Supplementary Material No. 5:

Ethics Approval and Summary of substantial protocol amendments

Research Ethics Committees Approval

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

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

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

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

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

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

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

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

TBC: to be confirmed

TOPS Protocol Version 2.0 (10 Mar 2010)

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

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

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

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

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

TOPS Protocol Version 3.0 (01 May 2013)

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

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

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

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

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

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

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

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

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

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

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

TOPS Protocol Version 5.0 (22 August 2018)

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

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

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

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

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