SUPPLEMENTARY APPENDIX

Supplement to: Timing Of Primary Surgery (TOPS) For Cleft Palate Repair

This appendix has been provided by the authors to give readers additional information about the work. A full and comprehensive Statistical Analysis Plan is available at NEJM.org detailing the requirements and process for the analysis of the speech and language recordings, additional information on criteria for the attainment of an outcome, and the statistical analyses.

Contents

[S1. TOPS Study Group 4](#_Toc142924427)

[S2. Eligibility Criteria 7](#_Toc142924428)

[a. Inclusion Criteria 7](#_Toc142924429)

[b. Exclusion Criteria 7](#_Toc142924430)

[S3. Data Collection 8](#_Toc142924431)

[a. Speech Recordings 8](#_Toc142924432)

[b. Photographs 8](#_Toc142924433)

[c. Impressions 8](#_Toc142924434)

[d. Software for Speech Outcome Assessment 8](#_Toc142924435)

[S4. Details of Endpoint Measurement and Classification 9](#_Toc142924436)

[a. Primary Outcome 9](#_Toc142924437)

[b. Secondary Outcomes 9](#_Toc142924438)

[S5. Timing and Objectives of Interim Analyses 11](#_Toc142924439)

[a. Interim Monitoring and Analyses 11](#_Toc142924440)

[b. Interim Analysis at the End of the Initial Funding Period 12](#_Toc142924441)

[S6. Summary of Analyses 12](#_Toc142924442)

[a. Study Population 12](#_Toc142924443)

[b. Compliance 12](#_Toc142924444)

[c. Withdrawals 13](#_Toc142924445)

[d. Data Completion and Missing Data 13](#_Toc142924446)

[e. Details of Additional and Exploratory Analysis of Primary Outcome 13](#_Toc142924447)

[Adjusted Results 13](#_Toc142924448)

[Results by Country 13](#_Toc142924449)

[Multiple Imputation 13](#_Toc142924450)

[Composite Estimand 13](#_Toc142924451)

[f. Safety Evaluations 14](#_Toc142924452)

[g. Resource Use 14](#_Toc142924453)

[Secondary Surgery 14](#_Toc142924454)

[SLT Intervention 14](#_Toc142924455)

[S7. Elaboration of Results 15](#_Toc142924456)

[a. Participant Flow 15](#_Toc142924457)

[b. Compliance 15](#_Toc142924458)

[c. Withdrawals 15](#_Toc142924459)

[d. Data Completeness and Missing data 16](#_Toc142924460)

[e. Safety 16](#_Toc142924461)

[f. Secondary Surgeries 16](#_Toc142924462)

[S8. Data Sharing Statement 17](#_Toc142924463)

[S9. Supplementary Figures 18](#_Toc142924464)

[Figure S 1: Participant Flow Diagram 18](#_Toc142924465)

[Figure S 2: Forest Plot of Insufficient Velopharyngeal Function at 5 Years by Country 19](#_Toc142924466)

[S10. Supplementary Tables 20](#_Toc142924467)

[Table S 1: Representativeness of Study Participants 20](#_Toc142924468)

[Table S 2: Schedule of Assessments 21](#_Toc142924469)

[Table S 3 Summary of Speech Recording Types by Time Point 22](#_Toc142924470)

[Table S 4 Specification of VPC Sum Scoring Components 22](#_Toc142924471)

[Table S 5: Classifying Severity in Better Ear 22](#_Toc142924472)

[Table S 6: Description of Speech End Points by Recording Type 23](#_Toc142924473)

[Table S 7: Description of Hearing and Middle Ear Function Endpoints 25](#_Toc142924474)

[Table S 8: Description of Dentofacial Development Endpoints 26](#_Toc142924475)

[Table S 9: Reasons for Ineligibility 27](#_Toc142924476)

[Table S 10: Reasons for Consent Not Provided 28](#_Toc142924477)

[Table S 11: Compliance with Allocated Timing 28](#_Toc142924478)

[Table S 12: Reasons for Surgery Outside of Allocated Window 29](#_Toc142924479)

[Table S 13: Compliance with Treatment: Days Deviated from Allocated Window 30](#_Toc142924480)

[Table S 14: Withdrawals 31](#_Toc142924481)

[Table S 15: Other Reasons for Withdrawal 32](#_Toc142924482)

[Table S 16: Outcome Completion Summary 33](#_Toc142924483)

[Table S 17: Demographic Characteristics Categorized by Primary Outcome Status (Observed or Missing) 36](#_Toc142924484)

[Table S 18: Clinical Characteristics Categorized by Primary Outcome Status (Observed or Missing) 37](#_Toc142924485)

[Table S 19: Adjusted and Unadjusted Odds Ratios for Primary Endpoint 38](#_Toc142924486)

[Table S 20: Insufficient Velopharyngeal Function at 5 Years by Country 38](#_Toc142924487)

[Table S 21: Intra-operative and Early Post-operative Events 39](#_Toc142924488)

[Table S 22: Observations Monitored 48 Hours Post-surgery 40](#_Toc142924489)

[Table S 23: Late Complications (from discharge up to 30 days post-operatively) 41](#_Toc142924490)

[Table S 24: Listing of Serious Adverse Events 42](#_Toc142924491)

[Table S 25: Listing of Unanticipated Problems Submitted 43](#_Toc142924492)

[Table S 26: Summary of Secondary Surgeries 44](#_Toc142924493)

[Table S 27: 'Other' Reasons Provided for Secondary Surgery 44](#_Toc142924494)

[Table S 28: Speech Therapy Received up to 1 Year Visit 45](#_Toc142924495)

[Table S 29: Speech Therapy Received up to 3 Year Visit 46](#_Toc142924496)

[Table S 30: Speech Therapy Received up to 5 Year Visit 48](#_Toc142924497)

[S11 References 50](#_Toc142924498)

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# S2. Eligibility Criteria

## 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.

## 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);

f. Where the language spoken at home is not the majority language in the country

of residence.

# S3. Data Collection

Data for TOPS comprised of clinical data collected by sites using case report forms, speech recordings (audio and video), photographs, and impressions. The schedule of assessments is provided in Table S 2.

## Speech Recordings

The types of speech recordings taken by timepoint, and used for outcome assessment, are summarized in Table S 3. Audio files may be used instead of video where video is not available.

## Photographs

Photographs were taken at surgery and at 5 years of age for each child in the study.

Photographs of the child’s unrepaired palate taken at surgery do not contribute to any outcome.

Photographs of the child’s face profile included frontal and right/left lateral. The left lateral photograph was used to measure dentofacial development. If the left was not provided or failed quality checks but the right lateral photograph was provided and passed quality checks, the right photograph was used.

## Impressions

Impressions were taken at surgery and at 5 years of age for each child in the study.

At surgery, a maxillary arch impression was taken. This impression does not contribute to any outcome.

At five years, dental impressions were taken and used to calculate the Maxillary arch constriction score.

## Software for Speech Outcome Assessment

As part of the trial, bespoke software was developed to facilitate speech outcome assessment by Speech and Language Therapists (SLTs) in the TOPS trial:

* TimeStamper for recordings taken at 1year
* SPEAK for recordings taken at 3 and 5 years. SPEAK software versions are developed for age specific assessment.

The Statistical Analysis Plan (see NEJM.org and *Conroy 2021*) gives details on the use of the software across assessors to determine speech outcomes and examples of the software output.

# S4. Details of Endpoint Measurement and Classification

## Primary Outcome

The primary outcome is defined as a dichotomous outcome of whether the child has been perceived by SLTs, following independent review of speech recordings, to have insufficient velopharyngeal function at age 5 years or not. Velopharyngeal insufficiency (VPI) is measured by the Velopharyngeal Composite Score (VPC sum), which is a sum of scores, based on three components: hypernasality, non-oral errors, and VPI symptoms. The primary outcome is based on recordings of the single word test (Phonetics).

Each component is classified and each classification mapped on to a score (see Table S 4). The sum of the three scores gives the VPC sum on the scale 0–6. Scores ≥ 4 on this scale are considered insufficient.

## Secondary Outcomes

***1. Velopharyngeal function at age five years:***

*a. Velopharyngeal composite score summary (VPC sum)*: ordinal outcome measured on a scale of 0-6. Each child attempts a minimum of 18 and a maximum of 36 predetermined target consonants (in words).

*b. Insufficient velopharyngeal function (VPC rate):* a dichotomous outcome of whether the child has “insufficient” VPC rate.

***2. Velopharyngeal function at age three years:***

*a. VPC rate:* a dichotomous outcome of whether the child has “insufficient” VPC rate.

*b. Velopharyngeal insufficiency symptoms:* a bounded continuous outcome, the percentage of times that a target consonant uttered has a VPI symptom. Each child attempts a minimum of 15 and a maximum of 30 predetermined target consonants (in words).

***3. Canonical babbling at age twelve months:***

*a. Canonical babbling present:* a dichotomous outcome of whether the child is “canonical” or “not canonical”.

*b. Canonical babbling ratio:* a bounded continuous outcome, the proportion of times that a syllable produced is “canonical”. Determined as the average proportion from the three SLTs undertaking independent review.

*c. Consonant inventory:* a continuous outcome of the number of unique consonants, identified by at least two of three SLTs undertaking independent review, uttered by a child.

***4. Articulation at age three years:***Each child is required to have attempted a minimum of 15 and a maximum of 30 predetermined target consonants (in words) for articulation assessment.

*a. Percent consonants correct (PCC):* a bounded continuous outcome, the percentage of times that a target consonant is uttered correct.

*b. Percent correct placement (PCP):* a bounded continuous outcome, the percentage of times that a target consonant has the correct place of articulation.

*c. Percent correct manner (PCM):* a bounded continuous outcome, the percentage of times that a target consonant has the correct manner of articulation.

*d. Non-oral consonant errors:* a bounded continuous outcome, the percentage of times that a target consonant is realized as a non-oral error.

*e. Oral consonant errors:* a bounded continuous outcome, the percentage of times that a target consonant is realized as an oral error.

*5.* ***Articulation at age five years:***Each child is required to have attempted a minimum of 18 and a maximum of 36 predetermined target consonants (in words).

*a. PCC:* a bounded continuous outcome, the percentage of times that a target consonant is uttered correct.

*b. PCP:* a bounded continuous outcome, the percentage of times that a target consonant has the correct place of articulation.

*c. PCM:* a bounded continuous outcome, the percentage of times that a target consonant has the correct manner of articulation.

*d. Non-oral consonant errors:* a bounded continuous outcome, the percentage of times that a target consonant is realized as a non-oral error.

*e. Oral consonant errors:* a bounded continuous outcome, the percentage of times that a target consonant is realized as an oral error.

*6****. Postoperative/long-term complications:***

*a. Dehiscence:* a dichotomous outcome of whether the child has a postoperative dehiscence, measured 48 hours and 30 days postoperatively.

*b. Infection:* a dichotomous outcome of whether the child has a postoperative infection, measured 48 hours and 30 days postoperatively.

*c. Evidence of fistula:* a dichotomous outcome of whether the child has a postoperative fistula, assessed as “Yes” or “Probably”, measured 30 days postoperatively and at three and five years of age*.*

*7****. Hearing level****:*

*a. At twelve months:*

*i. Abnormal Transient Otoacoustic Emission (TEOAE):* a dichotomous outcome of whether the child has abnormal TEOAE.

*ii. Abnormal sound field audiometry:* a dichotomous outcome of whether the child has abnormal sound field audiometry. Abnormal sound field audiometry is indicated by a measurement of >30 dB HL for at least one of four frequencies tested: 500 Hz, 1000 Hz, 2000 Hz or 4000 Hz.

*b. At three and five years:*

*i. Abnormal pure tone audiometry in at least one ear:* a dichotomous outcome of whether the child has abnormal pure tone audiometry. If testing by pure tone audiometry is not possible, sound field audiometry can be used in its place. Abnormal audiometry in at least one ear is indicated by a measurement of >20 dB HL using the pure tone method, >25 dB HL for sound field, for at least one of four frequencies tested: 500 Hz, 1000 Hz, 2000 Hz or 4000 Hz.

*ii. Abnormal pure tone audiometry in both ears:* a dichotomous outcome defined in the same way as Secondary Outcome 7bi, for participants who have both ears tested and both tested ears indicate abnormal audiometry.

*iii. Severity of better ear:* a short ordinal outcome of the severity of the better ear. If testing by pure tone audiometry is not possible, sound field audiometry can be used in its place. Each participant will be classified according to the average score in the better ear (see Table S 5) if pure tone, or both ears if sound field, across the four frequencies (500 Hz, 1000 Hz, 2000 Hz or 4000 Hz) [*British Society of Audiometry, 2011*].

***8. Middle ear function:***

*a. Flat line Tympanogram in at least one ear:* a dichotomous outcome of whether the child has flat line tympanogram, assessed at age twelve months, three and five years. Children with either ear measured as “Type B” will be classified as having flat line tympanogram in at least one ear.

*b. Flat line Tympanogram in both ears:* a dichotomous outcome of whether the child has flat line tympanogram, assessed at age twelve months, three and five years. Children with both ears measured as “Type B” will be classified as having flat line tympanogram in both ears.

***9. Dentofacial development at age five years:***

*a. Soft tissue ANB angle:* a continuous outcome of the angle between soft tissue nasion (points A and B) measured using a profile photograph. *[Bearn, 2002]*

*b. Maxillary arch constriction score:* a bounded continuous outcome, measured using the Huddart/Bodenham scoring system, on a maxilliary and mandibular arches impression. A score can range from -24 to 8 and is measured in whole numbers. *[Martin, 2016; Gray, 2005]*

***10. Growth at twelve months:***

*a. Nude weight:* a continuous outcome, measured in grams and recorded to the nearest whole number.

*b. Crown to heel length:* a continuous outcome, measured in centimeters and recorded to one decimal place.

*c. Occipitofrontal circumference:* a continuous outcome, measured in centimeters and recorded to one decimal place.

Reference summaries of the recordings/materials used are provided in Table S 6 to Table S 8.

# S5. Timing and Objectives of Interim Analyses

Assessment of the primary outcome at 5-years of age was made by a team of calibrated SLTs who attended a central event to analyze the speech recordings. Due to the plans for the event to take place following availability of the last recruited participants recording no formal stopping boundaries were specified within the design.

## Interim Monitoring and Analyses

Details on interim analyses are compatible with those found in Section 10.5 of the TOPS Protocol. The trial was monitored by an independent Data and Safety Monitoring Board (DSMB) which assessed the trial data and additionally considered current world-wide evidence. DSMB members complied with a trial-specific DSMB charter according to the International Conference on Harmonization Good Clinical Practice (ICH GCP) and the National Institute for Dental and Craniofacial Research guidelines.

The initial analysis of trial data for DSMB review was planned, following the completion of 20 surgical procedures, to assess recruitment rates and adverse events (AEs). Timings of subsequent analyses were determined on the basis of recruitment rates and anticipated that these would be approximately every 12 months. The DSMB monitored adherence to the TOPS Protocol and the quality of the accruing data. The DSMB could request additional interim meetings triggered by concern regarding reported serious adverse events (SAEs).

## Interim Analysis at the End of the Initial Funding Period

An interim analysis was planned to coincide with the end of the initial funding period. By this time point 300 participants were expected to have reached the 3-year assessment providing 51% power to detect a reduction in insufficient velopharyngeal function at 3 years from 40% to 29% using a chi-square test with statistical significance at the 0.05 level. The assessment of velopharyngeal function at age 3-years was intended to be a proxy for the primary outcome assessment at age 5 years with the purpose of the interim analysis being to inform the next funding period. This interim analysis was not performed due to the low numbers of infants at the timepoint required (n=142 following a 12-month extension). Despite the interim analysis not being undertaken, trial monitoring and review by the DSMB continued. Following each DSMB meeting, the DSMB made recommendations to the Trial Steering Committee (TSC) as to the continuation of the trial.

Clinical judgment was essential to the process to allow consideration of unexpected safety events and balance issues of safety and efficacy in light of any new external information.

# S6. Summary of Analyses

A full copy of the Statistical Analysis Plan is available at NEJM.org and published summary [*Conroy et al 2021*].

## Study Population

The flow of participants through each stage of the trial, including the number of individuals screened, randomized, receiving treatment as allocated, and included in the primary analysis is summarized within a CONSORT flow chart [*Schulz, 2010*] (Figure S 1)

Figure S 1). Additional tables present frequencies and percentages for:

* Reasons for ineligibility using frequencies and percentage (Table S 9)
* Reasons that parents of otherwise eligible infants provided for their decision to withhold consent to participate (Table S 10).

The comparability of the two randomized groups is presented in terms of:

* Baseline comparability using minimization factors, demographic characteristics and clinical genetics (main manuscript Table 1).
* Surgical comparability using baseline surgery characteristics (main manuscript Table 2)

Binary and categorical data are summarized by frequencies and percentages. Continuous data are presented by means and standard deviations (SDs), or medians and inter-quartile range (IQR). Tests of statistical significance are not undertaken.

## Compliance

Compliance with the randomized allocation is summarized with reasons for departure provided (Table S 11 and Table S 12). Absolute, early, and late deviations are presented with the numbers within each category provided along with means and standard deviations, medians, lower and upper quartiles, the interquartile range and min and max (Table S 13).

## Withdrawals

The timing of participant withdrawal in relation to surgery, level of withdrawal, who made the decision and reason for withdrawal is summarized for each randomized group. Frequencies and percentages are presented and the reasons, where known, provided. (Table S 14 and Table S 15).

## Data Completion and Missing Data

A table summarizing the number of participants with data available for analysis for each outcome is provided by treatment group. Where outcomes required a recording to be available missing data are categorized by whether the recording was taken or excluded due to quality issues. Frequencies and percentages are presented. (Table S 16)

Demographic and clinical characteristics can be seen split by whether the primary outcome was observed or missing. Frequencies and percentages are presented. (Table S 17 and Table S 18).

To further consider the impact of the missing data on the primary outcome a post hoc multiple imputation sensitivity analysis is provided as described in Section 6.e with results in Section 7. d.

## Details of Additional and Exploratory Analysis of Primary Outcome

### Adjusted Results

Results from a multilevel logistic regression model (for insufficient VPC sum) adjusting for operating surgeon, size of cleft at baseline (soft palate only vs. soft and hard palate), randomized group and an intercept are provided to check the robustness of the results to an unadjusted analysis approach. [*Kahan, 2013; Kahan, 2012; Hernandez, 2004, Pocock, 2002*]. Random effect is used for operating surgeon. The results of the adjusted and unadjusted analyses are presented in a table with 95% confidence intervals (Table S 19).

### Results by Country

In addition, a table summarizing insufficient VPC sum by country is provided (Table S 20). A Forest plot of country specific results using output from a logistic regression model including a treatment group and country covariates is provided (Figure S 2).

### Multiple Imputation

To further consider the impact of the missing data on the primary outcome a post hoc multiple imputation sensitivity analysis is provided (see section 7). Multiple imputation assumes a missing at random mechanism, requiring a model for the distribution of missing data given that observed. We undertook multiple imputation by chained equations with logistic regression to obtain a pooled risk ratio using R software version 4.2.0 in which 100 imputations were used across 50 iterations.

Variables considered for model inclusion were: sex (male, female), country (UK, Denmark, Sweden, Norway, Brazil), VPC rate at 5 years (sufficient, insufficient), VPC rate at 3 years (sufficient, insufficient), canonical babbling at 12 months (present, absent), cleft shape (U, V) and grade (1, 2,3, 4). Variables were retained for inclusion in the model where p<0.2 at a univariate level. The risk ratio and 95% confidence intervals are provided.

### Composite Estimand

The treatment policy estimand is used throughout TOPS analyses. This reflects consistency with the TOPS objective to evaluate speech as observed at 5 years regardless of intercurrent events. An alternative estimand is provided, in which children are classed as insufficient, regardless of their sufficiency at 5 years, if a secondary surgery was received for the reason of velopharyngeal insufficiency. A table is presented for secondary surgeries as described in Section g.

The alternative estimand categorizes participants as:

* insufficient velopharyngeal function where participants have:
  + a score of 4-6 on VPC-sum observed at 5 years
  + a secondary surgery due to VPI
* sufficient velopharyngeal function where participants have a score of 0 to 3 observed on the VPC-sum scale and who have not received a secondary surgery

This redefined binary endpoint is reported with the relative risk and 95% CI.

No adjustment is made for the level of SLT intervention provided by the trial site or by local teams. Available data summarizing SLT intervention are described in Section 7.

## Safety Evaluations

Intra operative events, early post-operative events, observations monitored 48 hours post-surgery and late complications defined as being from discharge up to 30 days post-operatively are presented in tables using frequencies and percentages (Table S 21 to Table S 23).

Serious adverse events and unanticipated problems are presented with line listings of events to provide further detail (Table S 24 and Table S 25). Tests of statistical significance are not undertaken.

## Resource Use

Resource use by treatment group is provided in relation to secondary surgeries and SLT intervention. Data regarding episodes or treatments for acute otitis media or use of pressure equalization tubes were not recorded. Statistical testing is not undertaken and resource use is reported using descriptive statistics only.

### Secondary Surgery

Tables for secondary surgery are provided at the participant and surgery level (allowing for multiple surgeries per participant). The reasons for secondary surgery are presented with frequencies and percentages split by treatment group. Age in years at initial secondary surgery is presented using means and standard deviations, min and max. (Table S 26 and Table S 27).

### SLT Intervention

SLT intervention is provided categorized by whether delivery was by the trial site team or by local teams. The available data are summarized by time point by therapy received (direct or indirect), and number of visits with accompanying descriptive statistics for continuous data. (Table S 28 to Table S 30).

# S7. Elaboration of Results

## Participant Flow

Participant flow from assessment of eligibility to inclusion within the primary outcome analysis set is provided in

Figure S 1. Reasons for ineligibility are provided in Table S 9.

Table S 10 summarizes the reasons that parents of eligible infants provided for their decision to withhold consent to participate.

## Compliance

Of the 552 participants in the intention-to-treat population, 31 (5.6%) did not receive surgery.

* 13 (4.7%) participants within the 6 months surgery group;
* 18 (6.6%) participants within the 12 months surgery group.

For participants who did receive surgery, the protocol timeframes were -2 to +4 weeks corrected for gestational age.

Table S 11 provides data on compliance with surgery timing as allocated per group and Table S 12 provides a summary of reasons for surgery conducted outside of the allocated time window. Table S 13 provides data on the extent of the deviations in days. Of the 40 participants in the 12-month group who received surgery outside the timeframe 11 were early deviations and 29 late. In the 6-month group 8 of the 34 deviations were early and 26 late.

## Withdrawals

Table S 14 summarizes information on randomized participants who subsequently withdrew from the study. A total of 6 participants were complete withdrawals from the study meaning that they withdrew permission to include data collected within the analyses. Key differences between the groups included the person(s) leading on the decision to withdraw: the 12-month group had higher proportion of parents/guardians leading the decision to withdraw while in the 6-month group this was more likely to be clinically led. Additional reasons for withdrawal are provided in Table S 15.

Infants with a syndromic cleft palate or severe developmental delay were excluded from the trial as per the study exclusion criteria. However, syndromes or developmental delays could be identified post randomisation.

Of the 552 participants in the intention-to-treat population, 88 (15.9%) participants had a syndrome or severe developmental delay identified post randomisation:

* 44 participants within the 6 months surgery group;
* 44 participants within the 12 months surgery group.

Of the 88, 9 withdrew from the trial ending follow up assessments, and the remainder stayed in the trial and completed assessments were possible.

## Data Completeness and Missing data

Table S 16 summarizes outcome availability.

Levels of missing data within TOPS had been anticipated to be low. Table S 16 to Table S 18 demonstrate comparability between treatment groups with regards to missing data levels and characteristics.

Results for multiple imputation of the primary outcome and VPC rate at 3 and 5 years are provided below.

|  |  |  |
| --- | --- | --- |
| **Outcome identifier** | **Outcome** | **RR [95%CI]** |
| Primary outcome | Velopharyngeal Insufficiency | 0.62 [0.37 to 1.03] p=0.07 |
| Secondary outcome 1b | VPC rate at 5 years | 0.99 [0.56 to 1.75] |
| Secondary outcome 2a | VPC rate at 3 years | 1.27 [0.72 to 2.22] |

## Safety

For intra-operative and early post-operative events, described as events occurring up to 48 hours post- surgery see Table S 21. Table S 22 provides observations monitored 48 hours post-surgery.

Table S 23 provides late complications defined as events occurring up to 30 days post-surgery. Only one type of late complication was reported, secondary bleeding.

Table S 24 provides line listings for Serious Adverse Events. Table S 25 provides line listings of unanticipated problems reported.

There were 5 unanticipated problems reported in 5 participants.

Four serious adverse events were reported within 4 (0.8%) randomized participants who received surgery (N=521). All resolved and all participants continued with follow up in the trial. Of these serious adverse events:

* Three of the four events were experienced by three participants that received surgery at 6 months (N=259).
  + One of the three were classified by the Principal Investigator (PI) as related to the intervention and unexpected. None were classified by the Chief Investigator (CI) as related to the intervention and unexpected.
  + None of the three were classified as an unanticipated problem by the PI or the CI.
* One of the four events was experienced by one participant that received surgery at 12 months (N=262).
  + This event was not classified by the PI or the CI as related to the intervention.
  + This event was not classified as an unanticipated problem by the PI or the CI.

## Secondary Surgeries

Table S 26 provides details of secondary surgeries. Secondary surgeries were required in 11% of infants, with frequencies balanced between groups. 32 infants required a total of 37 secondary surgeries within the 6-month group compared to 29 infants requiring a total of 34 secondary surgeries within the 6-month group. Reasons for secondary surgeries varied between groups with the 6-month group being higher for velopharyngeal insufficiency and the 12-month group higher for fistula.

# S8. Data Sharing Statement

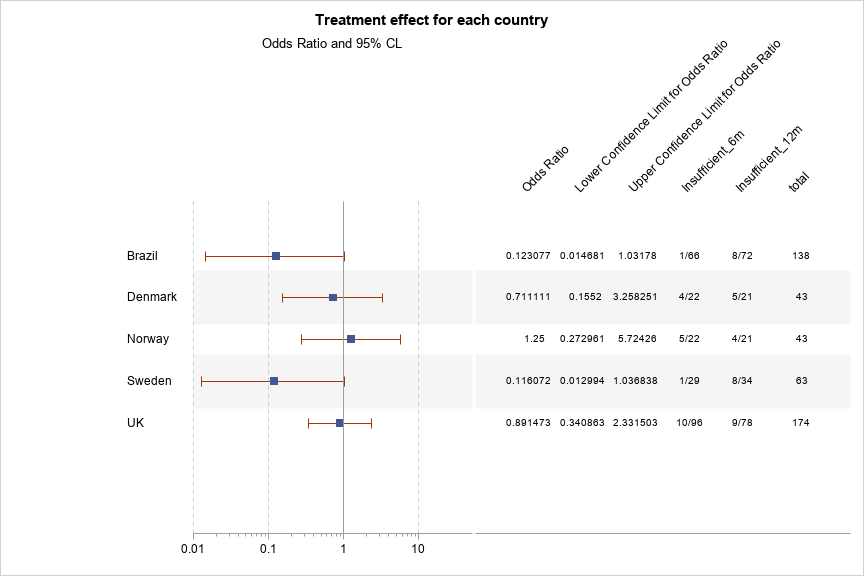
|  |  |
| --- | --- |
| Question | Authors’ response |
| Will individual participant data be available (including data dictionaries)? | Individual participant data that underlie the results reported in this article, after deidentification. Deidentification is extended to the Speech and Language Therapists as well as participants. |
| What other documents will be made available? | Protocol and statistical analysis plan |
| When will data be available? (start and end dates) | Beginning 6 months and ending 60 months following publication of the article. |
| With whom? | Researchers who provide a methodologically sound proposal and ethical approval as appropriate. |
| For what types of analyses? | To achieve aims in the approved proposal |
| By what mechanisms will data be made available? | Proposals should be sent to [lctc@liverpool.ac.uk](mailto:lctc@liverpool.ac.uk). A data access agreement will be required. |

# S9. Supplementary Figures

## Figure S 1: Participant Flow Diagram



## Figure S 2: Forest Plot of Insufficient Velopharyngeal Function at 5 Years by Country



# S10. Supplementary Tables

### Table S 1: Representativeness of Study Participants

|  |  |
| --- | --- |
| Category | Consideration |
| Condition under investigation | Isolated cleft palate |
| Special considerations related to: | |
| Sex and gender | Prevalence for isolated cleft palate is higher within females |
| Age | This condition is present at birth, however, there is some evidence that infants who are born preterm are more likely to have the condition than full-term infants. |
| Race or ethnic group | Cleft palate occurs with a birth prevalence of approximately 6 per 10 000 births (or ~1 in 1500 births), but with a very wide variation in different studies and populations. Outside of methodologic factors, the main factor in variability appears to be ethnicity, with higher prevalence in people of Northern European, Native American/First People, and Asian ancestry. |
| Geography | A number of environmental factors have been linked to a higher chance of a baby developing a cleft. This may explain variation in incidence rates. Maternal smoking, alcohol use and folic acid deficiency can be associated with the development of cleft palate and may confound geographical variation |
| Other considerations | All orofacial clefts (cleft lip, cleft palate, and cleft lip with cleft palate) have similar non-genetic risk factors. Non-genetic risk factors for cleft palate include maternal smoking, drinking alcohol, use of some medications (selected seizure medications such as barbiturates, valproate and topiramate), obesity and high fever. Some suggested additional risk factors include pre-gestational diabetes, substances that are folic acid antagonists, and systemic steroids. |
| Overall representativeness of this trial | This study was conducted in the UK, Scandinavia and Brazil, settings in which the surgical and post-operative care were adequately resourced. Brazil has a higher incidence of isolated cleft palate than that within the UK and Scandinavia and this is reflected within the recruitment figures. While some reports suggest higher incidence of isolated cleft palate within females’ numbers were equal within this study. Data relating to sex and race were collected on the TOPS form for Clinical genetic assessment. Sex was determined by anatomy at birth with options male and female. Options for race were Asian, Black, Chinese, Mixed, White, other and not stated. |

### Table S 2: Schedule of Assessments

| **Case Report Forms** | **Screening and randomization** | **Surgery** | **12 months** | **3 years** | **5 years** |
| --- | --- | --- | --- | --- | --- |
| Form S1: Screening log | X |  |  |  |  |
| Form C1: Genetics assessment | X |  |  |  |  |
| Form 1: Screening and randomization | X |  |  |  |  |
| Form 2: Surgery and postoperative care1 |  | X |  |  |  |
| Form C2: Blood sample for genetic assessment |  | X |  |  |  |
| Form 3: Late Complications2 |  | X |  |  |  |
| Form 4: 1 year speech assessment |  |  | X |  |  |
| Form 5: 1 year growth assessment |  |  | X |  |  |
| Form 6: 1 year audiology data collection |  |  | X |  |  |
| Form 7: Fistula assessment |  |  | X | X | X |
| Form 8: Audiology data collection 3 and 5 years |  |  |  | X | X |
| Form 9: 3 Year Speech Assessment |  |  |  | X |  |
| Form 10: Denver II assessment at 3 years |  |  |  | X |  |
| Form 11: 3 Year speech therapy questionnaire |  |  |  | X |  |
| Form 13: 5 Year Speech assessment |  |  |  |  | X |
| Form 14: 5 Year speech therapy questionnaire |  |  |  |  | X |
| Intelligibility in Context Scale |  |  |  |  | X |
| Form T1: Dental/ Maxillary arch sample transfer |  | X |  |  | X |
| Form T2: Log for transfer of speech recordings or participant photographs |  | X | X | X | X |
| Form T3: Speech recording sample transfer |  |  | X | X | X |
| Form A1: Serious Adverse Events | Complete for each SAE in first 30 days following surgery | | | | |
| Form M1: Concurrent medication | Complete for each concurrent medication during and for 30 days post-surgery | | | | |
| Form U1: Unanticipated Problems | Complete for each unanticipated problem for duration of the trial | | | | |
| Form 12: Secondary Surgery | Complete for each participant receiving additional surgery during trial | | | | |
| Form 15: Participant Transfer | Complete for each participant transferred from one TOPS site to another TOPS site during the trial (doesn’t apply to Bauru site) | | | | |
| Form W1: Withdrawal | Complete for each participant withdrawal during the trial | | | | |

1Post-operative care is described up to 48 hours post-surgery. Surgery should occur 2 weeks before to 4 weeks after the target date.

2Late Complications should be recorded up to 30 days post-surgery.

### Table S 3 Summary of Speech Recording Types by Time Point

|  |  |  |
| --- | --- | --- |
| Time point | Speech sample | Recording type |
| 12 months | Spontaneous speech (Play interaction) | Video |
| 3 years | Phonetics (single word test) | Video |
|  | Spontaneous speech | Video |
| 5 years | Phonetics (single word test) | Video |
|  | Spontaneous speech | Video |
|  | Nine-word string | Audio |
|  | Bus story | Video |

### Table S 4 Specification of VPC Sum Scoring Components

|  |  |  |
| --- | --- | --- |
| **Component** | **Classification** | **Score for component** |
| Hypernasality | Within normal limits | 0 |
|  | Mild resonance | 1 |
|  | Moderate/severe resonance | 2 |
| Non-oral errors | 0-2 errors | 0 |
|  | 3-5 errors | 1 |
|  | ≥6 errors | 2 |
| Velopharyngeal insufficiency symptoms | 0-2 symptoms | 0 |
|  | 3-5 symptoms | 1 |
|  | ≥6 symptoms | 2 |

### Table S 5: Classifying Severity in Better Ear

|  |  |
| --- | --- |
| **Average dB HL** | **Severity** |
| ≤20 dB HL | Normal |
| Between 21 and 40 dB HL | Mild |
| Between 41 and 70 dB HL | Moderate |
| Between 71 and 95 dB HL | Severe |
| >95 dB HL | Profound |

### Table S 6: Description of Speech End Points by Recording Type

| **Secondary endpoint** | **Description** | **Time point** | **Recordings used** | **Multiple ratings** |
| --- | --- | --- | --- | --- |
| ***Velopharyngeal function*** | | | | |
| Velopharyngeal composite score summary (VPC sum): | Scores of 0 to 2 given for each of hypernasality, non-oral errors, and velopharyngeal insufficiency symptoms. Score ranges from 0 to 6 with higher scores indicating increasing severity. | 5 years | Single word test with attempts at a minimum of 18/36 predetermined words. Hypernasality was assessed on a four-point scale by playing a nine-word string with pre-selected words from the 36 on a loop. | Non-oral errors and velopharyngeal insufficiency-symptoms were assessed by one SLT per child. The first language of the SLT was matched to the child’s language. Hypernasality was rated by a team of three SLTs (one UK, one Brazilian, one Danish) and a majority classification used. |
| Insufficient velopharyngeal function (VPC rate) | Children assessed as incompetent, marginally incompetent, competent. Insufficient function equates to ‘incompetent’ category. | 3 years  5 years | Recordings of spontaneous speech during free play, retelling the bus story, or a combination of the two. | Determined by 3 SLTs of the same language as the child with a majority decision. |
| Velopharyngeal insufficiency symptoms | Defined as the number of times a target sound had a velopharyngeal insufficiency symptom. | 3 years | Single word test with attempts at a minimum of 15/30 predetermined words. | Rating by one SLT of the same language as the child. |
| ***Canonical babbling*** | | | | |
| Canonical babbling present | Classification of ‘canonical’ or ‘not canonical’. | 1 year | Spontaneous speech recordings, where the child is recorded through free play | Three SLTs of any language – majority decision |
| Canonical babbling ratio | The proportion of syllables produced classed as being ‘canonical’. | Average across three raters (mean+/- SD) |
| Canonical babbling consonant inventory | The number of unique consonants uttered by a child. | A count of the number of unique consonants identified by at least two of three SLTs |
| ***Articulation*** | | | | |
| Percent consonant correct (PCC) | The proportion of times that a target consonant is uttered correct. | 3 years  5 years | Each child is required to have attempted a minimum of 15/30 predetermined target consonants (in words) for articulation assessment at 3 years and 18/36 at 5 years. | Rated by one SLT of the same language as the child. |
| Percent correct placement (PCP) | The proportion of times that a target consonant has the correct place of articulation. | 3 years  5 years | Rated by one SLT of the same language as the child. |
| Percent correct manner (PCM) | The proportion of times that a target consonant has the correct manner of articulation. | 3 years  5 years | Assessment by one SLT of the same language as the child. |
| Non-oral consonant errors | The proportion of times that a target consonant is realized as a non-oral error | 3 years  5 years | Assessment by one SLT of the same language as the child. |
| Oral consonant errors | The proportion of times that a target consonant is realized as an oral error | 3 years  5 years | Assessment by one SLT of the same language as the child. |

All speech and language assessments for each time point were undertaken in a central facility in the UK. This involved a total of 41 speech and language therapists (Brazil (n=6), Denmark (n=60, Norway (n=6), Sweden (n=9), and UK (n=14)).

### Table S 7: Description of Hearing and Middle Ear Function Endpoints

|  |  |  |  |
| --- | --- | --- | --- |
| **Secondary Endpoint** | **Description** | **Time point** | **Measurement** |
| Abnormal Transient Otoacoustic Emission (TEOAE) | a dichotomous outcome of whether the child has abnormal TEOAE. | 1 year |  |
| Abnormal sound field audiometry | a dichotomous outcome of whether the child has abnormal sound field audiometry. | 1 year | Abnormal sound field audiometry is indicated by a measurement of >30dB HL for at least one of four frequencies tested: 500 Hz, 1000 Hz, 2000 Hz, or 4000Hz. |
| Abnormal pure tone audiometry in at least one ear | a dichotomous outcome of whether the child has abnormal pure tone audiometry. | 3 years  5 years | If testing by pure tone audiometry is not possible, sound field audiometry can be used in its place. Abnormal audiometry in at least one ear is indicated by a measurement of >20dB HL using the pure tone method, >25dB HL for sound field, for at least one of four frequencies tested: 500 Hz, 1000 Hz, 2000 Hz, or 4000Hz. |
| Abnormal pure tone audiometry in both ears | a dichotomous outcome defined as above for participants who have both ears tested and both tested ears indicate abnormal audiometry. | 3 years  5 years | As above |
| Severity of better ear | Categorization of hearing level in each ear as normal; mild; moderate; severe; profound. The category for the ear attaining best hearing is reported. | 3 years  5 years | Each ear classified as Normal: ≤20dB HL; Mild: 21 to 40dB HL; Moderate: 41 to 70dB HL; Severe: 71 to 95dB; Profound: >95dB HL.  If testing by pure tone audiometry is not possible, sound field audiometry can be used in its place. Each participant will be classified according to the average score in the better ear if pure tone, or both ears if sound field, across the four frequencies (500 Hz, 1000Hz, 2000Hz, or 4000Hz) |
| ***Middle ear function*** | | | |
| Flat line tympanogram in at least one ear | a dichotomous outcome of whether the child has flat line tympanogram. | 1 year  3 years  5 years | Children with either ear measured as “Type B” will be classified as having flat line tympanogram in at least one ear. |
| Flat line tympanogram in both ears | a dichotomous outcome of whether the child has flat line tympanogram, in both ears | 1 year  3 years  5 years | Children with both ears measured as “Type B” will be classified as having flat line tympanogram in both ears. |

### Table S 8: Description of Dentofacial Development Endpoints

|  |  |
| --- | --- |
| ***Dentofacial development at 5 years*** | **Details** |
| Soft tissue ANB angle | the angle between soft tissue nasion (points A and B) measured using a profile photograph |
| Maxillary arch constriction score | A score can range from −24 to 8 and is measured in whole numbers measured using the modified Huddart/Bodenham scoring system, on a maxillary and mandibular arch impression. The more negative the score the greater the constriction. |

### Table S 9: Reasons for Ineligibility

|  |  |
| --- | --- |
| **Reason ineligible** | **Number of participants** |
| Infant is not medically fit for operation at age 6 months corrected for gestational age | 369 (35.8) |
| Language spoken at home is not the majority language of the country of residence and/or parent/carer is not a native speaker of that language. | 132 (12.8) |
| Known associated syndrome or developmental delay | 378 (36.6) |
| Congenital sensorineural hearing loss or structural middle ear anomalies | 20 (1.9) |
| Cleft too wide for closure with Sommerlad technique | 76 (7.4) |
| Other variation in the anatomical presentation is such that one stage closure with the Sommerlad technique would be inappropriate | 27 (2.6) |
| Submucous cleft palate | 38 (3.7) |
| Unable to complete clinical genetics assessment prior to 6 month admission age | 35 (3.4) |
| Unsuitable | 125 (12.1) |
| *Congenital cardiopathy* | *7 (5.6)* |
| *Chromosomal abnormalities* | *2 (1.6)* |
| *Deceased* | *4 (3.2)* |
| *Misdiagnosed* | *4 (3.2)* |
| *Missed by trial staff/Late diagnosis* | *17 (13.6)* |
| *Mother has no speech* | *1 (0.8)* |
| *Not able to participate due to personal circumstances* | *55 (44.0)* |
| *Other – Failed Denver (D)* | *1 (0.8)* |
| *Suspected syndrome* | *4 (3.2)* |
| *Too poorly to participate* | *17 (13.6)* |
| *Trial closed to recruitment* | *2 (1.6)* |
| *No reason provided* | *11 (8.8)* |
| Total number of reasons provided for 1032 ineligible patients | 1200 |

### Table S 10: Reasons for Consent Not Provided

|  |  |
| --- | --- |
| Reason consent not given 3 | Number of patients |
| 1: Timing preference – 6 month surgery | 85 (28.4) |
| 2: Timing preference - 12 month surgery | 11 (3.7) |
| 3: Parent/carer declined participation – no reason given | 160 (53.5) |
| 4: Other reason | 43 (14.4) |
| *Did not feel ready at 12 months* | *1 (2.3)* |
| *Older sibling also had cleft palate, parents wish to have treated the same* | *2 (4.7)* |
| *Parents wish to follow current protocol* | *9 (20.9)* |
| *Parents did not feel baby was fit to participate* | *1 (2.3)* |
| *Parents did not want child to be reminded of cleft by being video recorded* | *1 (2.3)* |
| *Parents felt that the hospital was more competent to perform surgery at 8/9 months* | *1 (2.3)* |
| *Parents not willing to be involved in research* | *4 (9.3)* |
| *Parents undecided at time or screening* | *1 (2.3)* |
| *Trial not convenient for parents* | *20 (46.5)* |
| *No reasons recorded* | *3 (7.0)* |
| Total | 299 |

3 Categories 1-4 are mutually exclusive

### Table S 11: Compliance with Allocated Timing

|  |  | **Number of participants** | **Received surgery** | | |
| --- | --- | --- | --- | --- | --- |
| **Total** | **Within allocated time window** | **Outside allocated time window** |
| **Site** | **Surgery Group** | **N** | **NR** | **Nw**  **(Nw/N%) , (Nw/NR%)** | **No**  **(No/N%), (No/NR%)** |
| Overall | 12-month | 273 | 255 (93.4) | 215 (78.8), (84.3) | 40 (14.7), (15.7) |
|  | 6-month | 279 | 266 (95.3) | 232 (83.2), (87.2) | 34 (12.2), (12.8) |
|  | Total | 552 | 521 (94.4) | 447 (81.0), (85.8) | 74 (13.4), (14.2) |

### Table S 12: Reasons for Surgery Outside of Allocated Window

|  |  |  |  |
| --- | --- | --- | --- |
| **Reason** | **6 month surgery** | **12 month surgery** | **Overall** |
| **Number of participants outside surgery window** | 34 | 40 | 74 |
| Cancelled by anesthetist | 1 (2.9) | 0 (0.0) | 1 (1.4) |
| Delayed due to neurological investigation. | 1 (2.9) | 0 (0.0) | 1 (1.4) |
| Did not want surgery at 12 months | 0 (0.0) | 1 (2.5) | 1 (1.4) |
| Family unable to attend earlier | 1 (2.9) | 1 (2.5) | 2 (2.7) |
| Misunderstanding | 0 (0.0) | 1 (2.5) | 1 (1.4) |
| Not fit for surgery | 17 (50.0) | 20 (50.0) | 37 (50.0) |
| Scheduling and/or site issues | 14 (41.2) | 10 (25.0) | 24 (32.4) |
| Withdrew from timing of surgery | 0 (0.0) | 4 (10.0) | 4 (5.4) |
| No reason given | 0 (0.0) | 3 (7.5) | 3 (4.1) |

### Table S 13: Compliance with Treatment: Days Deviated from Allocated Window

| **Site** | **Surgery group** | **Absolute; days deviated** | | **Early; days deviated** | | **Late; days deviated** | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Mean (sd); Median (LQ, UQ, IQR); [Min, Max]** | **Ne (%)** | **Mean (sd); Median (LQ, UQ, IQR); [Min, Max]** | **NL (%)** | **Mean (sd); Median (LQ, UQ, IQR); [Min, Max]** |
| Overall | 12-month | 40 | 105.8 (110.9); 60.5 (32.50, 160.00, 127.5); [1.0, 455.0] | 11 (27.5) | 47.3 (44.4); 33.0 (3.00, 86.00, 83.0); [1.0, 116.0] | 29 (72.5) | 128.0 (120.8); 64.0 (42.00, 204.00, 162.0); [7.0, 455.0] |
| 6-month | 34 | 53.0 (73.2); 20.5 (4.00, 73.00, 69.0); [1.0, 338.0] | 8 (23.5) | 3.8 (4.3); 1.0 (1.00, 7.00, 6.0); [1.0, 11.0] | 26 (76.5) | 68.2 (77.8); 33.5 (15.00, 82.00, 67.0); [1.0, 338.0] |
| Total | 74 | 81.5 (98.5); 46.0 (10.00, 116.00, 106.0); [1.0, 455.0] | 19 (25.7) | 28.9 (39.9); 7.0 (1.00, 53.00, 52.0); [1.0, 116.0] | 55 (74.3) | 99.7 (106.2); 61.0 (26.00, 154.00, 128.0); [1.0, 455.0] |

### Table S 14: Withdrawals

|  |  |  |  |
| --- | --- | --- | --- |
| **Withdrawals:** | **6 month surgery** | **12 month surgery** | **Overall** |
| Number randomized | 281 | 277 | 558 |
| Number of withdrawals; n (%) | 21 (7.5) | 25 (9.0) | 46 (8.2) |
| **Level of withdrawal** |  |  |  |
| No further follow up, consent to use data collected; n (%) | 19 (90.5) | 21 (84.0) | 40 (87.0) |
| Complete withdrawal; n (%) | 2 (9.5) | 4 (16.0) | 6 (13.0) |
| Consent to use data collected revoked; n (%) | 2 (9.5) | 3 (12.0) | 5 (10.9) |
| Consent form copy not obtained; n (%) | 0 (0.0) | 1 (4.0) | 1 (2.2) |
| **Reasons for withdrawal** |  |  |  |
| Identification of a severe developmental delay; n (%) | 7 (33.3) | 1 (4.0) | 8 (17.4) |
| Identification of a syndrome; n (%) | 2 (9.5) | 0 (0.0) | 2 (4.3) |
| Other; n (%) | 11 (52.4) | 22 (88.0) | 33 (71.7) |
| Reason not given; n (%) | 1 (4.8) | 2 (8.0) | 3 (6.5) |
| **Decision maker for withdrawal** |  |  |  |
| Clinician; n (%) | 10 (47.6) | 3 (12.0) | 13 (28.3) |
| Parent/Guardian; n (%) | 7 (33.3) | 20 (80.0) | 27 (58.7) |
| Parent/Guardian and Clinician; n (%) | 2 (9.5) | 2 (8.0) | 4 (8.7) |
| Unknown; n (%) | 2 (9.5) | 0 (0.0) | 2 (4.3) |
| **Timing of withdrawal** | | | |
| Withdrawal before surgery; n (%) | 10 (52.6) | 10 (47.6) | 20 (50.0) |
| Withdrawal after surgery; n (%) | 9 (47.4) | 11 (52.4) | 20 (50.0) |

### Table S 15: Other Reasons for Withdrawal

|  |  |  |  |
| --- | --- | --- | --- |
|  | **6 months** | **12 months** | **Overall** |
| **Reason** |  |  |  |
| Burden | 1 (9.1) | 6 (27.3) | 7 (21.2) |
| Co-morbidity | 0 (0.0) | 1 (4.5) | 1 (3.0) |
| Misunderstanding | 0 (0.0) | 1 (4.5) | 1 (3.0) |
| Moved | 0 (0.0) | 3 (13.6) | 3 (9.1) |
| No follow up | 1 (9.1) | 0 (0.0) | 1 (3.0) |
| No personal benefit | 0 (0.0) | 1 (4.5) | 1 (3.0) |
| Not medically fit for surgery | 5 (45.5) | 1 (4.5) | 6 (18.2) |
| Site resource/staffing difficulties | 1 (9.1) | 0 (0.0) | 1 (3.0) |
| Unsuitable for Sommerlad technique | 1 (9.1) | 0 (0.0) | 1 (3.0) |
| Wanted allocation to surgery at other time | 1 (9.1) | 7 (31.8) | 8 (24.2) |
| Not provided | 1 (9.1) | 2 (9.1) | 3 (9.1) |
| **Total** | **11** | **22** | **33** |

### Table S 16: Outcome Completion Summary

| **Summary** | **6 month surgery** | **12 month surgery** | **Overall** |
| --- | --- | --- | --- |
| **Total** | 279 | 273 | 552 |
| **PO SO1a and SO5 - 5 year speech (Phonetics)** |  |  |  |
| Recording - Eligible | 235 (84.2) | 226 (82.8) | 461 (83.5) |
| Recording - Ineligible - Less than 18 words | 3 (1.1) | 0 (0.0) | 3 (0.5) |
| Recording - Ineligible - Quality | 4 (1.4) | 1 (0.4) | 5 (0.9) |
| Recording not received | 30 (10.8) | 38 (13.9) | 68 (12.3) |
| Recording not received - due to COVID-19 | 7 (2.5) | 8 (2.9) | 15 (2.7) |
| **SO1b - 5 year speech (VPC-rate)** |  |  |  |
| Recording - Eligible | 236 (84.6) | 221 (81.0) | 457 (82.8) |
| Recording - Ineligible - Quality | 6 (2.2) | 6 (2.2) | 12 (2.2) |
| Recording not received | 30 (10.8) | 38 (13.9) | 68 (12.3) |
| Recording not received - due to COVID-19 | 7 (2.5) | 8 (2.9) | 15 (2.7) |
| **SO2a - 3 year speech (VPC-rate)** |  |  |  |
| Recording - Eligible | 228 (81.7) | 223 (81.7) | 451 (81.7) |
| Recording - Ineligible - Quality | 10 (3.6) | 12 (4.4) | 22 (4.0) |
| Recording not received | 41 (14.7) | 38 (13.9) | 79 (14.3) |
| **SO2b and 4 - 3 year speech (Phonetics)** |  |  |  |
| Recording - Eligible | 218 (78.1) | 215 (78.8) | 433 (78.4) |
| Recording - Ineligible - Less than 15 words | 10 (3.6) | 13 (4.8) | 23 (4.2) |
| Recording - Ineligible - Quality | 10 (3.6) | 7 (2.6) | 17 (3.1) |
| Recording not received | 41 (14.7) | 38 (13.9) | 79 (14.3) |
| **SO3 - 12 month speech** |  |  |  |
| Recording - Eligible | 242 (86.7) | 242 (88.6) | 484 (87.7) |
| Recording - Ineligible - CSG confirmed exclusion | 0 (0.0) | 1 (0.4) | 1 (0.2) |
| Recording - Ineligible - The baby says too little | 8 (2.9) | 8 (2.9) | 16 (2.9) |
| Recording not received | 29 (10.4) | 22 (8.1) | 51 (9.2) |
| **SO6a - Dehiscence** |  |  |  |
| No | 14 (5.0) | 18 (6.6) | 32 (5.8) |
| Yes | 265 (95.0) | 255 (93.4) | 520 (94.2) |
| **SO6b - Infection** |  |  |  |
| No | 20 (7.2) | 27 (9.9) | 47 (8.5) |
| Yes | 259 (92.8) | 246 (90.1) | 505 (91.5) |
| **SO6c - Fistula** |  |  |  |
| No | 13 (4.7) | 17 (6.2) | 30 (5.4) |
| Yes | 266 (95.3) | 256 (93.8) | 522 (94.6) |
| **SO7ai at 12 months - TEOAE** |  |  |  |
| Audiometry visit not completed | 66 (23.7) | 52 (19.0) | 118 (21.4) |
| Not Tested | 162 (58.1) | 157 (57.5) | 319 (57.8) |
| Tested | 51 (18.3) | 64 (23.4) | 115 (20.8) |
| **SO7aii at 12 months - Soundfield audiometry** |  |  |  |
| Audiometry visit not completed | 66 (23.7) | 52 (19.0) | 118 (21.4) |
| Not tested | 39 (14.0) | 48 (17.6) | 87 (15.8) |
| Tested | 174 (62.4) | 173 (63.4) | 347 (62.9) |
| **SO7bi at 3 years - Abnormal pure tone audiometry in at least one ear** |  |  |  |
| Audiometry visit not completed | 74 (26.5) | 68 (24.9) | 142 (25.7) |
| Not Tested | 34 (12.2) | 31 (11.4) | 65 (11.8) |
| Tested | 171 (61.3) | 174 (63.7) | 345 (62.5) |
| **SO7bii at 3 years - Abnormal pure tone audiometry in both ears** |  |  |  |
| Audiometry visit not completed | 74 (26.5) | 68 (24.9) | 142 (25.7) |
| Not Tested | 34 (12.2) | 31 (11.4) | 65 (11.8) |
| Not Tested - one ear only | 62 (22.2) | 65 (23.8) | 127 (23.0) |
| Tested | 109 (39.1) | 109 (39.9) | 218 (39.5) |
| **S07biii at 3 years - severity of better ear** |  |  |  |
| Audiometry visit not completed | 74 (26.5) | 68 (24.9) | 142 (25.7) |
| Not Tested | 36 (12.9) | 35 (12.8) | 71 (12.9) |
| Tested | 169 (60.6) | 170 (62.3) | 339 (61.4) |
| **SO7bi at 5 years - Abnormal pure tone audiometry in at least one ear** |  |  |  |
| Audiometry visit not completed | 71 (25.4) | 81 (29.7) | 152 (27.5) |
| Not Tested | 13 (4.7) | 8 (2.9) | 21 (3.8) |
| Tested | 195 (69.9) | 184 (67.4) | 379 (68.7) |
| **SO7bii at 5 years - Abnormal pure tone audiometry in both ears** |  |  |  |
| Audiometry visit not completed | 71 (25.4) | 81 (29.7) | 152 (27.5) |
| Not Tested | 13 (4.7) | 8 (2.9) | 21 (3.8) |
| Not Tested - one ear only | 4 (1.4) | 3 (1.1) | 7 (1.3) |
| Tested | 191 (68.5) | 181 (66.3) | 372 (67.4) |
| **S07biii at 5 years - severity of better ear** |  |  |  |
| Audiometry visit not completed | 71 (25.4) | 81 (29.7) | 152 (27.5) |
| Not Tested | 14 (5.0) | 10 (3.7) | 24 (4.3) |
| Tested | 194 (69.5) | 182 (66.7) | 376 (68.1) |
| **SO8a at 12 months - Flat line tympanometry in at least one ear** |  |  |  |
| Audiometry visit not completed | 66 (23.7) | 52 (19.0) | 118 (21.4) |
| Not tested | 29 (10.4) | 18 (6.6) | 47 (8.5) |
| Tested | 175 (62.7) | 201 (73.6) | 376 (68.1) |
| Tested - removed due to FVT/Perforation | 9 (3.2) | 2 (0.7) | 11 (2.0) |
| **SO8b at 12 months - Flat line tympanometry in both ears** |  |  |  |
| Audiometry visit not completed | 66 (23.7) | 52 (19.0) | 118 (21.4) |
| Not Tested - one ear only | 5 (1.8) | 4 (1.5) | 9 (1.6) |
| Not tested | 32 (11.5) | 18 (6.6) | 50 (9.1) |
| Tested | 167 (59.9) | 197 (72.2) | 364 (65.9) |
| Tested - removed due to FVT/Perforation | 9 (3.2) | 2 (0.7) | 11 (2.0) |
| **SO8a at 3 years - Flat line tympanometry in at least one ear** |  |  |  |
| Audiometry visit not completed | 74 (26.5) | 68 (24.9) | 142 (25.7) |
| Not Tested | 24 (8.6) | 22 (8.1) | 46 (8.3) |
| Tested | 173 (62.0) | 180 (65.9) | 353 (63.9) |
| Tested - removed due to FVT/Perforation | 8 (2.9) | 3 (1.1) | 11 (2.0) |
| **SO8b at 3 years - Flat line tympanometry in both ears** |  |  |  |
| Audiometry visit not completed | 74 (26.5) | 68 (24.9) | 142 (25.7) |
| Not Tested | 24 (8.6) | 23 (8.4) | 47 (8.5) |
| Not Tested - one ear only | 2 (0.7) | 11 (4.0) | 13 (2.4) |
| Tested | 165 (59.1) | 162 (59.3) | 327 (59.2) |
| Tested - removed due to FVT/Perforation | 14 (5.0) | 9 (3.3) | 23 (4.2) |
| **SO8a at 5 years - Flat line tympanometry in at least one ear** |  |  |  |
| Audiometry visit not completed | 71 (25.4) | 81 (29.7) | 152 (27.5) |
| Not Tested | 15 (5.4) | 10 (3.7) | 25 (4.5) |
| Tested | 189 (67.7) | 179 (65.6) | 368 (66.7) |
| Tested - removed due to FVT/Perforation | 4 (1.4) | 3 (1.1) | 7 (1.3) |
| **SO8b at 5 years - Flat line tympanometry in both ears** |  |  |  |
| Audiometry visit not completed | 71 (25.4) | 81 (29.7) | 152 (27.5) |
| Not Tested | 15 (5.4) | 10 (3.7) | 25 (4.5) |
| Not Tested - one ear only | 4 (1.4) | 8 (2.9) | 12 (2.2) |
| Tested | 173 (62.0) | 167 (61.2) | 340 (61.6) |
| Tested - removed due to FVT/Perforation | 16 (5.7) | 7 (2.6) | 23 (4.2) |
| **SO9a - Soft tissue ANB** |  |  |  |
| Photograph excluded due to quality | 19 (6.8) | 13 (4.8) | 32 (5.8) |
| Photograph included | 181 (64.9) | 180 (65.9) | 361 (65.4) |
| Photograph not received | 79 (28.3) | 80 (29.3) | 159 (28.8) |
| **SO9b - Maxillary arch constriction score** |  |  |  |
| Impression excluded due to quality | 12 (4.3) | 10 (3.7) | 22 (4.0) |
| Impression included | 188 (67.4) | 172 (63.0) | 360 (65.2) |
| Impression not received | 79 (28.3) | 91 (33.3) | 170 (30.8) |
| **SO10a - Nude weight** |  |  |  |
| Growth assessment not completed | 36 (12.9) | 24 (8.8) | 60 (10.9) |
| No | 7 (2.5) | 8 (2.9) | 15 (2.7) |
| Yes | 236 (84.6) | 241 (88.3) | 477 (86.4) |
| **SO10b - Crown to heel length** |  |  |  |
| Growth assessment not completed | 36 (12.9) | 24 (8.8) | 60 (10.9) |
| No | 5 (1.8) | 12 (4.4) | 17 (3.1) |
| Yes | 238 (85.3) | 237 (86.8) | 475 (86.1) |
| **SO10c - Occipitofrontal circumference** |  |  |  |
| Growth assessment not completed | 36 (12.9) | 24 (8.8) | 60 (10.9) |
| No | 9 (3.2) | 14 (5.1) | 23 (4.2) |
| Yes | 234 (83.9) | 235 (86.1) | 469 (85.0) |

PO=Primary Outcome and SO=Secondary Outcome with numbering mapping to the list of outcomes as per section 0.

### Table S 17: Demographic Characteristics Categorized by Primary Outcome Status (Observed or Missing)

|  | **Observed** | **Missing** | **Overall** |
| --- | --- | --- | --- |
| **Number of participants** | 461 | 91 | 552 |
| **Gender** |  |  |  |
| Male; n (%) | 186 (40.4) | 39 (43.3) | 225 (40.9) |
| Not recorded | 1 | 1 | 2 |
| **Gestational age (weeks)** |  |  |  |
| N | 459 | 90 | 549 |
| Mean (sd) | 39.33 (1.73) | 39.04 (2.01) | 39.28 (1.78) |
| Median (LQ, UQ, IQR) | 39.57 (38.29, 40.57, 2.29) | 39.29 (38.00, 40.14, 2.14) | 39.43 (38.29, 40.43, 2.14) |
| [Min, Max] | [28.00, 42.57] | [32.43, 42.14] | [28.00, 42.57] |
| Not recorded | 2 | 1 | 3 |
| **Size of Cleft** |  |  |  |
| Soft palate only; n (%) | 160 (34.7) | 26 (28.6) | 186 (33.7) |
| Soft and hard palate; n (%) | 301 (65.3) | 65 (71.4) | 366 (66.3) |
| Not recorded | 0 | 0 | 0 |

### Table S 18: Clinical Characteristics Categorized by Primary Outcome Status (Observed or Missing)

|  | **Observed** | **Missing** | **Overall** |
| --- | --- | --- | --- |
| **Number of participants** | 461 | 91 | 552 |
| **Ethnicity** |  |  |  |
| White; n (%) | 411 (89.2) | 83 (91.2) | 494 (89.5) |
| Black; n (%) | 10 (2.2) | 0 | 10 (1.8) |
| Asian; n (%) | 10 (2.2) | 1 (1.1) | 11 (2.0) |
| Chinese; n (%) | 0 | 0 | 0 |
| Mixed; n (%) | 23 (5.0) | 6 (6.6) | 29 (5.3) |
| Other; n (%) | 4 (0.9) | 0 | 4 (0.7) |
| Not stated; n (%) | 3 (0.7) | 1 (1.1) | 4 (0.7) |
| **Weight (kg)** |  |  |  |
| N | 453 | 89 | 542 |
| Mean (sd) | 5.32 (1.12) | 5.28 (1.16) | 5.31 (1.13) |
| Median (LQ, UQ, IQR) | 5.26 (4.57, 6.10, 1.53) | 5.05 (4.54, 5.86, 1.32) | 5.24 (4.57, 6.08, 1.51) |
| [Min, Max] | [2.42, 9.00] | [3.39, 9.18] | [2.42, 9.18] |
| Not recorded | 8 | 2 | 10 |
| **Length (cm)** |  |  |  |
| N | 448 | 84 | 532 |
| Mean (sd) | 59.24 (4.59) | 58.87 (5.92) | 59.18 (4.82) |
| Median (LQ, UQ, IQR) | 59.50 (56.50, 62.00, 5.50) | 59.00 (56.00, 62.00, 6.00) | 59.50 (56.40, 62.00, 5.60) |
| [Min, Max] | [39.50, 72.00] | [22.50, 74.00] | [22.50, 74.00] |
| Not recorded | 13 | 7 | 20 |
| **Occipitofrontal circumference (cm)** |  |  |  |
| N | 451 | 86 | 537 |
| Mean (sd) | 39.96 (2.29) | 39.99 (2.17) | 39.96 (2.27) |
| Median (LQ, UQ, IQR) | 40.00 (38.50, 41.50, 3.00) | 39.50 (38.80, 41.20, 2.40) | 40.00 (38.50, 41.50, 3.00) |
| [Min, Max] | [32.40, 55.50] | [35.50, 45.00] | [32.40, 55.50] |
| Not recorded | 10 | 5 | 15 |
| **Interpretation of Denver** |  |  |  |
| Normal; n (%) | 419 (91.3) | 79 (87.8) | 498 (90.7) |
| Suspect; n (%) | 37 (8.1) | 10 (11.1) | 47 (8.6) |
| Untestable; n (%) | 3 (0.7) | 1 (1.1) | 4 (0.7) |
| Not recorded | 2 | 1 | 3 |
| **Diagnosis** |  |  |  |
| Known syndrome; n (%) | 1 (0.2) | 0 | 1 (0.2) |
| Unknown syndrome; n (%) | 0 | 0 | 0 |
| Severe developmental delay; n (%) | 1 (0.2) | 0 | 1 (0.2) |
| Uncertain; n (%) | 76 (16.5) | 20 (22.5) | 96 (17.5) |
| Non-syndromic; n (%) | 382 (83.0) | 69 (77.5) | 451 (82.1) |
| Not recorded | 1 | 2 | 3 |

### Table S 19: Adjusted and Unadjusted Odds Ratios for Primary Endpoint

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Odds ratio** | **95% CI** | **p-value** |
| ***Adjusted analysis4*** |  |  |  |
| Size of cleft |  |  |  |
| Soft palate only | . | . | . |
| Soft and hard palate | 1.01 | (0.54, 1.87) | 0.98 |
| Surgery group |  |  |  |
| 12 months surgery | . | . | . |
| 6 months surgery | 0.53 | (0.30, 0.96) | 0.037 |
| ***Unadjusted analysis*** |  |  |  |
| Surgery group |  |  |  |
| 12 months surgery | . | . | . |
| 6 months surgery | 0.56 | (0.31, 1.00) | 0.05 |

4 analysis adjusted using random effect for surgeon – covariance estimate and standard error 0.34 and 0.25 respectively

### Table S 20: Insufficient Velopharyngeal Function at 5 Years by Country

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Recruiting site** | **Brazil** | **Denmark** | **Norway** | **Sweden** | **UK** |
| ***Overall*** |  |  |  |  |  |
| Number of participants | 138 (29.9) | 43 (9.3) | 43 (9.3) | 63 (13.7) | 174 (37.7) |
| Sufficient5; n (%) | 129 (93.5) | 34 (79.1) | 34 (79.1) | 54 (85.7) | 155 (89.1) |
| Insufficient5; n (%) | 9 (6.5) | 9 (20.9) | 9 (20.9) | 9 (14.3) | 19 (10.9) |
| ***6 month surgery*** |  |  |  |  |  |
| Number of participants | 66 (28.1) | 22 (9.4) | 22 (9.4) | 29 (12.3) | 96 (40.9) |
| Sufficient5; n (%) | 65 (98.5) | 18 (81.8) | 17 (77.3) | 28 (96.6) | 86 (89.6) |
| Insufficient5; n (%) | 1 (1.5) | 4 (18.2) | 5 (22.7) | 1 (3.4) | 10 (10.4) |
| ***12 month surgery*** |  |  |  |  |  |
| Number of participants | 72 (31.9) | 21 (9.3) | 21 (9.3) | 34 (15.0) | 78 (34.5) |
| Sufficient5; n (%) | 64 (88.9) | 16 (76.2) | 17 (81.0) | 26 (76.5) | 69 (88.5) |
| Insufficient5; n (%) | 8 (11.1) | 5 (23.8) | 4 (19.0) | 8 (23.5) | 9 (11.5) |

5Sufficient and insufficient defined as VPC-sum score of 0-3 and 4-6 respectively.

### Table S 21: Intra-operative and Early Post-operative Events

|  |  |  |  |
| --- | --- | --- | --- |
| ***Event*** | **6 months surgery** | **12 months surgery** | **Overall** |
| Number of participants received surgery | 266 | 255 | 521 |
| **Intra-operative events** |  |  |  |
| Blood transfusion during surgery |  |  |  |
| Yes; n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Not recorded | 2 | 1 | 3 |
| Anesthetic Complications |  |  |  |
| Yes; n (%) | 7 (2.7) | 0 (0.0) | 7 (1.4) |
| Not recorded | 2 | 1 | 3 |
| Bleeding |  |  |  |
| Yes; n (%) | 5 (1.9) | 3 (1.2) | 8 (1.5) |
| Not recorded | 2 | 1 | 3 |
| **Early complications during hospital stay** | |  |  |
| Postoperative airway problems |  |  |  |
| Yes; n (%) | 26 (9.8) | 24 (9.4) | 50 (9.7) |
| Not recorded | 2 | 1 | 3 |
| Blood Transfusion post-surgery |  |  |  |
| Yes; n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Not recorded | 2 | 1 | 3 |
| Anti-coagulants given |  |  |  |
| Yes; n (%) | 5 (1.9) | 3 (1.2) | 8 (1.6) |
| Not recorded | 5 | 3 | 8 |
| Readmitted to the operating room |  |  |  |
| Yes; n (%) | 0 (0.0) | 16 (0.4) | 1 (0.2) |
| Not recorded | 2 | 1 | 3 |
| 6 Participant reintubated to prevent airway problems due to swollen tongue | | | |

### Table S 22: Observations Monitored 48 Hours Post-surgery

|  |  |  |  |
| --- | --- | --- | --- |
| ***Observation*** | **6 months surgery** | **12 months surgery** | **Overall** |
| Number of participants received surgery | 266 | 255 | 521 |
| **Oxygen saturation levels** |  |  |  |
| Clinically significant abnormality; n (%) | 8 (3.0) | 8 (3.1) | 16 (3.1) |
| Not clinically significant abnormality; n (%) | 252 (94.7) | 232 (91.0) | 484 (92.9) |
| Monitored but clinical significance unknown; n (%) | 2 (0.8) | 2 (0.8) | 4 (0.8) |
| Not monitored; n (%) | 4 (1.5) | 13 (5.1) | 17 (3.3) |
| **Carbon dioxide and oxygen** |  |  |  |
| Clinically significant abnormality; n (%) | 0 (0.0) | 1 (0.4) | 1 (0.2) |
| Not clinically significant abnormality; n (%) | 8 (3.0) | 9 (3.5) | 17 (3.3) |
| Not monitored; n (%) | 258 (97.0) | 245 (96.1) | 503 (96.5) |
| **Arterial blood gases** |  |  |  |
| Clinically significant abnormality; n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Not clinically significant abnormality; n (%) | 2 (0.8) | 0 (0.0) | 2 (0.4) |
| Monitored but clinical significance unknown; n (%) | 0 (0.0) | 1 (0.4) | 1 (0.2) |
| Not monitored; n (%) | 264 (99.2) | 254 (99.6) | 518 (99.4) |
| **Heart rate** |  |  |  |
| Clinically significant abnormality; n (%) | 2 (0.8) | 3 (1.2) | 5 (1.0) |
| Treatment required; n (%) | 1 (50.0) | 0 (0.0) | 1 (20.0) |
| Treatment not required; n (%) | 1 (50.0) | 3 (100.0) | 4 (80.0) |
| Not clinically significant abnormality; n (%) | 258 (97.0) | 241 (94.5) | 499 (95.8) |
| Monitored but clinical significance unknown; n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Not monitored; n (%) | 6 (2.3) | 11 (4.3) | 17 (3.3) |
| **Blood pressure** |  |  |  |
| Clinically significant abnormality; n (%) | 3 (1.1) | 1 (0.4) | 4 (0.8) |
| Treatment required; n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Treatment not required; n (%) | 3 (100.0) | 1 (100.0) | 4 (100.0) |
| Not clinically significant abnormality; n (%) | 88 (33.1) | 87 (34.1) | 175 (33.6) |
| Monitored but clinical significance unknown; n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Not monitored; n (%) | 175 (65.8) | 167 (65.5) | 342 (65.6) |
| **Respiration** |  |  |  |
| Clinically significant abnormality; n (%) | 8 (3.0) | 7 (2.7) | 15 (2.9) |
| Treatment required; n (%) | 6 (75.0) | 5 (71.4) | 11 (73.3) |
| Treatment not required; n (%) | 2 (25.0) | 1 (14.3) | 3 (20.0) |
| Treatment required unknown; n (%) | 0 (0.0) | 1 (14.3) | 1 (6.7) |
| Not clinically significant abnormality; n (%) | 248 (93.2) | 235 (92.2) | 483 (92.7) |
| Not monitored; n (%) | 10 (3.8) | 13 (5.1) | 23 (4.4) |
| **Body Temperature** |  |  |  |
| Clinically significant abnormality; n (%) | 9 (3.4) | 13 (5.1) | 22 (4.2) |
| Treatment required; n (%) | 5 (55.6) | 6 (46.2) | 11 (50.0) |
| Treatment not required; n (%) | 2 (22.2) | 6 (46.2) | 8 (36.4) |
| Treatment required unknown; n (%) | 2 (22.2) | 1 (7.7) | 3 (13.6) |
| Not clinically significant abnormality; n (%) | 247 (92.9) | 225 (88.2) | 472 (90.6) |
| Monitored but clinical significance unknown; n (%) | 0 (0.0) | 1 (0.4) | 1 (0.2) |
| Not monitored; n (%) | 10 (3.8) | 16 (6.3) | 26 (5.0) |

### Table S 23: Late Complications (from discharge up to 30 days post-operatively)

|  |  |  |  |
| --- | --- | --- | --- |
| ***Complication*** | **6 months surgery** | **12 months surgery** | **Overall** |
| Number of participants at 30 day follow up | 258 | 244 | 502 |
| Secondary bleeding |  |  |  |
| Yes; n (%) | 1 (0.4) | 3 (1.2) | 4 (0.8) |
| Not recorded | 2 | 0 | 2 |

### Table S 24: Listing of Serious Adverse Events

| **SAE No.** | **Surgery group** | **Main diagnostic symptom reported** | **Severity** | **Seriousness** | | **Relationship to intervention**  **(Most likely cause, if  unrelated or unlikely)** | | **Expectedness** | | **Unanticipated problem** | | **Action taken** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Principal Investigator (PI)** | **Chief Investigator (CI)** | **PI** | **CI** | **PI** | **CI** | **PI** | **CI** |  |
| *1* | 6 months | Poor feeding | Moderate | Required inpatient hospitalisation | Required inpatient hospitalisation | Unlikely (Other/Parental Anxiety) | Unlikely | Unexpected | Unexpected | No | No | Hospital re-admission |
| *2* | 6 months | Upper airway obstructive features | Severe | Prolonged existing hospitalisation | Prolonged existing hospitalisation | Probably | Unlikely | Unexpected | Unexpected | No | No | Prolongation of hospital stay |
| *3* | 12 months | Anaphylactic shock, pulmonary oedema, increased airway pressure, low O2 saturation | Severe | Life-threatening | Life-threatening | Unrelated (Prior or concomitant treatment) | Unrelated | Unexpected | Expected | No | No | Attendance at hospital emergency department |
| *4* | 6 months | Dehiscence during upper air way Infection | Moderate | Other important medical condition (Required additional surgery) | Required inpatient hospitalisation | Possibly (Other illness) | Unlikely | Expected | Expected | No | No | Hospital re-admission |

### Table S 25: Listing of Unanticipated Problems Submitted

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **SAE number** | **Surgery group as received** | **Detailed description of event7** | **Description of why an unanticipated problem (PI)** | **Action taken** |
| *NA* | 12 month | The child took the bottle from the immediate postoperative period on. four days after two sutures opened. Had a flu on the 7th day, with yellowish nasal discharge. Mother was using saline solution. Had fever of 38degrees on the 2nd day of the flu. Currently no fever. The child is normal without changes in the general condition. On the 8th day postoperative day, the child was running, fell down and scraped his nose and eyelid. On examination, without infectious signs. Had early loss of only a few oral sutures. Nasal aspect is intact | Two sutures opened unexpectedly four days after surgery and thereafter the child fell and injured the nose and eyelid region | The mother received medical advice and no other corrective actions were necessary |
| *NA* | 6 months | 02 days after surgical procedure (palatoplasty) (the child) had fever signs and respiratory difficulties due to bronchiolitis. 05 days after, palatal infection was observed due to brochiolitis | not informed |  |
| *NA* | 12 month | Extrusion of prolene suture through oral mucose in velum | The complication may not be considered to be an unanticipated problem. It will be important to collect data from other centres. | The stitches were removed on [date removed] by a consultant ENT surgeon at a local hospital, in general anaesthesia. |
| *NA* | 12 month | Anafylaxitic reaction for anesthesia investigation show allergic reaction to tracrium | See detailed description of event |  |
| *NA* | 6 months | Patient got infected (?) and feverish postoperatively. No treatment was given, spontaneous recovery. At follow up visit dehiscence of posterior part of soft palate was discovered | We don’t expect infections and dehiscence | Patient will receive re-operation after 6 months |

7Wording /spelling of descriptions as reported

### Table S 26: Summary of Secondary Surgeries

|  |  | **6 months surgery** | **12 months surgery** | **Overall** | |
| --- | --- | --- | --- | --- | --- |
| ***Secondary surgeries summary: Participant level*** | |  |  |  | |
| Number of participants: intention to treat | N | 279 | 273 | 552 | |
| Participants requiring secondary surgery | n (%) | 32 (11.5) | 29 (10.6) | 61 (11.1) | |
| Number of secondary surgeries |  |  |  |  | |
| 1 | n (%) | 27 (84.4) | 24 (82.8) | 51 (83.6) | |
| 2 | n (%) | 5 (15.6) | 5 (17.2) | 10 (16.4) | |
| Age at initial secondary surgery (years) |  |  |  |  | |
|  | Mean ± sd | 2.93 ± 1.39 | 3.15 ± 1.18 | 3.03 ± 1.29 | |
|  | [Min, Max] | [0.76, 5.22] | [1.34, 4.95] | [0.76, 5.22] | |
| Reason for surgeryA |  |  |  |  | |
| Dehiscence | n (%) | 10(3.6) | 7(2.6) | 17(3.1) | |
| Fistula | n (%) | 7(2.5) | 12(4.4) | 19(3.4) | |
| Velopharyngeal Insufficiency | n (%) | 27(9.7) | 16(5.9) | 43(7.8) | |
| Other see Table S27 | n (%) | 2(0.7) | 3(1.1) | 5(0.9) | |
| ***Details of secondary surgery: Surgery level*** | |  |  |  |
| Number of surgeries | N | 37 | 34 | 71 | |
| Age at secondary surgery (years) | Mean ± sd | 3.09 ± 1.36 | 3.25 ± 1.21 | 3.17 ± 1.28 | |
|  | [Min, Max] | [0.76, 5.22] | [1.34, 4.95] | [0.76, 5.22] | |
| Reason for secondary surgery |  |  |  |  | |
| Dehiscence | n (%) | 10 (27.0) | 9 (28.1) | 19 (27.5) | |
| Fistula | n (%) | 7 (18.9) | 13 (39.4) | 20 (28.6) | |
| Velopharyngeal Insufficiency | n (%) | 30 (81.1) | 17 (53.1) | 47 (68.1) | |
| Other, see Table S 27 | n (%) | 2 (5.4) | 3 (8.8) | 5 (7.0) | |

AMore than one reason may be indicated for surgery

### Table S 27: 'Other' Reasons Provided for Secondary Surgery

|  |  |  |  |
| --- | --- | --- | --- |
| **Row** | **Surgery group** | **Number of secondary surgeries** | **Other reason for additional surgery** |
| 1 | 6-months | 1st | Reflux |
| 2 | 12-months | 1st | nasal reflux |
| 3 | 12-months | 1st | Delayed hard palate closure - protocol, so planned residual cleft closure |
| 4 | 12-months | 1st | Second stage repair |
| 5 | 6-months | 2nd | Division of buccal pedicle |

### Table S 28: Speech Therapy Received up to 1 Year Visit

|  | **6 month surgery** | **12 month surgery** | **Overall** |
| --- | --- | --- | --- |
| **Number of participants** | 279 | 273 | 552 |
| **Form completed** n(%) | 194 (69.5) | 190 (69.6) | 384 (69.6) |
| **Seen by SLT based at trial site since birth;** |  |  |  |
| Yes; n (%) | 191 (98.5) | 188 (98.9) | 379 (98.7) |
| No; n (%) | 3 (1.5) | 2 (1.1) | 5 (1.3) |
|  |  |  |  |
| *Number of visits;* |  |  |  |
| N | 191 | 188 | 379 |
| Mean (sd) | 1.77 (0.65) | 1.51 (0.57) | 1.64 (0.62) |
| Median | 2.00 | 1.00 | 2.00 |
| (LQ, UQ, IQR) | (1.00, 2.00, 1.00) | (1.00, 2.00, 1.00) | (1.00, 2.00, 1.00) |
| [Min, Max] | [1.00, 4.00] | [1.00, 4.00] | [1.00, 4.00] |
| **Counselling/advice to parents;** |  |  |  |
| Yes; n (%) | 186 (97.4) | 180 (95.7) | 366 (96.6) |
| No; n (%) | 5 (2.6) | 8 (4.3) | 13 (3.4) |
| *Number of visits;* |  |  |  |
| N | 185 | 177 | 362 |
| Mean (sd) | 1.74 (0.61) | 1.46 (0.53) | 1.60 (0.59) |
| Median | 2.00 | 1.00 | 2.00 |
| (LQ, UQ, IQR) | (1.00, 2.00, 1.00) | (1.00, 2.00, 1.00) | (1.00, 2.00, 1.00) |
| [Min, Max] | [1.00, 4.00] | [1.00, 3.00] | [1.00, 4.00] |
| Item not recorded | 1 | 3 | 4 |
| **Treatment speech therapy - information**; |  |  |  |
| Yes; n (%) | 15 (7.9) | 10 (5.3) | 25 (6.6) |
| No; n (%) | 175 (92.1) | 178 (94.7) | 353 (93.4) |
| Item not recorded | 1 | 0 | 1 |
| *Number of visits;* |  |  |  |
| N | 15 | 10 | 25 |
| Mean (sd) | 1.27 (0.80) | 1.00 (0.00) | 1.16 (0.62) |
| Median | 1.00 | 1.00 | 1.00 |
| (LQ, UQ, IQR) | (1.00, 1.00, 0.00) | (1.00, 1.00, 0.00) | (1.00, 1.00, 0.00) |
| [Min, Max] | [1.00, 4.00] | [1.00, 1.00] | [1.00, 4.00] |
| **Treatment speech therapy – early intervention** |  |  |  |
| Yes; n (%) | 2 (1.1) | 6 (3.2) | 8 (2.1) |
| No; n (%) | 188 (98.9) | 182 (96.8) | 370 (97.9) |
| Item not recorded | 1 | 0 | 1 |
| *Number of visits;* |  |  |  |
| N | 2 | 6 | 8 |
| Mean (sd) | 1.00 (0.00) | 1.00 (0.00) | 1.00 (0.00) |
| Median | 1.00 | 1.00 | 1.00 |
| (LQ, UQ, IQR) | (1.00, 1.00, 0.00) | (1.00, 1.00, 0.00) | (1.00, 1.00, 0.00) |
| [Min, Max] | [1.00, 1.00] | [1.00, 1.00] | [1.00, 1.00] |
| Not recorded | 0 | 0 | 0 |

### Table S 29: Speech Therapy Received up to 3 Year Visit

|  | **6 month surgery**  (n=279) | **12 month surgery**  (n=273) | **Overall**  (n=552) |
| --- | --- | --- | --- |
| **Number of participants** | 245 (87.8) | 240 (87.9) | 485 (87.9) |
| **Seen by SLT;** |  |  |  |
| Yes; n (%) | 227 (92.7) | 225 (93.8) | 452 (93.2) |
| No; n (%) | 18 (7.3) | 15 (6.3) | 33 (6.8) |
|  |  |  |  |
| **Seen by SLT at trial site since 12 monthsA:** |  |  |  |
| Yes; n (%) | 219 (96.5) | 220 (97.8) | 439 (97.1) |
| No; n (%) | 8 (3.5) | 5 (2.2) | 13 (2.9) |
| **Reviewed/monitored;** |  |  |  |
| Yes; n (%) | 219 (100.0) | 219 (99.5) | 438 (99.8) |
| No; n (%) | 0 (0.0) | 1 (0.5) | 1 (0.2) |
| *Number of visits;* |  |  |  |
| N | 216 | 214 | 430 |
| Mean (sd) | 2.09 (1.95) | 2.07 (1.95) | 2.08 (1.95) |
| Median (LQ, UQ, IQR) | 1.00 (1.00, 3.00, 2.00) | 1.00 (1.00, 3.00, 2.00) | 1.00 (1.00, 3.00, 2.00) |
| [Min, Max] | [0.00, 16.00] | [1.00, 18.00] | [0.00, 18.00] |
| Not recorded | 3 | 5 | 8 |
| **Received direct therapy** |  |  |  |
| Yes; n (%) | 15 (6.8) | 10 (4.6) | 25 (5.7) |
| No; n (%) | 204 (93.2) | 209 (95.4) | 413 (94.3) |
| Not recorded | 0 | 1 | 1 |
| *Number of visits;* |  |  |  |
| N | 15 | 10 | 25 |
| Mean (sd) | 5.20 (4.09) | 11.60 (13.40) | 7.76 (9.35) |
| Median | 4.00 | 7.50 | 5.00 |
| (LQ, UQ, IQR) | (2.00, 7.00, 5.00) | (4.00, 13.00, 9.00) | (3.00, 9.00, 6.00) |
| [Min, Max] | [1.00, 17.00] | [1.00, 47.00] | [1.00, 47.00] |
| **Received indirect therapy;** |  |  |  |
| Yes; n (%) | 3 (1.4) | 1 (0.5) | 4 (0.9) |
| No; n (%) | 216 (98.6) | 218 (99.5) | 434 (99.1) |
| Not recorded | 0 | 1 | 1 |
| *Number of visits;* |  |  |  |
| N | 3 | 1 | 4 |
| Mean (sd) | 3.33 (2.52) | 1.00 (.) | 2.75 (2.36) |
| Median | 3.00 | 1.00 | 2.00 |
| (LQ, UQ, IQR) | (1.00, 6.00, 5.00) | (1.00, 1.00, 0.00) | (1.00, 4.50, 3.50) |
| [Min, Max] | [1.00, 6.00] | [1.00, 1.00] | [1.00, 6.00] |
|  |  |  |  |
| **Seen by local SLT;** |  |  |  |
| Yes; n (%) | 47 (20.7) | 50 (22.2) | 97 (21.5) |
| No; n (%) | 180 (79.3) | 175 (77.8) | 355 (78.5) |
| **Reviewed/monitored;** |  |  |  |
| Yes; n (%) | 21 (75.0) | 29 (82.9) | 50 (79.4) |
| No; n (%) | 7 (25.0) | 6 (17.1) | 13 (20.6) |
| Not recorded | 19 | 15 | 34 |
| *Number of visits;* |  |  |  |
| N | 21 | 29 | 50 |
| Mean (sd) | 2.62 (2.20) | 4.79 (5.14) | 3.88 (4.27) |
| Median | 2.00 | 3.00 | 2.50 |
| (LQ, UQ, IQR) | (1.00, 3.00, 2.00) | (2.00, 5.00, 3.00) | (1.00, 5.00, 4.00) |
| [Min, Max] | [1.00, 9.00] | [1.00, 22.00] | [1.00, 22.00] |
| **Received direct therapy** |  |  |  |
| Yes; n (%) | 15 (53.6) | 19 (55.9) | 34 (54.8) |
| No; n (%) | 13 (46.4) | 15 (44.1) | 28 (45.2) |
| Not recorded | 19 | 16 | 35 |
| *Number of visits;* |  |  |  |
| N | 14 | 19 | 33 |
| Mean (sd) | 7.64 (5.37) | 13.16 (18.46) | 10.82 (14.53) |
| Median | 6.00 | 5.00 | 5.00 |
| (LQ, UQ, IQR) | (4.00, 10.00, 6.00) | (2.00, 22.00, 20.00) | (4.00, 10.00, 6.00) |
| [Min, Max] | [1.00, 20.00] | [1.00, 72.00] | [1.00, 72.00] |
| Not recorded | 1 | 0 | 1 |
| **Received indirect therapy**; |  |  |  |
| Yes; n (%) | 7 (25.0) | 6 (17.6) | 13 (21.0) |
| No; n (%) | 21 (75.0) | 28 (82.4) | 49 (79.0) |
| Not recorded | 19 | 16 | 35 |
| *Number of visits;* |  |  |  |
| N | 7 | 5 | 12 |
| Mean (sd) | 4.43 (4.76) | 8.80 (6.83) | 6.25 (5.86) |
| Median | 3.00 | 7.00 | 3.50 |
| (LQ, UQ, IQR) | (2.00, 4.00, 2.00) | (4.00, 10.00, 6.00) | (3.00, 8.50, 5.50) |
| [Min, Max] | [1.00, 15.00] | [3.00, 20.00] | [1.00, 20.00] |
| Not recorded | 0 | 1 | 1 |

### Table S 30: Speech Therapy Received up to 5 Year Visit

|  | **6 month surgery**  (n=279) | **12 month surgery**  (n=273) | **Overall**  (n=552) |
| --- | --- | --- | --- |
| **Number of participants** | 244 (87.5) | 234 (85.7) | 478 (86.6) |
| **Seen by SLT;** |  |  |  |
| Yes; n (%) | 185 (75.8) | 172 (73.5) | 357 (74.7) |
| No; n (%) | 59 (24.2) | 62 (26.5) | 121 (25.3) |
|  |  |  |  |
| **Seen by SLT at trial site since 3 yearA:** |  |  |  |
| Yes; n (%) | 168 (90.8) | 150 (87.2) | 318 (89.1) |
| No; n (%) | 17 (9.2) | 22 (12.8) | 39 (10.9) |
| **Reviewed/monitored;** |  |  |  |
| Yes; n (%) | 166 (98.8) | 146 (98.0) | 312 (98.4) |
| No; n (%) | 2 (1.2) | 3 (2.0) | 5 (1.6) |
| Not recorded | 0 | 1 | 1 |
| **Received direct therapy** |  |  |  |
| Yes; n (%) | 14 (8.4) | 16 (10.8) | 30 (9.5) |
| No; n (%) | 153 (91.6) | 132 (89.2) | 285 (90.5) |
| Not recorded | 1 | 2 | 3 |
| *Number of visits;* |  |  |  |
| N | 14 | 16 | 30 |
| Mean (sd) | 6.14 (7.67) | 9.50 (11.44) | 7.93 (9.85) |
| Median | 3.00 | 6.00 | 5.50 |
| (LQ, UQ, IQR) | (2.00, 7.00, 5.00) | (2.50, 10.50, 8.00) | (2.00, 10.00, 8.00) |
| [Min, Max] | [1.00, 29.00] | [1.00, 47.00] | [1.00, 47.00] |
| **Received indirect therapy;** |  |  |  |
| Yes; n (%) | 0 | 0 | 0 |
| No; n (%) | 166 (100.0) | 148 (100.0) | 314 (100.0) |
| Not recorded | 2 | 2 | 4 |
| *Number of visits;* |  |  |  |
| N | 0 | 0 | 0 |
| Mean (sd) | . | . | . |
| Median (LQ, UQ, IQR) | . | . | . |
| [Min, Max] | . | . | . |
|  |  |  |  |
| **Seen by local SLT;** |  |  |  |
| Yes; n (%) | 74 (40.0) | 70 (40.7) | 144 (40.3) |
| No; n (%) | 111 (60.0) | 102 (59.3) | 213 (59.7) |
| **Reviewed/monitored;** |  |  |  |
| Yes; n (%) | 36 (69.2) | 40 (72.7) | 76 (71.0) |
| No; n (%) | 16 (30.8) | 15 (27.3) | 31 (29.0) |
| Not recorded | 22 | 15 | 37 |
| *Number of visits;* |  |  |  |
| N | 36 | 39 | 75 |
| Mean (sd) | 4.72 (9.38) | 4.67 (9.62) | 4.69 (9.44) |
| Median | 2.00 | 3.00 | 2.00 |
| (LQ, UQ, IQR) | (1.00, 4.00, 3.00) | (1.00, 5.00, 4.00) | (1.00, 5.00, 4.00) |
| [Min, Max] | [1.00, 50.00] | [1.00, 62.00] | [1.00, 62.00] |
| Not recorded | 0 | 1 | 1 |
| **Received direct therapy** |  |  |  |
| Yes; n (%) | 36 (69.2) | 43 (76.8) | 79 (73.1) |
| No; n (%) | 16 (30.8) | 13 (23.2) | 29 (26.9) |
| Not recorded | 22 | 14 | 36 |
| *Number of visits;* |  |  |  |
| N | 36 | 43 | 79 |
| Mean (sd) | 18.06 (18.59) | 17.40 (21.56) | 17.70 (20.14) |
| Median | 10.00 | 12.00 | 11.00 |
| (LQ, UQ, IQR) | (4.50, 32.00, 27.50) | (3.00, 21.00, 18.00) | (4.00, 22.00, 18.00) |
| [Min, Max] | [1.00, 64.00] | [1.00, 99.00] | [1.00, 99.00] |
| **Received indirect therapy**; |  |  |  |
| Yes; n (%) | 20 (38.5) | 10 (18.2) | 30 (28.0) |
| No; n (%) | 32 (61.5) | 45 (81.8) | 77 (72.0) |
| Not recorded | 22 | 15 | 37 |
| *Number of visits;* |  |  |  |
| N | 16 | 8 | 24 |
| Mean (sd) | 7.19 (7.40) | 22.13 (19.84) | 12.17 (14.39) |
| Median | 4.50 | 19.50 | 5.50 |
| (LQ, UQ, IQR) | (1.50, 9.50, 8.00) | (3.50, 40.00, 36.50) | (2.00, 18.50, 16.50) |
| [Min, Max] | [1.00, 25.00] | [1.00, 50.00] | [1.00, 50.00] |
| Not recorded | 4 | 2 | 6 |

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