety Monitoring Board for comment and approval. The main features of these planned statistical analyses are included here in the main protocol.

10.2 Method of Randomisation

The randomisation number and intervention allocation will be generated by the Data Coordinating Centre using a minimisation routine incorporating a random element to reduce predictability. The minimisation program will be web based. Following fully informed written proxy consent, participants will be randomised to receive their surgical intervention at age 6 months or 12 months.

10.3 Outcome Measures – see sections 5.1 and 5.2

10.4 Sample Size

In this trial, 300 patients per arm will allow a reduction in insufficient velopharyngeal function at five 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 the pilot trial in 50 five year old patients, collected during the planning period for this grant application. 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%.

10.5 Interim Monitoring and Analyses

The trial will be monitored by an independent Data and Safety Monitoring Board which will assess the trial data and take into account the current world-wide evidence. Data and Safety Monitoring Board members will comply with a trial-specific Data and Safety Monitoring Board charter according to International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the National

Institute for Dental and Craniofacial Research guidelines (http://www.nidcr.nih.gov/Research/ToolsforResearchers/Toolkit/DSMBGuidelines.htm, accessed 07-Jan-2013.).

The initial analysis of trial data for Data and Safety Monitoring Board review is planned, following the completion of 20 surgical procedures, to assess recruitment rates and Adverse Events. Subsequent timing of the next analysis of the data will be determined on the basis of recruitment rates at the initial Data and Safety Monitoring Board meeting although it is anticipated that this will be approximately after a further 12 months. The Data and Safety Monitoring Board will monitor adherence to the trial protocol and the quality of the accruing data. Additional interim analyses may also be triggered by concern regarding reported Serious Adverse Events.

10.6 Analysis Plan

The trial will be analysed and reported using the "Consolidated Standard of Reporting Trials" ("CONSORT") and the International Conference on Harmonisation E9 guidelines. The main features of the statistical analysis plan are included here.

The primary analysis comparing the timing of surgery will use the principle of intention to treat based on all the randomised participants, as far as is practically possible.

The need to conduct a secondary analysis based on a 'per protocol' (PP) data set will be determined by the percentage of major protocol deviations. A level of 10% or more will trigger discussions within the Trial Management Group. The purpose of any protocol analysis will be to examine the robustness of the primary analysis under the intention to treat principle.

Outcomes will be reported as follows and listed as in Sections 5.1. and 5.2.

Descriptive statistics

All outcomes will be summarised using descriptive statistics overall and split by treatment group as follows:

- Continuous and long ordinal outcomes will be summarised by the mean, standard deviation, minimum and maximum (medians and interquartile ranges will be reported for skewed data).
- Dichotomous, categorical and short ordinal outcomes will be summarised using counts and percentages.

Formal statistical testing

A p-value of 0.05 or less will be used to declare statistical significance for all analyses. Rather than adjust for multiplicity relevant results from other studies already reported in the literature will be taken into account in the interpretation of results.

The approach to formal statistical testing is dependent on outcome type as follows:

- *Dichotomous outcomes*:- Outcomes of this type 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 outcome* will be compared between the two groups 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.

11 ADVERSE EVENT REPORTING

11.1 Terms and Definitions

Medical Monitor
A person employed by the Funder, who is responsible for determining that a clinical study is being conducted in accordance with the protocol. The Medical Monitor has medical authority for checking data and documentation from the trial and for the evaluation of its safety aspects.

Adverse Event (AE)
Any untoward medical occurrence in a participant to whom a research procedure has been administered, including occurrences which are not necessarily caused by or related to that procedure.

Serious Adverse Event (SAE)
In this trial a Serious Adverse Event (SAE) is defined as an untoward occurrence that:
(a) Results in death;
(b) Is life-threatening*;
(c) Requires hospitalisation or prolongation of existing hospitalisation**;
(d) Results in persistent or significant disability or incapacity;
(e) Is otherwise considered medically significant by the investigator***.

In this trial congenital anomalies or birth defects will not be included as they are inherent in the trial population.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, and due to social factors, such as parental anxiety which did not result in any intervention, do not constitute a Serious Adverse Event.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a Serious Adverse Event/experience when, based upon appropriate medical judgment, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Further details about Safety Reporting can be found in supplementary document #32 "Safety Reporting Guidelines".

Unanticipated Problems (UPR)

Unanticipated Problems will be reported as a requirement of National Institute of Health in compliance with the Office for Human Research Protections (OHRP).

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

(a) **Unexpected** (in terms of nature, severity or frequency) given the research procedures that are detailed in the protocol or protocol related documents, and the characteristics of the participant population being studied;

(b) **Probably, possibly or almost certainly related to participation in the research** (for definitions of causality see table 7.0, section 11.4);

(c) **Suggests that the research places participants or others at a greater risk** of harm (including physical, psychological, economic or social harm) than was previously known or recognised.

An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in order to protect the safety, welfare, or rights of participants or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- implementation of additional procedures for monitoring subjects;
- suspension of enrolment of new subjects;
- suspension of research procedures in currently enrolled subjects;
- modification of informed consent documents to include a description of newly recognised risks;
- Provision of additional information about newly recognised risks to previously enrolled subjects.

Unanticipated problems will be recorded and reported throughout the study.

11.2 Adverse Event and Unanticipated Problems Inclusions and Exclusions

11.2.1 Include

- An exacerbation of a pre-existing illness;
- An increase in frequency or intensity of a pre-existing episodic event/condition;
- A condition (even though it may have been present prior to the start of the trial) detected after the trial procedure;
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the trial procedure;
- Other medically significant event.

11.2.2 Do not include

- A congenital abnormality or birth defect;
- Prolongation of hospital stay due to social factors, for example, geographical location of the infant's home;
- Medical or surgical procedures- the condition which leads to the procedure is the Adverse Event;
- Pre-existing disease or conditions present before treatment that do not worsen;
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery;
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition.

11.3 Notes on Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.
Regardless of the classification of an Adverse Event as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe Adverse Events. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 11.1, hence, a severe Adverse Event need not necessarily be a Serious Adverse Event.

11.4 Relationship to Trial Intervention

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table 7.
If any doubt about the causality exists the local investigator should inform the Data Coordinating Centre who will notify the Chief Investigator (Professor Bill Shaw at the Administrative Centre). In the case of discrepant views on causality between the Principal Investigator and the Chief Investigator, the Data and Safety Monitoring Board will be informed of both views.

Table 7. Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the Adverse Event (AE) should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after the surgical intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after the surgical intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

11.5 Follow-up After Adverse Events and Unanticipated Problems

All Adverse Events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.
When reporting Serious Adverse Events the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

11.6 Reporting Procedures

11.6.1 Responsibilities of the site

The Principal Investigator is responsible for reporting all Adverse Events, Serious Adverse Events and Unanticipated Problems that are observed or reported during the 30 day period post surgery. Supplementary trial specific document #32 "Safety Reporting Guidelines" describes further details.
Any questions concerning Adverse Event reporting should be directed to the Data Coordinating Centre in the first instance. A flowchart is given (Figure 6, section 11.6.2.2) to aid in determining reporting requirements.

11.6.1.1 Adverse events

Adverse Events will be recorded on the surgery and post-operative care case report forms, during surgery and the 30 day post-operative period, and reported to the Data Coordinating Centre. Scheduled visit Case Report Forms will routinely report the following:

1. Post operative progress; length of time required in:
    a. Intensive care and/or;
    b. High dependency care and/or;
    c. Ward care.
2. Peri- and early post operative complications relating to:
    a. Anesthetic;
    b. Airway;
    c. Bleeding;
    d. Wound dehiscence (Wound dehiscence should also be reported as Serious Adverse Event in cases where complete or major separation of the muscle repair occurred and a full re-repair is required);
    e. Readmission to operating room;
    f. Any other complications related to surgery.
3. Late post operative complications relating to:
    a. Secondary bleeding;
    b. Infection.

<u>Any other complications.</u>

1. Observations (minimum 48 hours) of:
    a. Arterial blood gasses and/or carbon dioxide & oxygen and/or oxygen Saturation levels (where applicable);
    b. Vital signs (Heart and respiratory rate, blood pressure).
2. Post operative requirements for:
    a. Pain relief;
    b. Anti-inflammatory therapy;
    c. Antibiotic therapy.
3. Stage at which feeding is introduced.

If any of the above Adverse Events meets the definition of a Serious Adverse Event the Site Coordinator should complete the Serious Adverse Event Case Report Form A1 and notify the Data Coordinating Centre. Serious Adverse Events should also

be assessed using the definition of an unanticipated problem, and reported on form U1 (Figure 6, section 11.6.2.2).

All Case Report Forms should be completed and submitted to the Data Coordinating Centre within four weeks of completion of trial visits/ procedures, however if any Adverse Events meet the definition of a Serious Adverse Event (section 11.6.1.3) or Unanticipated Problem (section 11.6.1.2), the Site Coordinator should complete the relevant Serious Adverse Event Case Report Form A1 or Unanticipated Problem Case Report from (U1) and notify the Data Coordinating Centre within 24 hours (or next working day) of becoming aware of the Serious Adverse Event or Unanticipated Problem.

Minimum information required for reporting Adverse Events

- Trial identifier;
- Enrollment site;
- Randomisation number;
- A description of the event;
- Date of onset;
- Current status;
- Whether trial intervention was completed (if peri-operative event);
- How the event is classified (and reason/s why if the event is classified as serious or unanticipated problem);
- Investigator assessment of the association between the event and trial intervention.

11.6.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) occurring to a research participant should be reported, by the Principal Investigator, to the Data Coordinating Centre 24hours or the next working day after being made aware of the event. Serious Adverse Events should be reported on Form A1 – Serious Adverse Event Reporting. All other Adverse Events should be reported by fully completing all trial Case Report Forms for surgery and post operative care.

The Serious Adverse Event form should be completed by the responsible investigator i.e. the physician or their delegated representative named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The Principal Investigator should assess the Serious Adverse Event for the likelihood that it is a response to the timing of the surgical procedure. In the absence of the Principal Investigator the form should be completed and signed by a designated member of the site trial team and faxed to the data coordinating centre. The responsible Principal Investigator will review the serious Adverse Event form, make changes as appropriate, sign and then re-fax to the data coordinating

centre as soon as possible. The initial report shall be followed by detailed, written reports.

Send the SAE form by fax (within 24 hours or next working day) to the Trial Coordinator at the Data Coordinating Centre:

Fax Number: 00 44 (0) 151 795 8770

Principal Investigators will report any SAEs as required by their local regulatory bodies, local Research Ethics Committees, Research and Development Offices and/or any other appropriate regulatory body within the time frames designated.

In the case of a Serious Adverse Event the participant will be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol assessments if necessary.

Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the Data Coordinating Centre as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.
The patient will be identified by randomisation number and date of birth only.

Trial sites will collect Serious Adverse Event information for 30 days post surgical intervention.

11.6.1.3 Unanticipated Problems

Incidents or events that meet the OHRP criteria for unanticipated problems will be reported, by the Principal Investigator, to the Data Coordinating Centre. Unanticipated problems should be reported to the DCC using Form U1 within 24 hours or the next working day of the Principal Investigator being made aware of the event.

All Unanticipated problems should be reported, for the duration of the trial, using Case Report form U1- Unanticipated Problems. Form U1 will record:

- information appropriate to identifying the protocol;
- a detailed description of the Adverse Event, incidence, experience or outcome;

- an explanation for the basis of determining that the Adverse Event, incidence, experience or outcome represents an unanticipated problem; and
- a description of any deviations from the protocol and/or corrective actions that have been taken or are proposed in response to the unanticipated problem.

In this multicentre study changes to the Protocol or Patient Information Sheet and Consent Form proposed by a local investigator at one institution engaged in the research independently in response to an unanticipated problem will be reviewed in consultation with the Administrative Centre, Data Coordinating Centre and the Study Sponsor to determine whether changes at one site could have significant implications for the entire research study.

Unanticipated problems will be recorded throughout the trial.

11.6.2 Responsibilities of the Data Coordinating Centre

The Trial Sponsor (University of Manchester) has delegated the reporting of Serious Adverse Events and Unanticipated Problems to the Data Coordinating Centre. Staff at the Data Coordinating Centre will liaise with the Chief Investigator who will evaluate all Serious Adverse Events and Unanticipated Problems received for seriousness, expectedness and causality. The causality assessment given by the Principal Investigator at each site cannot be overruled and in the case of disagreement, both opinions will be provided with the report. Supplementary document #32 "Safety Reporting Guidelines" describes further details.

All SAE and expedited UPR reports will also be copied by the Data Coordinating Centre and sent to NIDCR's Centralized Safety System at: rho_productsafety@rhoworld.com

These reports will then be forwarded to and reviewed by the NIDCR Medical Monitor.

11.6.2.1 Unanticipated Problem Reporting

Upon receipt of Form U1 or A1 the Data Coordinating Centre will ensure that the Institutional Review Board (the University of Manchester, IRB00002184; Fax +44 161 306 0101) receive reports of Unanticipated Problems within 1 week of receipt from the Principal Investigator for Unanticipated Problems that are also Serious Adverse Events and within 2 weeks for all other Unanticipated Problems.

The Data coordinating Centre also undertakes the reporting of Unanticipated Problems to the National Institute of Dental and Craniofacial Research, Clinical Research Operations Management Support (CROMS) contractor, at one of the following numbers or by email:

Safety Fax Line: 00 1 888-746-3293
Safety Hot Line: 00 1 888-746-7231
Product Safety E-mail: rho_productsafety@rhoworld.com

11.6.2.2 Serious Adverse Event Reporting

Serious Adverse Events which are both related and unexpected will be reported within 15 days of receipt.
Related and unexpected SAEs will be reported to the main REC using the SAE report form for non-CTIMPs, available from National Research Ethics Service NRES website:
(http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/ accessed on the 07-Jan-2013).
Any outstanding SAEs at the time of the annual report to NRES will be included on the annual progress report form for all other research (http://www.nres.nhs.uk/applications/after-ethical-review/annual-progress-reports/ accessed 07-Jan-2013).

Local investigators will report any SAEs as required by their local regulatory bodies, local Research Ethics Committees and/or Research and Development Offices within the time frames designated.
All Serious Adverse Events will also be reported to the Sponsor (Manchester University).

The Data coordinating Centre also undertakes the reporting of Serious Adverse Events to the National Institute of Dental and Craniofacial Research, Clinical Research Operations Management Support (CROMS) contractor, at one of the following numbers or by email:

Safety Fax Line: 00 1 888-746-3293
Safety Hot Line: 00 1 888-746-7231
Product Safety E-mail: rho_productsafety@rhoworld.com

These reports will then be forwarded to and reviewed by the NIDCR Medical Monitor. The Medical Monitor assessment will be forwarded back to the Data Coordinating Centre when completed, usually within 5 working days.

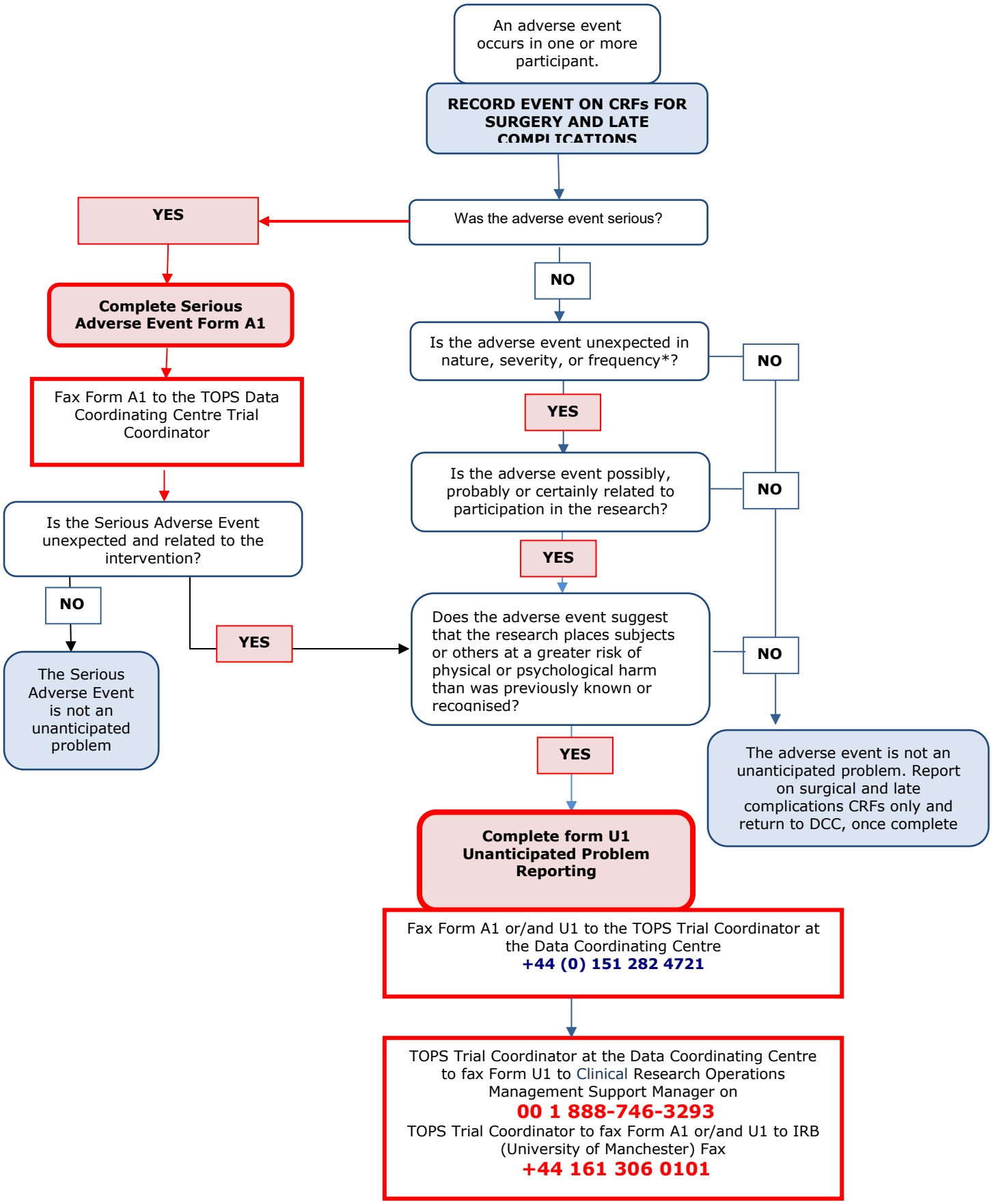


Figure 6.

Flow Chart for Adverse Event Reporting

*The Data coordinating centre undertakes the responsibility for assessing frequency.

12 ETHICAL CONSIDERATIONS

12.1 Ethical Considerations

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), and the Office of Human Research Protections (OHRP) Common Rule, 45 CFR 46.

This protocol will have gained favourable opinion from the Multicentre Research Ethics Committee in the UK and from relevant ethics committees for each participating centre. All participating centres will have gained all local site- specific approvals required before commencement of the trial and any patient is recruited.

This is a randomised trial; therefore, neither the participants nor clinicians will be able to choose the timing of the surgical intervention according to personal preference. This is to ensure that the groups of patients receiving either surgery at 6 months or at 12 months are similar.

Informed consent will be obtained from the infant's parent/guardian following ample time to read the Patient Information Sheet and Consent Form, and consult with the cleft team. Families who decline to participate will receive surgery in line with the hospital's current practice and will receive the same level of care and support as families participating in the trial. 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.

To minimise blood sample collection consent will be sought to access results for those patients who have had a routine karyotype and detailed analysis of the chromosome 22q11 region by fluorescent in situ hybridisation (FISH) or other analysis (MPLA or CGH; see 9.1.3.2.). If a routine karyotype is unavailable a blood sample will be collected, with consent from the parent, during anesthesia at the time of surgical repair or during other routine blood sample collection.

12.2 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator will comply with International Conference on Harmonisation Good Clinical Practice guidelines and to the ethical principles that have their origin in the Declaration of Helsinki.

Before parent/guardian(s) are given the full consent form, the surgeon or other designated member of the Team will discuss the nature of the trial, randomisation, trial procedures, the importance of compliance with trial procedures, potential risks and benefits, and the duration of the trial. This may include the use of the drawing on the information sheet to make a simple sketch of cleft repair. The infant's parent/guardian will be told that they do not have to participate and, that treatment will not be compromised if the infant's parent/guardian does not participate or ceases participation at any time.

The parent or legal guardian must then be given ample time to read and understand the form and to ask questions. At least one parent or guardian must be a native language speaker according to the trial inclusion criteria (section 6.1)
The original copy of the Patient Information Sheet and Consent will be retained in the medical notes, copies of the Patient Information Sheet and Consent will be made and one copy of the document will be given to the parents, one will be retained by the Trial Coordinator, a copy of the consent form only will be sent to the Data Coordinating Centre (the consent form will not be sent to the Data Coordinating Centre where country specific regulations prohibit the transfer of the consent form, instead a consent form checklist will be completed by the site and sent to the Data coordinating Centre). The correct randomisation number should be inserted onto the consent form before sent to the Data Coordinating Centre. Consent forms should be sent to the Data Coordinating Centre within 30 days after randomisation.

Where consent is required for additional assessments (for example completion of the ICS questionnaire and access to local speech therapy information), consent should be sought at the earliest opportunity and prior to the assessments taking place. Consent for additional assessments may be sought by post. However, researchers should ensure that the parent/legal guardian is happy with the additional assessments when they next come into the clinic and document this in the patient notes.

13 TRIAL MONITORING

13.1 Risk Assessment

In accordance with the Data Coordinating Centre Standard Operating Procedure this trial has undergone a risk assessment, completed in partnership between the Data Coordinating Centre and the Administrative Centre (supplementary trial specific document #9). In conducting this risk assessment, the contributors considered potential patient, organisational and trial hazards, the likelihood of their occurrence, the resulting impact should they occur and measures that will be taken to manage the risk.

The outcome of the risk assessment is expressed as a percentage, assigned according to the following categories:

Score ≤ 33% = Low risk
Score ≥34 to ≤ 67% = Moderate risk
Score ≥ 68 to ≤ 100% = High risk

The outcome of the trial risk assessment was a score of **21.9%** therefore it has been judged to be a **Low** risk trial. The risk assessment has been used to plan the details of trial management and the approach to, and extent of, monitoring required to be undertaken in the trial.

Trial Oversight committees related to the monitoring of the trial are detailed in section 15.

Trial monitoring will be completed as per the TOPS Trial Monitoring Plan (Supplementary Trial Specific Document #4).

13.2 Source Documents

Each participating site should maintain appropriate medical and research records for this trial, in compliance with International Conference on Harmonisation – E6-Good Clinical Practice guidelines Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants.

Source data will be identified and documented in the TOPS Trial Monitoring Plan (Supplementary Trial Specific Document #4).

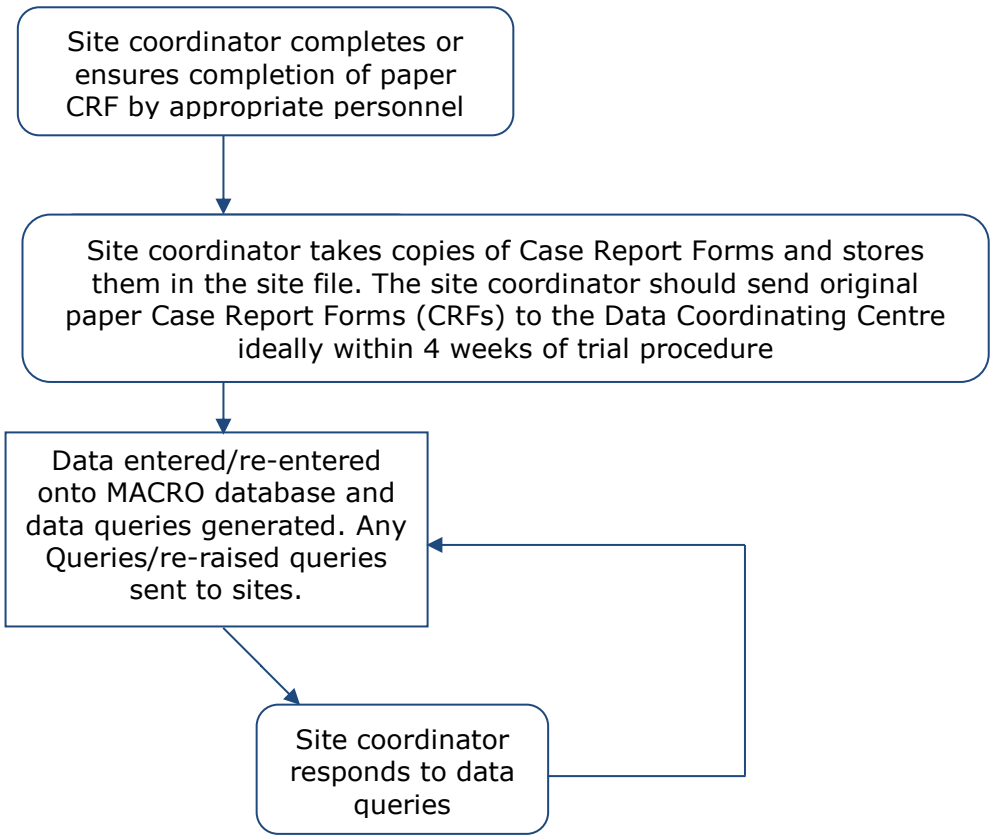
13.3 Data Capture Methods

Data will be recorded onto paper Case Report Forms (CRFs); CRFs are listed on supplementary trial specific document #6. Original Case Report Forms (CRFs) will be posted to the Data Coordinating Centre (DCC) for centralised data entry into MACRO and copies will be held in the site files.
The original Case Report Forms (CRFs) will be stored securely in the Data Coordinating Centre (DCC).

The completed Case Report Forms (CRFs) will be entered onto the MACRO database by the Data Manager or appropriately trained personnel at the Data Coordinating Centre (DCC). The database data entry screen will resemble the paper copy of the Case Report Form. Extensive data validation checks are performed on the data as it is entered, raising discrepancies as necessary.

Where there are issues with the data being entered on the database the DCC Data Manager will generate data query forms and send these to sites. Sites will answer data queries and return the data query forms to the Data Coordinating Centre (DCC). The database stores a full audit trail of all changes to data, reasons for change, username details and timestamps.

Figure 7. Data flow management



13.4 Case Report Forms

The trial Case Report Form (CRF) is the primary data collection instrument for the trial. All data requested on the CRF will be recorded. All missing data will be explained. Not done or not applicable should be completed if a test was not done or was not applicable for that participant. All entries should be printed in block capitals using black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it (figure 8). All such changes must be initialled and dated. Do not erase or white out errors.

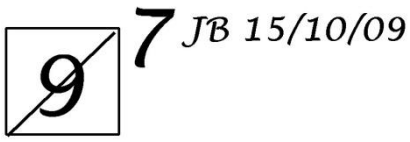


Figure 8. Correction of errors on the Case Report Form

For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Amendments to data recorded on the Case Report Form should always be handled at the local site. If the Chief Investigator or Trial Coordinator believes that an amendment to the data held on the Case Report Form is absolutely necessary they may do so providing that the amendment is agreed in writing and a copy of the amended Case Report Form sent to the local site.

Case Report Form completion guidelines are available in the TOPS Supplementary Study Specific Document #7 – Case Report Form Completion Guidelines.

13.5 Monitoring at Data Coordinating Centre

Full details of the monitoring at the Data Coordinating Centre are given in the Supplementary Trial Specific Document #4 - Trial Monitoring Plan. The main features of the trial monitoring analysis plan are included here.

Source documents will be identified for all of the information collected on to Case Report Forms and will be detailed in the Trial Monitoring Plan. Data collected onto the Case Report Forms should be consistent and verifiable with source data. Source data for each Case Report Form will be identified prior to the intervention phase of the trial for each participating enrollment site. Where no prior record of the data exists (e.g. audiological data collection) the Case Report Form will be the source document.

The Data Coordinating centre will review the dates of informed consent and the provision of patient information. The Data Coordinating Centre will also review recruitment rates, withdrawals and losses to follow up.

All data entered into the MACRO database will be monitored by the Data Coordinating centre and discrepancies queried with the Site Coordinator. In line with GCP requirements, an audit trail will be maintained of what data has been changed, the time of each change, and the person who changed it together with the reason for change.

13.6 Trial Site Monitoring

The Principal Investigator at each trial site will be responsible for assuring compliance to the trial protocol. Principal Investigators will regularly review trial progress with team members and conduct periodic reviews to ensure that trial teams are able to follow the protocol.

On site visits will be conducted throughout the trial, on a site by site basis as triggered by centralised monitoring, to ensure that difficulties in adherence to the study protocol are assessed and that the rights and safety of participants are protected. During these visits, representatives from the Data Coordinating Centre and the Administrative Centre if appropriate, will review a random sample of Case Report Forms and source documents to ensure that the information on the forms is complete and consistent with the source documents and, that missing visits are recorded. The Principal Investigator at each site will ensure that the representatives from the Administrative and Data Coordinating Centres have access to all trial documents and clinical records.

Following each site visit representatives of the Data Coordinating Centre will prepare a monitoring report which will be presented to the Principal Investigator at the site, the Trial Management Group and the National Institute of Dental and Craniofacial Research Programme Official. These reports will be reviewed and a programme of additional guidance or training developed where required.

As Funder, the National Institute of Dental and Craniofacial Research may also audit the trial as necessary.

13.7 Confidentiality

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.

Electronic and paper Case Report Forms will be labelled with unique patient identifier allocated upon randomisation. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. The Data Coordinating Centre will preserve the confidentiality of participants taking part in the trial. The University of Liverpool is a registered data controller with the Information Commissioner's Office (Registration number Z6390975; http://www.ico.gov.uk/), as required by the Data Protection Act 2018 .

13.7.1 Records Retention

The Principal Investigator at each enrolment site must make arrangements to store the essential trial documents, including the Investigator Site File, until notification is received from the Data Coordinating Centre that the records no longer need to be retained. This will be for a maximum period of 15 years. The Principal Investigator must obtain written permission from the Data Coordinating Centre before disposing of any records and should notify the Data Coordinating Centre promptly in the event of accidental loss or destruction of any study records. If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee (e.g. to an alternative Principal Investigator). In addition, the Site Coordinator is responsible for the archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). The Site Coordinator is required to ensure the continued storage of the documents, even if the Principal Investigator, for example, leaves the clinic/hospital or retires before the end of the required storage period. Delegation should be documented in writing.

The Data Coordinating Centre undertakes to store originally completed report forms and separate copies of the above documents for the same period except for source documents pertaining to the individual investigational site, which are kept by the Principal Investigator only.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent/assent forms being supplied to the Data Coordinating Centre by recruiting centres. This requires that the randomisation number be recorded on the consent form. The Data coordinating Centre will preserve the confidentiality of participants taking part in the trial and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

Where country specific regulations prohibit the transfer of the consent form to the Data Coordinating Centre consent will be monitored locally by the Site Coordinator using a consent form checklist; a copy of this completed checklist will be sent by

fax or other agreed method if restrictions at site limit the use of fax to the Data Coordinating Centre. Consent will also be monitored by the Trial TOPS Trial Coordinator at triggered site visits.

13.7.2 Quality Assurance and Quality Control of Data

Quality Assurance (QA) includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. Quality Control (QC) includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. Site visits will be conducted, and source data verification performed, if indicated to be required as a result of central monitoring processes. To this end:

- Coordinated by the Data Coordinating Centre Trial Coordinator, in conjunction with members of the Administrative Centre team, site initiation visits will be performed to enable training of local research personnel;
- The Data Coordinating Centre Trial Coordinator will document the completion of the initiation checklist for each site to verify appropriate approvals are in place prior to initiation of the site;
- The Data Coordinating Centre Trial Coordinator will document, as part of the initiation checklist, that all relevant personnel have undergone trial specific training;
- Data will be centrally monitored by the Data Coordinating Centre Trial Coordinator to check:
    - Adverse Event reporting rates between centres;
    - Screening, recruitment and dropout rates between centres;
    - Data entry consistency. The Trial Coordinator will monitor and follow-up data queries; – Central monitoring reports will thus be generated for the Trial management Group, who will oversee the activity and in accordance with the monitoring plan, will identify when additional intervention, e.g. site visits, should be undertaken – Independent oversight of the trial will be provided by the Data and Safety Monitoring Board and independent members of the Trial Steering Committee.

Details of Quality Assurance and Quality Control are described in supplementary document #34 (“Quality Management Plan”).

14 INDEMNITY

The University of Manchester is acting as 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.

15 TRIAL COMMITTEES

15.1 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 as listed in Supplementary Trial Specific Document #2- Trial Committee Composition. 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.

15.2 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 as detailed in Supplementary Trial Specific Document #2 – Trial Committee Composition.

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. Further details are described in the Trial Steering Committee Terms of Reference (supplementary trial specific document #11).

15.3 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, 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 (further information is provided in the Data and Safety Monitoring Board charter).

The full terms of reference and roles of the Data and Safety Monitoring Board are detailed in the Data and Safety Monitoring Board Charter (Supplementary Trial Specific Document #10 - DSMB Charter).

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.

16 PUBLICATIONS

Following completion of the study, the Chief Investigator is expected to publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry. This trial has been registered with ClinicalTrials.gov, which is sponsored by the National Library of Medicine.

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. All publications shall adhere to the publication policy detailed in Supplementary Trial Specific Document # 5 Publication Policy, and will be submitted, at least 2 weeks prior to submission, for review by all appropriate Trial committees and the National Institute for Dental and Craniofacial Research.

The objectives of the publication policy are:

1. To assure and expedite orderly and timely presentations to the scientific community of all pertinent data resulting from the trial;

2. To assure scientifically accurate presentation and papers from investigators;

3. To assure that all investigators, particularly those of junior rank, have the opportunity to participate and be recognised in the trial-wide presentations and publications;

4. To assure that press releases, interviews, presentations, and publications of trial materials are accurate and do not compromise the scientific integrity of this collaborative trial;

5. To establish procedures that allows the Trial Steering Committee and Data and Safety Monitoring Board to review publications and presentations in a timely manner;

6. To maintain a complete up-to-date list of presentations and publications, and to distribute such lists to all investigators;

7. To clarify and ensure proper acknowledgement of National Institutes of Health and non-National Institutes of Health support of studies and publications.

17 PROTOCOL AMENDMENTS

17.1 Version 1.1 (02-November-2009)

Original approved version.

17.2 Version 2.0 (10-March-2010)

Amendments in v2.0

Page number	Section	Details
Throughout	n/a	Version number, date, formatting, typographical and grammatical errors
Throughout	n/a	References to the Manual of Procedures removed.
3 and 5	Contact details	Contact details amended
7	Glossary	CTIMP, OCP and TOPS added to glossary
8	Protocol summary	Primary objective stated as Insufficient velopharnygeal function at age 5 years
8	Protocol summary	Growth at 12 months added as a secondary outcome Wording of outcome measure 5 amended (postoperative complications)
8,	Protocol summary	Total speech and language intervention at age 3 and 5 years added as a secondary outcome Total speech therapy sessions at age 3 and 5 years added as a secondary outcome
9	Protocol summary	Diagram modified to include "end of follow up"
11	2.1.2	Reference number 12 updated
12, 13,14	2.1.2	Background information and references updated
15	2.2	Table 2: Timing of primary surgery in Umea changed to 6 months
18	4.1	Green light process clarified and includes speech therapist calibration
19	4.1.1 4.1.2	surgical calibration clarified speech calibration clarified
20-21	4.1.2.1	Pilot study added to include a minimum of 1 and a maximum of 5 x practice speech recordings for each age group (10-14 months, 24-28 months, 58-62 months) depending on the experience of the speech therapist
21	4.1.2.2 4.1.2.3	Video recording clarified Transfer of recordings clarified
21	4.1.3	Local research personnel training revised to clarify involvement of the DCC
22	5.2	Growth at 12 months added as a secondary outcome Wording of outcome measure 5 amended (postoperative complications) Total speech and language intervention at age 3 and 5 years added as a secondary outcome Total speech therapy sessions at age 3 and 5 years added as a secondary outcome

23	6.1 6.2	Inclusion criteria updated to One parent/carer a native language speaker of the majority language in the country of residence. Exclusion criteria added: Where the language spoken at home is not the majority language in the country of residence
24	6.3.1	Participant withdrawal paragraph clarified
25	6.3.2	However, more than one visit may be necessary to complete all evaluations. If evaluations are completed on different dates all evaluations should be completed within the timeframes specified below.
26	7.1	Pre-surgical assessment – added "usually at around age 3 months".
26	7.2	"if so randomised"
27	7.3	Randomisation paragraph restructured. Patient id number composition refined to include size of cleft.
28	8.2	Additional information added about the calculation of gestational age
30	9.1.2.2	Details of growth measurements added Stratification statement removed. Extreme anatomical variations clarified
30		
30,31	9.1.3.1 9.1.3.1.1	Title changed to Maxillary Arch Impression and Photographs at Surgery Additional details on transfer of maxillary arch impression transfer and analysis
31	9.1.3.1.2	Details added on photographs to be taken at surgery
32	9.1.4.1	Details of growth measurements added
32	9.1.4.2	Information on speech recording equipment added
33,34	9.1.4.4.1	Detailed instructions on speech sample collection added
34	9.1.4.5	Addition of section on speech sample analysis Addition of figure 4
35	9.1.4.5	Inclusion of information on how to manage parents who need assistance to complete the OM8-30 questionnaire.
36,37	9.1.4.6	Additional detail added on the preparation of dental impressions
37	9.1.4.6	Additional details on transfer of dental impression transfer and analysis
37	9.1.4.8	Includes details of contact with participants using annual birthday cards
38	9.1.4.6	Table 3 amended
40	10.2	Randomisation procedure amended to delete the generation of randomisation lists. Detail of minimisation removed to reduce predictability.
40	10.3	Outcome measures now cross reference section 5.1 and 5.2
40	10.5	Importantly, statistical considerations alone are not adequate to determine the end of the trial
42	10.6	*Canonical babbling at age 12 months* –This outcome, recorded as present or absent,

		Articulation at 3 years and 5 years – Each child will be assessed on how many target sounds they can produce (there will be 30 target sounds for children aged 3 years and 33 for children aged 5 years).
42		*Postoperative/long term complications: infection, wound dehiscence and fistula- (amended in line with secondary outcomes)*
49	11.6.1.2	Adverse Event form A2 referenced Follow-up may continue after completion of protocol assessments if necessary.
54	11.7.2.2 Figure 5	Figure amended
58	13.3	The database data entry screen will resemble the paper copy of the Case Report Form All changes to data entered onto the database Figure 6 amended
60	13.6	DSMB and TSC not to receive reports
61	13.7.1	Records retention - minimum of 15 years
64	15.1	Composition of TMG and method of meetings amended
64	15.2	Method of TSC meetings amended
64	15.3	Method of DSMB meetings amended
67	17.2	Protocol amendments for version 2.0 listed
70-73	18	Reference list updated

17.3 Version 2.1 (6th September 2010)

Page number	Section	Details
Throughout	n/a	Version number, date, formatting, typographical and grammatical errors
20, 27, 56	12.2	Inserted: (the consent form will not be sent to the Data Coordinating Centre where country specific regulations prohibit the transfer of the consent form).
38	Table 3	Corrected to show updated Case Report Form numbers
57	13.1	Risk assessment score amended to reflect risk assessment V2.6 11-08-2010
61	13.7.1	Records retention section updated to correct typographical error (minimum). Records retained for a maximum of 15 years. Clarification of consent monitoring for sites that are unable to send consent form to the Data Coordinating Centre

17.4 Version 3.0 (01-May-2013)

Page number	Section	Details
Throughout	n/a	Version number, date, formatting, typographical and grammatical errors
Throughout	n/a/	Speech and language pathologist amended to speech and language therapist.
Throughout	n/a	Participant ID amended to randomisation number
3	Contact Details	Data Coordinating Centre fax number updated to 00 44 (0)151-282-4721. Details of Committee members have been removed and are now detailed in the supplementary study specific document.
3		Reduced number of entries in "Contact Details": now, only the most essential are listed, while a complete list will be updated as part of the Supplementary Trial Specific Document "#2 – Trial Committees"; also, address details corrected for AC
7	Protocol summary	Removal of reference to OM8-30
8	Schematic of Trial Design	Removed all references/boxes to 2 and 4 year phone call follow up visit.
14	Table 2	Title amended to reflect date data collected
18	4.1.2	Reference to hearing calibration removed. Hearing assessments are in line with standard practice.
19	4.1.2.1	For practice speech recordings added "to ensure that they are familiar with the prescribed standardised approach and that recordings are suitable (in quality and content) for analysis (section 9.1.4)." Insertion of "instead the site coordinator will complete a consent form checklist and send a copy of this to the Data Coordinating Centre)" to specify the procedure for sending the PISC checklist. Where is specified that consent form or consent checklist will be sent to Data Coordination Centre by fax the following was added: "or other agreed method". Amended the age range for children attending for calibration recordings Amended that infants recorded for calibration purposes should ideally be with cleft palate, but this is not essential.

20	4.1.2.3	Included information on the transfer of digital recordings and reference to supplementary document number 27.
20	4.1.3	Updated to reflect documentation of site visit on site initiation visit report. Removal of reference to No Carbon copy of CRFs and change of instruction to centralise data entry to DCC. Also removal of instruction to transfer audio, video etc data via MACRO to posting it using double encrypted USB devices, or other agreed method.
22	5.2	Removal of reference to OM8-30
23	6.2	Exclusion criteria clarified to "structural" middle ear anomalies Exclusion criteria for "A known associated syndrome or severe developmental delay" has been changed to "Infants with syndromic cleft palate (except Van der Woude syndrome, which can be included if hearing is not affected) or severe developmental delay"
24	6.3.1.1.	Removal of withdrawal reasons: "The patient's status changes so that surgery must be postponed indefinitely" and "Inability to attend follow up visits".
24	6.3.1.2	Section added to detail the exclusion of participants with a syndrome or severe developmental delay post randomisation.
25	6.3.2	Clarifying that contact details from families will be maintained according to local policies.
26	7.2	Screening log update to include data on uptake of consent Addition of information on the use of the patient tracking log
27	7.2	Addition of procedure for completing and sending of consent checklist. Addition of information on scheduling the clinical genetics assessment.
28	7.3	Randomisation system web link updated.
28	7.3.1	Addition of back up randomisation envelopes for Bauru
29	8.1	References updated.
31	9.1.2.2	Change of reference to the inclusion/exclusion section 6 instead of 5.
31	9.1.2.2	Inclusion of crown heel length, weight and OFC with genetics assessment.
32	9.1.2.3	Inclusion of crown heel length, weight and OFC with genetics assessment.
32	9.1.3	Addition of text to clarify that soon after the screening visit, completion of the clinical genetics assessment and confirmation of eligibility, consented infants will be randomised.
33	9.1.3.1.1	Clarification of details recorded on a copy of maxillary arch impression. Participant date of birth removed. Deletion of specific brand of 3D scanner and replacing wording with generic description.
34	9.1.4.1	Removal of reference to section 9.1.4.3.
35	9.1.4.3	Clarification on the timing of the DENVERII developmental assessment (screening and 3 years).

35 36	9.1.4.4.1 9.1.4.4.1	Clarification on how to operate the camera. Amendment of the speech assessment material to read "The speech assessment material will consist of age appropriate tests that are described in supplementary document #17 for 3 year assessment and supplementary document #18 for 5 year assessment".
38	9.1.4.6	The OM8-30 will no longer be used as a data collection tool due to issues with the analysis of the data and the inability to resolve with the authors of the questionnaire. Section describing OM8-30 deleted.
38	9.1.4.7	Amended procedure for sending photographs to Data Coordinating Centre.
39	9.1.4.7 9.1.4.8	Deletion of specific brand of 3D scanner and replacing wording with generic description. 2-4 year follow up of late complications and AEs removed. Complete removal of this section so no phone follow up at all. Therefore section 9.1.4.9 Annual Birthday Cards, becomes section 9.1.4.8. Sending of birthday cards to participants has been made optional.
40	Table 3	Table updated to reflect current CRF numbers ,addition of patient tracking log, removal of L1: patient locator information removal of OM8-30, and complete removal of 2 and 4 year phone follow up. C2 form has moved from screening to surgical visit.
41	9.2	Amended definition of Trial Closure.
43	10.5	Updated web link for NIDCR DSMB guidelines.
44 45	10.6 10.6	Amended reference to supplementary trial specific document from #7 to #8. Removal of reference to OM8-30 in Audiological assessment. Update of information on analysis of audiology outcomes and inclusion of information on growth outcomes: "*Growth at 12 months* - nude weight, crown-heel length, occipitofrontal circumference will be compared between the two groups using the difference in values and presented with 95% confidence interval." "*Audiological assessment* – Audiometry (12 months), Pure tone audiometry (3 years, 5 years), and typanometry (12 months, 3 years, 5 years) outcomes will be listed by patient and appropriately summarised by surgical timing group"

46	11.1	Addition of: 'and due to social factors, such as parental anxiety which did not result in any intervention'
50	11.6.1	Timing of reporting of events amended to 30 days postoperatively Insertion of reference to an Adverse Event reporting flowchart, Figure 6, Section 11.6.2.2
50,51,52	11.6.1.1 11.6.1.2	Amended where AEs are recorded (now captured on Form 2 surgery and post op care and form 3 late post op complications) and the timing of reporting defined to during surgery and 30 days postoperatively Timing of SAE assessment amended to 30 days postoperatively. Addition of: SAE will be recorded on A1 form. Addition of: Serious Adverse Events should also be assessed using the definition of an unanticipated problem. and reported on form U1.
50	11.6.1.1	Clarification that any other complications will be recorded if related to surgery. Addition of: 'Wound dehiscence should also be reported as Serious Adverse Event in cases where complete or major rapture of the muscle occurred and full repair is required'
51	11.6.1.1	Timing of submitting of data on CRFs to DCC changed from 1 week to 4 weeks.
52,53 53	11.6.1.3 11.6.2	UPRs now collected on U1 form for the duration of the trial. Insertion of..."All SAE and expedited UPR reports will also be copied by the DCC and sent to NIDCR's centralised safety system at rho_productsafety@rhoworld.com"..."These reports will then be forwarded to and revised by the NIDCR Medical Monitor".
54	11.6.2.1 11.6.2.2	Amendment of the safety reporting numbers and e-mail for NIDCR.
54	11.6.2.2	Updated to include process of medical monitor review
55	Figure 6	Amended to reflect updated CRF numbers and amended contact details.
57	12.2	Insertion of reference to consent form checklist being sent to DCC where country specific regulations prohibit the transfer of the consent form. Insertion of "… randomisation number should be inserted onto the consent form before being sent to DCC. Consent forms should ideally be sent to DCC within 30 days after randomisation".

58	13.1	Amendment of reference to supplementary trial specific document #8 to read #9 and to reference to Trial Oversight Committee related to monitoring to read ....”detailed in section 15”.
59	13.3	Data Capture Methods have been amended to reflect the centralised data entry in Data Coordinating Centre into MACRO database. Figure 7 data management flow also amended as above.
60	13.4	Removal of No Carbon required references. Addition of reference to supplementary trial specific document # 7 - Case Report Form Completion Guidelines
61	13.6	Amendment to site visits stating “…site visits will be conducted throughout the trial on a site by site basis as triggered by centralised monitoring….”
62	13.7	Deleted ‘CRFs labeled with participant’s initials and date of birth’
62,63	13.7.1	Inserted “using a consent form checklist; a copy of this completed checklist will be sent by fax or other agreed method if restrictions at site limit the use of fax to the Data Coordinating Centre” to clarify the process of monitoring consent in countries where transfer of the consent forms themselves to the DCC are prohibited. “Routine site visits” was amended to “triggered site visits”.
67	15.3	Inserted “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.” Amended the Supplementary Trial Specific Document number to #10 – DSMB Charter.

17.5 Version 4.0 (26-August-2015)

Page number	Section	Details
Throughout	n/a	Version number, date, formatting, typographical and grammatical errors.
Throughout	n/a	References to supplementary trial specific documents entered (as appropriate).
1	n/a	Insertion of sign-off line for trial statistician.
3	Contact Details	Name of Data Coordinating Centre, and address of Administrative Centre updated.
6	Glossary	Addition of abbreviation ICS (Intelligibility in Context Scale questionnaire); see 9.1.4.4. and 9.1.4.5.3
7/8	1	Changed Secondary outcomes No. 2 and No. 3 (“Insufficient velopharyngeal function at age 3 years” / “Velopharyngeal composite score summary at age 3 years and 5 years”) to “Velopharyngeal composite

		score summary at age 5 years" / "Insufficient velopharyngeal function at age 3 years", as advised by the lead speech and language therapists (Core Speech Group) because VPC-sum was recently found not to be reliable with 3-year olds. Also, addition of details to secondary outcomes No. 3-8, including replacement of outcome No. 4 ("Articulation at age 3 years and 5 years") with two separate outcomes "Articulation at age 3 years" and "Articulation at age 5 years" (now outcome No. 4 and 5, both with added details), and replacing "Audiological assessment (audiometry and tympanometry)" with two separate outcomes, now No. 7 and No. 8 ("Hearing level" / "Middle Ear Function"); also deleting the two outcomes "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.
11-13	2.1.2	Insertion of recent publications, correction of wording describing background literature, and clarification of recent background literature.
19	4.1.2	Clarification of details of calibration of assessments.
20/21	4.1.2.1	Clarification that the consent forms should be signed by the parents/guardians and by the researcher taking consent. In Sweden only dates of consent signatures between parents and re-searchers can vary as agreed at the beginning of the trial.
21	4.1.2.3	Clarification that sites should ensure that they maintain their own copies of recordings before sending recordings to Data Coordinating Centre; insertion of mention of procedures for quality checking speech recordings.
22	4.1.2.4	Addition of details for quality assessments.
23	5.1	Update of details regarding primary outcome, and correction of process and timelines for analysis of data; deletion of interim analysis.
23/24	5.2	Changed Secondary outcomes; see above, as change in section 1 (Protocol summary).
26/27	6.3.1	Clarification of procedures for withdrawal of patients.
27	6.3.2	Amendment of wording to describe aims for scheduling follow-up visits.
27	6.3.3	Introduction of new Case Report Form #15 for transfers of Participant from one TOPS clinical site to another TOPS clinical site.
29	7.2	Clarification that the consent forms should be signed by the parents/guardians and by the researcher taking consent. In Sweden only dates of consent signatures between parents and re-searchers can vary as agreed at the beginning of the trial.
29	7.2	Clarification inserted of when changes in TOPS procedures will require re-consent of the participant(s).
31	7.3.1	Removal of section "7.3.1 – Back up randomisation envelopes (Brazil only)", because this procedure is no longer in use and no longer required.

35	9.1.3	Clarification inserted that if children are late or very late to receive their surgery, they will remain in the trial according to the principle of "intention to treat".
36	9.1.3.1	Insertion of new section on recording additional surgeries: Details of additional surgeries relating to palate repair are recorded on a dedicated Case Report Form (#12), to capture reasons for the secondary surgery and methods of re-repair, if applicable.
36	9.1.3.2.1	(former 9.1.3.1.1) Correction of procedural detail regarding labelling of maxillary arch impressions prior to sending to Administrative Centre: impressions are not to be labelled with local ID number (such as NHS number), but with trial specific randomisation number and the date the model was collected.
36	9.1.3.2.1	(former 9.1.3.1.1) Correction of procedural detail regarding sending of maxillary arch impressions: these are no longer to be batched in pairs.
36	9.1.3.2.1	(former 9.1.3.1.1) Insertion of time for sending maxillary arch impressions to the Administrative Centre, defined as 6 weeks after surgery.
36	9.1.3.2.1	(former 9.1.3.1.1) Insertion of details of communication process between sites, AC and DCC, regarding receipt of Maxillary arch impressions. In particular, addition of fact that the T1 forms are faxed to the Data Coordinating Centre on the day of receipt.
37	9.1.3.2.2	(former 9.1.3.1.2) Insertion of description of procedure regarding photographs taken at surgery: Photographs should be transferred to the Data Coordinating Centre using an encrypted USB drive.
38	9.1.4	Insertion of new Table 3, clarifying the expected visit windows for follow-up visits.
38	9.1.4	Explanation of what happens if surgery is delayed and up to what point the speech recordings and other appointments are followed up until if an appropriate protocol window was missed. Insertion of new table (now Table 4) to show details.
39	9.1.4.1	Insertion of clarification that 12-month visit dates are corrected for gestational age.
39	9.1.4.2	Addition of details on 12-month Speech Assessments.
40	9.1.4.3	Clarification of method to determine date of visits: Insertion of sentence "Visits at age three and five should be scheduled based on the child's date of birth i.e. without correction for gestational age."
40	9.1.4.4	Clarification of the fact that, in parallel to video speech recordings, backup audio will be recorded by means of a digital audio recorder.
40	9.1.4.4	Clarification of the fact that no return visit is required at 3 and 5 years if the video fails providing that the back-up audio recording is available.
41	9.1.4.4	Addition of new questionnaire (Intelligibility in Context Scale (ICS) questionnaire), which is for parents to be completed; insertion of wording "As part of the 5 year assessments, the Intelligibility in

		Context Scale (ICS) questionnaire will be given to the parents to complete. The data gathered with this questionnaire will be used to estimate the degree to which children's speech is understood by different listeners."
41	9.1.4.4	Addition of nasalance assessments using nasometer; insertion of wording "In addition, at the 5 year assessments, nasality in speech production (nasalance) will be determined using NasometerTM II (Model 6450, KayPENTAX) instruments at all trial sites. The outcomes of nasalance readings will be recorded on Form 13 (5 Year Speech Assessment) and will be submitted to the Data Coordinating Centre, while the nasality recordings are to be kept at the clinical site."
41	Figure 3	Figure re-designed, to clarify the setup.
41-42	9.1.4.5	Addition of details regarding editing and analysis of speech recordings.
42	9.1.4.5	Clarification of the choice of speech therapists participating on analysis of speech recordings: while for recordings of 12 month old children, the language of the analysing speech and language therapist does not have influence on the outcome of analysis, for recordings of 3-year and 5-year old children, it is essential that the first language of the speech and language therapist analysing the speech samples is the same as the child's.
43	9.1.4.5	Update of Figure 4.
43/44	9.1.4.5.1	Insertion of description of assessment and analysis of velopharyngeal function, including VPC-sum.
44	9.1.4.5.1	Insertion of new table 5, showing transfer rules for VPC-sum.
45	9.1.4.6	Correction of wording describing standardisation of audiological tests, stating "Standardised protocols for the audiological tests will be documented."
45	9.1.4.7	Addition of detail to procedure of taking photographs at the 5 year assessments: description now reads "The background will be blue."
46	9.1.4.7	Correction of procedure regarding labelling of Dental impressions prior to sending to Administrative Centre: date of birth of the participant is not to be included in the label of the impressions.
46	9.1.4.7	Correction of procedural detail regarding sending of maxillary arch impressions: these are no longer to be batched in pairs.
46	9.1.4.7	Insertion of time for sending dental impressions at 5 years to the Administrative Centre, defined as 6 weeks after the 5-year visit.
46	9.1.4.7	Correction of notification procedure regarding dental impressions: the T1 forms are faxed to the Data Coordinating Centre on the day of receipt.
47	9.1.4.8	New section 9.1.4.8 on data collection from local Speech and Language therapists, including information on use of new supplementary PISC.
48	Table 3 (now Table 6)	Updated table 3 (now Table 6), which has been renamed Table 6, now to include Case Report Forms

		(CRFs) #12 and #15, and Intelligibility in Context Scale (ICS) questionnaire; also corrected CRF numbers (original #12 to #13; #13 to #14), and the order of CRFs to improve clarity; deletion of superfluous row regarding form T2, as this is listed further below in the same table.
49	9.2	Correction of description of procedure for database lock.
50	10.4	Deletion of paragraph on interim analysis, as this no longer applies.
50/51	10.5	Deletion of paragraph on interim analysis, as this no longer applies.
52	10.6	Correction and clarification regarding analysis of primary and secondary outcome measures; details of statistical analysis are described in the separate TOPS Statistical Analysis Plan document (supplementary trial specific document #8).
56	11.4	Updating of table number; now Table 7.
61	11.6.2.2	Removal of statement that details of Serious Adverse Event throughout the trial will be distributed to all Site Investigators.
64	12.2	Addition of provisions for supplementary consent form (see new section 9.1.4.8).
66	13.3	Correction of data capture methods regarding use of MACRO, data queries and tracking of database changes.
66	Figure 7	Correction of Figure 7 ("Data flow management") according to change in section 13.3
71	14	Clarification of the trial sponsorship situation: The University of Manchester is acting as sole sponsor for the TOPS trial. In this section, two paragraphs clarifying the legal situation were inserted, replacing a series of paragraphs which are not applicable to 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."
87-91	18	Correction and addition of publications cited.

17.6 Version 5.0 (22-August-2018)

Page number	Section	Details
Throughout	n/a	Version number, date, formatting, typographical and grammatical errors.
3	Contact details	Gallya Gannot has replaced Jane Atkinson as funder representative
3	Contact details	Kevin McBryde has replaced Holli Hamilton as medical monitor
3	Contact details	Data Coordinating Centre fax number has changed from +44 (0) 151 282-4721 to +44 (0) 151 795 8770
7	Objectives	1. Velopharyngeal function at age 5 years broken down into 2 parts; a. Velopharyngeal composite score summary (VPC sum) b. Insufficient velopharyngeal function (VPC rate)
7	Objectives	2. Velopharyngeal function at age 3 years broken down into two parts: a. Velopharyngeal composite score summary (VPC sum) b. Velopharyngeal insufficiency symptoms;
8	Objectives	e. Oral consonant errors added under point 4. Articulation at 3 years
8	Objectives	b. Percent correct placement (PCP) and c. Percent correct manner (PCM) added under point 5. Articulation at age 5 years
23	5.2 Secondary Endpoints	1. Velopharyngeal function at age 5 years broken down into 2 parts; a. Velopharyngeal composite score summary (VPC sum); superscript a, b added b. Insufficient velopharyngeal function (VPC rate); superscript d added
23	5.2 Secondary Endpoints	2. Velopharyngeal function at age 3 years broken down into two parts: a. Velopharyngeal composite score summary (VPC sum); superscript c added b. Velopharyngeal insufficiency symptoms; superscript a added
23	5.2 Secondary Endpoints	3. Canonical babbling at age 12 months: a. Canonical babbling present; superscript e added b. Canonical babbling ratio; superscript e added c. Consonant inventory; superscript e added
23	5.2 Secondary Endpoints	4. Articulation at age 3 years: a. Percent consonants correct (PCC); superscript a added b. Percent correct placement (PCP); superscript a added c. Percent correct manner (PCM); superscript a added

		d. Non-oral consonant errors; superscript a added e. Oral consonant errors added; superscript a added
23	5.2 Secondary Endpoints	5. Articulation at age 5 years: a. Percent consonants correct (PCC) added b. Percent correct placement (PCP) added
23 & 24	5.2 Secondary Endpoints (throughout)	Numbers listing secondary end points updated
24	5.2 Secondary Endpoints	Sources of secondary speech endpoints added (superscript letters explained): a Pictures b 9 word string c Spontaneous speech d Spontaneous speech (retelling of bus story) e Video of play interaction
59	11.6.1.2 Serious Adverse Events	DCC Fax Number changed from 00 44 (0) 151 282 472100 to 44 (0) 151 795 8770
69	13.7 Confidentiality	Data Protection Act 1998 changed to Data Protection Act 2018

17.7 Version 6.0 (31-March-2020)

Page number	Section	Details
Throughout	n/a	Version number, date, formatting, typographical and grammatical errors. MCRN CTU now Liverpool Clinical Trials Centre; logo change on front cover
1	Signatures	The main CI has changed from Professor Bill Shaw to three CO-CIs: Kevin Munro (Main), Tanya Walsh and Bill Shaw. 'Trial statistcian' changed to 'Lead statistician'. Details updated to reflect this.
3	Contact details	MCRN CTU now Liverpool Clinical Trials Centre, all associated parties' addresses changed in contact details table
3	Contact details	Dena Fischer has replaced Gallya Gannot as funder representative National Institute of Dental and Craniofacial Research National Institutes of Health Email : dena.fischer@nih.gov
7	Protocol Summary; Population	Error on sample size: should be 648. ~~650~~
23	5.1 Primary Endpoint	Typo in VPC-sum corrected. "is an overall score on the scale ~~1~~0-6." see Table 5, all components can equal 0, 0+0+0=0 is possible
24	Sources of secondary speech endpoints	Source of secondary endpoints d changed from Spontaneous speech (retelling of bus story) to Spontaneous speech / retelling of bus story as this better reflects that the assessment can be

		a combination of the 2 depending on the number of syllables etc.
38	9.1.4 Table 3	Typo corrected; infants who have had surgery at 6 months have a visit ~~26~~ 52 weeks from birth
41	9.1.4.5 Speech sample analysis	changed from: In the case of the 3 year and 5 year assessments, the first language of the speech and language therapist analysing the speech samples needs to be the same as the child's, while for the analysis of 12-month recordings, this is not required. To: In the case of the 3 year and 5 year assessments, *with the exception of hypernasality,* the first language of the speech and language therapist analysing the speech samples needs to be the same as the child's, while for the analysis of 12-month recordings, this is not required.
43	Figure 4 Pathway of speech sample (audio and video) collection and analysis.	"Analysis transcribed in detail onto Case Report Form" changed to "Speech assessment analysed in bespoke software with output files used for statistical analysis" to reflect that What comes out of SPEAK and Timestamper does not go directly on to a CRF

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