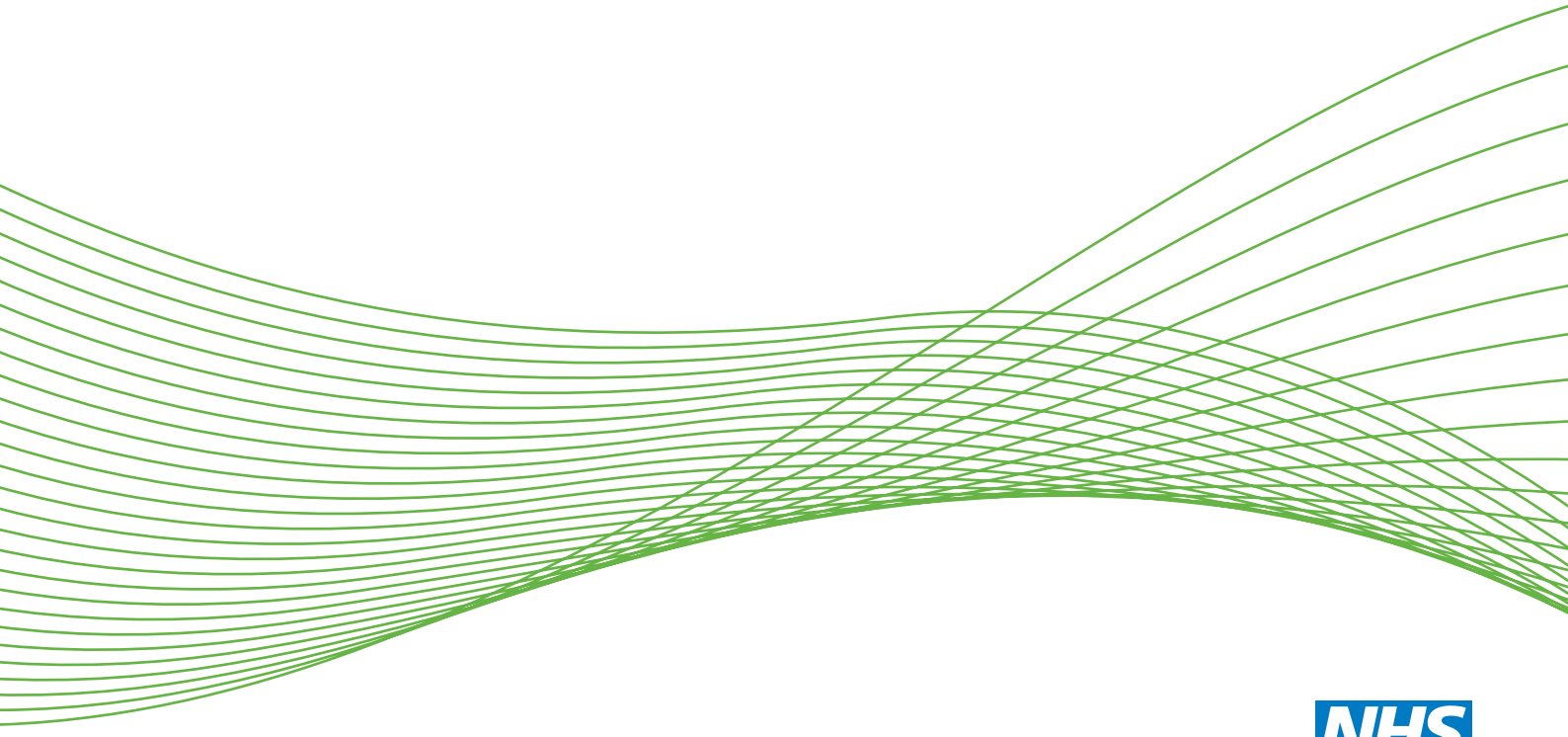
HEALTH TECHNOLOGY ASSESSMENT

VOLUME 18 ISSUE 41 JUNE 2014
ISSN 1366-5278

United Kingdom Oscillation Study: long-term outcomes of a randomised trial of two modes of neonatal ventilation

Anne Greenough, Janet Peacock, Sanja Zivanovic, Mireia Alcazar-Paris, Jessica Lo, Neil Marlow and Sandy Calvert



National Institute for Health Research

DOI 10.3310/hta18410

United Kingdom Oscillation Study: long-term outcomes of a randomised trial of two modes of neonatal ventilation

Anne Greenough,[1]* Janet Peacock,[2] Sanja Zivanovic,[1] Mireia Alcazar-Paris,[1] Jessica Lo,[2] Neil Marlow[3] and Sandy Calvert[4]

[1]Division of Asthma, Allergy and Lung Biology, Medical Research Council (MRC) Centre for Allergic Mechanisms in Asthma, King's College London, London, UK
[2]Division of Health and Social Care Research, King's College London, London, UK
[3]Institute for Women's Health, University College London, London, UK
[4]Department of Child Health, St George's Hospital, University of London, London, UK

*Corresponding author

Declared competing interests of authors: Anne Greenough has held grants from various ventilator manufacturers and received honoraria for giving lectures and advising various ventilator manufacturers.

Published June 2014
DOI: 10.3310/hta18410

This report should be referenced as follows:

Greenough A, Peacock J, Zivanovic S, Alcazar-Paris M, Lo J, Marlow N, *et al*. United Kingdom Oscillation Study: long-term outcomes of a randomised trial of two modes of neonatal ventilation. *Health Technol Assess* 2014;**18**(41).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Five-year impact factor: 5.804

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: www.hta.ac.uk/

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 08/116/10. The contractual start date was in March 2011. The draft report began editorial review in May 2013 and was accepted for publication in January 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland www.prepress-projects.co.uk).

Editor-in-Chief of *Health Technology Assessment* and NIHR Journals Library

Professor Tom Walley Director, NIHR Evaluation, Trials and Studies and Director of the HTA Programme, UK

NIHR Journals Library Editors

Professor Ken Stein Chair of HTA Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andree Le May Chair of NIHR Journals Library Editorial Group (EME, HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

Professor Aileen Clarke Professor of Public Health and Health Services Research, Warwick Medical School, University of Warwick, UK

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Peter Davidson Director of NETSCC, HTA, UK

Ms Tara Lamont Scientific Advisor, NETSCC, UK

Professor Elaine McColl Director, Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Professor of Health Sciences Research, Faculty of Education, University of Winchester, UK

Professor Jane Norman Professor of Maternal and Fetal Health, University of Edinburgh, UK

Professor John Powell Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, University College London, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Please visit the website for a list of members of the NIHR Journals Library Board:
www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: nihredit@southampton.ac.uk

Abstract

United Kingdom Oscillation Study: long-term outcomes of a randomised trial of two modes of neonatal ventilation

Anne Greenough,[1]* Janet Peacock,[2] Sanja Zivanovic,[1] Mireia Alcazar-Paris,[1] Jessica Lo,[2] Neil Marlow[3] and Sandy Calvert[4]

[1]Division of Asthma, Allergy and Lung Biology, Medical Research Council (MRC) Centre for Allergic Mechanisms in Asthma, King's College London, London, UK
[2]Division of Health and Social Care Research, King's College London, London, UK
[3]Institute for Women's Health, University College London, London, UK
[3]Institute for Women's Health, University College London, London, UK
[4]Department of Child Health, St George's Hospital, University of London, London, UK

*Corresponding author anne.greenough@kcl.ac.uk

Background: One in 200 infants in the UK is born extremely prematurely, i.e. before 29 weeks of gestation. Seventy-five per cent of such infants survive, but many have long-term respiratory and/or functional problems.

Objectives: To compare respiratory and functional outcomes of school-age children born extremely prematurely who received either high-frequency oscillation (HFO) or conventional ventilation (CV) immediately after birth to test the hypothesis that the use of HFO would be associated with superior small airway function at school age without adverse effects.

Design: Follow-up of a randomised trial, the United Kingdom Oscillation Study, in which infants were randomised to receive HFO or CV within 1 hour of birth.

Setting: King's College Hospital NHS Foundation Trust, London, UK.

Participants: Three hundred and nineteen children aged between 11 and 14 years were recruited (160 had received HFO); the planned sample size was 320.

Interventions: HFO versus CV.

Main outcome measures: The results of comprehensive lung function assessments (primary outcome small airway function), echocardiographic examinations and respiratory, health-related quality of life and functional assessment questionnaires.

Results: Significant baseline differences in maternal and neonatal characteristics between the two groups favoured the CV group, who had a higher mean birthweight (56 g) and were born later (0.3 weeks), and a greater proportion of whom had received surfactant. There were no significant differences between the two groups in their characteristics when assessed at 11–14 years of age. The children who had received HFO had significantly superior small airway function; their forced expiratory flow at 75% vital capacity *z*-score was 0.23 higher than that of the CV group [95% confidence interval (CI) 0.02 to 0.45]. Thirty-seven per cent of the HFO group and 46% of the CV group had small airway function results that were below the tenth centile. There were significant differences between ventilation groups in favour of HFO for other lung function results as expressed by *z*-scores {forced expiratory volume at 1 minute (FEV_1) [difference 0.35 (95% CI 0.09 to 0.60)], the ratio of FEV_1 to forced vital capacity [0.58 (95% CI 0.16 to 0.99)], diffusing capacity of the lung for carbon monoxide [0.31 (95% CI 0.04 to 0.58)], maximum

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

vital capacity [0.31 (95% CI 0.05 to 0.57)]} and expressed as % predicted {peak expiratory flow rate [5.85 (95% CI 2.21 to 9.49)] and respiratory resistance at 5 Hz [–7.13 Hz (95% CI –2.50 to –1.76 Hz)]}. There were no significant differences between ventilation groups with regard to the echocardiographic results, respiratory morbidity in the last 12 months, health problems, Health Utilities Index scores or Strengths and Difficulties Questionnaire (SDQ) scores. When SDQ scores were dichotomised, there was a significant finding for one subscale: a greater proportion of HFO children reported emotional symptoms. This finding was not replicated by parents' or teachers' reports. Two hundred and twenty-four teachers completed questionnaires regarding the children's educational attainment and provision. There were statistically significant differences in attainment in three subjects in favour of HFO: art and design, information technology, and design and technology. The HFO children had lower risk of receiving special education needs support [odds ratio 0.56 (95% CI 0.32 to 1.00)], but the difference was not significant.

Conclusions: Follow-up at 11–14 years of age of extremely prematurely born infants entered into a randomised trial of HFO versus CV has demonstrated significant differences in lung function in favour of HFO. There was no evidence that this was offset by poorer functional outcomes; indeed, HFO children did better in some school subjects. It will be important to determine whether or not these differences are maintained after puberty as this is the last positive effect on lung function.

Trial registration: Current Controlled Trials ISRCTN98436149.

Funding details: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 18, No. 41. See the NIHR Journals Library website for further project information.

Contents

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

List of tables

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

List of figures

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

List of abbreviations

ADHD	attention deficit hyperactivity disorder
BPD	bronchopulmonary dysplasia
CI	confidence interval
CV	conventional ventilation
$D_{L,CO}$	diffusing capacity of the lung for carbon monoxide
FEF	forced expiratory flow
FEF_{25}	forced expiratory flow at 25% vital capacity
FEF_{50}	forced expiratory flow at 50% vital capacity
FEF_{75}	forced expiratory flow at 75% vital capacity
*F*eNO	fraction of exhaled nitric oxide
FEV_1	forced expiratory volume at 1 minute
FiO_2	fraction of inspired oxygen
FRC	functional residual capacity
FRC_{He}	functional residual capacity measured by helium gas dilution
FRC_{pleth}	functional residual capacity measured by whole-body plethysmography
FVC	forced vital capacity
HFO	high-frequency oscillation
HFOV	high-frequency oscillatory ventilation
HUI-3	Health Utilities Index version 3
IMD	Index of Multiple Deprivation
IT	information technology
KCH	King's College Hospital
LCI	lung clearance index
mPAP	mean pulmonary artery pressure
OR	odds ratio
$PaCO_2$	partial pressure of carbon dioxide
*P*ao	pressure at airway opening
PaO_2	partial pressure of oxygen
PEF	peak expiratory flow rate
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
R5Hz	respiratory resistance at 5 Hz
RA	right artial
R_{aw}	inspiratory and expiratory airway resistance
RR	relative risk
RV	residual volume
RVENT	right ventricular
SD	standard deviation
SDQ	Strengths and Difficulties Questionnaire
SEN	special educational needs
tE	expiratory time
TLC	total lung capacity
tPTEF	time taken to achieve peak expiratory flow
UKOS	United Kingdom Oscillation Study
V_{pleth}	plethysmographic volume shift during airway occlusion
VA	alveolar volume
VC_{MAX}	vital capacity

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Plain English summary

Background

One in 200 babies in the UK is born extremely prematurely, that is before 29 weeks of gestation. Advances in neonatal care have meant that 75% of such babies survive, but many have long-term breathing problems and difficulties at school. The majority of such babies require breathing support from birth. Our aim was to determine if the breathing support technique used immediately after birth influenced breathing problems and school performance in children born extremely prematurely.

Methods

Children entered into a multicentre, randomised trial, the United Kingdom Oscillation Study, were assessed when aged between 11 and 14 years. The children had been randomised to receive either high-frequency oscillation (HFO) or conventional ventilation (CV) within 1 hour of birth. At 11–14 years of age, they underwent comprehensive lung function and cardiac assessments. Respiratory, health-related quality of life and school performance assessment questionnaires were completed by the children, their parents and their teachers.

Results

Three hundred and nineteen children were assessed; 160 had been supported by HFO. On average, the children in the HFO group had significantly better breathing test results than those in the CV group and their teachers reported them to have better achievements in art and design, information technology, and design and technology.

Conclusion

These results demonstrate that use of HFO rather than CV immediately after birth in extremely prematurely born infants is associated with better breathing and educational outcomes at 11–14 years of age.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Scientific summary

Background

One in 200 infants in the UK is born extremely prematurely, that is before 29 weeks of gestation. Advances in neonatal care have meant that 75% of such babies survive, but many have long-term respiratory and/or functional problems; for example, up to 40% develop bronchopulmonary dysplasia (BPD). Infants with BPD have frequent hospital admissions in the first 2 years after birth, particularly for respiratory infections. Supplementary oxygen at home may be required for many months. BPD infants who require home oxygen compared with those who do not have greater health-care utilisation with an associated doubling of their cost of care throughout the preschool years; the families' quality of life has also been reported to be poorer. At preschool and school age, troublesome recurrent respiratory symptoms are common. In one cohort of children who had BPD, 28% coughed more than once per week and 7% wheezed more than once per week in the preschool years, and in a cohort of 7- to 8-year-olds, whereas only 7% of term controls were wheezing, 30% of BPD children and 24% of prematurely born children without BPD were also affected. Troublesome symptoms and lung function abnormalities are even seen in young adults who had BPD. Nine per cent of very prematurely born infants have serious disability at 2 years of age. At school age, BPD is associated with poor cognitive and academic achievement, which is the predominant problem leading to educational special needs support. This poor cognitive and academic achievement, together with motor, attention and behavioural problems, contributes to functional deficits that may persist to adult life.

Infants born extremely prematurely usually require respiratory support which, although often life-saving, is frequently associated with lung damage which leads to the long-term respiratory problems described above. The United Kingdom Oscillation Study (UKOS) was a multicentre, randomised trial undertaken to determine whether use of high-frequency oscillation (HFO) or conventional ventilation (CV) from within 1 hour of birth would reduce mortality and the incidence of BPD. A total of 797 infants born before 29 weeks of gestation were randomised from 25 centres.

The aim of this follow-up study was to determine the long-term outcomes of children at 11–14 years of age who had been recruited into UKOS and, in particular, to test the hypothesis that use of HFO in the newborn period would be associated with superior small airway function at school age. In addition, we wished to assess the effects of HFO compared with CV on a broad range of respiratory health and educational outcomes as the results of those follow-up assessments of children from the randomised trial would robustly inform the true risk–benefit ratio of the use of HFO in very prematurely born infants. A null (no difference) finding would be as clinically important as any difference that might be observed, as it would resolve the uncertainty surrounding the long-term effects of HFO and CV and determine whether or not HFO could be safely used to support very prematurely born infants. A subsidiary aim was to track the lung function in the subset of children previously assessed at 1 year, as those results would highlight whether or not changes in lung function over time differed according to ventilation mode.

Study design

Comprehensive lung function and cardiac assessments were undertaken when the children were 11–14 years of age at King's College Hospital (KCH) NHS Foundation Trust, London, UK. All assessments were made by a research fellow and research nurse blind to the child's randomised mode of ventilation. Respiratory, health-related quality of life and functional assessment questionnaires were completed. Parents and their children who were unable to attend the London centre completed the questionnaires only.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Sample size

The primary outcome was small airway function. A sample size of 320 allowed a difference of 0.36 standard deviations (SDs) in the mean lung function results to be detected with 90% power at the 5% significance level. Differences in lung function of equal to 1.0 SD have been demonstrated in children with and without adverse respiratory outcomes; thus, our sample size allowed detection of a clinically important difference in lung function. Secondary outcomes were other aspects of respiratory health and symptoms, multiattribute health status as assessed by Health Utilities Index version 3 (HUI-3), the Strengths and Difficulties Questionnaire (SDQ), special educational needs (SEN) support and subject-specific educational attainment.

Results

Three hundred and nineteen children (160 received HFO) were recruited into this follow-up study (planned sample size 320): 59 took part by completing the detailed questionnaires only, four completed the assessment only and 256 completed both the questionnaires and assessment at KCH.

Comparison of the baseline characteristics of those who were and were not recruited demonstrated significant differences with regard to only the mother's ethnic group. Children who were recruited were more likely to have a Caucasian mother (90% vs. 73%), and were less likely to have a mother who smoked during pregnancy (24% vs. 38%). Differences in the birthweight *z*-score was of borderline significance; recruited children had, on average, a lower *z*-score than those not recruited (mean –0.59 vs. –0.41).

There were four maternal and neonatal characteristics factors that differed significantly between the two ventilation groups: the CV group had a higher mean birthweight (923 g vs. 867 g), and were born at a slightly later gestational age (mean gestational age 27.0 weeks vs. 26.7 weeks), a greater proportion were born at 26–28 weeks of gestation rather than a lower gestational age (81% vs. 68%) and a greater proportion had received surfactant (99% vs. 95%).

There were no significant differences between the two groups in their characteristics when they were assessed at 11–14 years of age. There was a statistically significant difference in the primary outcome of small airway function [forced expiratory flow at 75% vital capacity (FEF_{75})]; the *z*-score was higher in the HFO group (mean FEF_{75} *z*-score was –1.19 vs. –0.97). This difference was significant both in the unadjusted model that allowed for multiple births, but did not include any covariates, and in the fully adjusted model which additionally adjusted for the baseline neonatal factors that had shown imbalance between the groups. The adjusted difference in mean *z*-scores was 0.23 [95% confidence interval (CI) 0.02 to 0.45]. There were a greater percentage of children with lung function results below the tenth centile in the CV group (46%) than in the HFO group (37%). There were similar mean differences between the groups for both forced expiratory flow at 50% vital capacity (FEF_{50}) and forced expiratory flow at 25% vital capacity (FEF_{25}). There were also significant differences between the ventilation groups with regard to a number of the other lung function results: forced expiratory volume at 1 minute (FEV_1), peak expiratory flow rate (PEF), diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$), maximum vital capacity (VC_{MAX}), respiratory resistance at 5 Hz and the FEV_1 : forced vital capacity (FVC) ratio. The results were all worse in the CV group. There were no significant differences with regard to airway hyper-reactivity and exhaled nitric oxide between the two groups. Sensitivity analyses were performed on the lung function measurement results; pubertal stage and cotinine levels were added to the fully adjusted model. This further analysis demonstrated findings consistent with those of the previous analysis, with significant differences in the primary outcome and the above secondary outcomes with similar effect sizes. Multiple imputation was used to allow for incomplete lung function data for some tests, which certain children were unable to do. Those analyses gave results that were unchanged from those reported above. Further

analyses adjusting for factors, such as Index of Multiple Deprivation score, that differed between those recruited and those not recruited did not change the findings.

Analysis of the lung function results of 42 children who had been assessed at 1 year of age and at age 11–14 years showed that their small airway function had deteriorated, as demonstrated by an increase in gas trapping.

There were no significant differences between the two ventilation groups with regard to the echocardiographic results.

There were no significant differences between ventilation groups with regard to respiratory morbidity in the last 12 months or health problems as documented by the parent-completed questionnaire. The HUI-3 was completed separately by the child and their parent(s); there were no significant differences by ventilation group. The SDQ was completed by the child, their parent and their teacher; there were no significant differences between the ventilation groups. When the SDQ scores were dichotomised, the only significant difference between the two groups was for the children's report of emotional symptoms, with a higher proportion in the HFO group [odds ratio (OR) 2.50 (95% CI 1.13 to 5.56)], but this was not confirmed by parental or teacher reports.

Two hundred and twenty-four teachers completed questionnaires regarding the children's educational attainment and provision, and returned them directly to the researchers. There were statistically significant differences in attainment in three subjects – art and design, information technology (IT) and design and technology; the attainment was better in the HFO group. There was a trend towards a smaller proportion of the HFO children receiving SEN support compared with the CV children [41% vs. 53%; OR 0.56 (95% CI 0.32 to 1.00)]. The results of the teacher rating scale for attention deficit hyperactivity disorder did not differ significantly by ventilation group.

Conclusions

We have demonstrated that school children born extremely prematurely who were supported by HFO in the neonatal period had significantly better lung function than those who were supported by CV. The HFO group had significantly better small airway function (FEF_{75}), as we had hypothesised. In addition, they also had superior large airway function and those results are particularly compelling as there were similar findings from different assessments of large airway function (FEV_1, FEF_{50}, FEF_{25}) including from the non-volitional test impulse oscillometry. In addition, the HFO group had better $D_{L,CO}$ results, suggesting a greater lung surface area for gas exchange. There were significant differences in the baseline characteristics of the two groups who were successfully followed up, all of which favoured the CV children. They were born at a significantly higher birthweight and gestational age, and a greater proportion had received surfactant. The differences between the two groups, with respect to the above lung function test results, remained significant after adjusting for those differences in baseline characteristics. The difference in the mean FEF_{75} results between the two groups was due to a shift in the entire CV group's distribution downwards, rather than an effect on only certain children. Thus, the use of HFO would potentially benefit all extremely prematurely born infants. The differences in lung function, although statistically significant, were relatively small, on average approximately 0.30 *z*-scores. Those differences were not associated with increased respiratory morbidity as documented by symptom status and need for medication on the parent-completed questionnaires or greater number of hospital admissions, but only three of the whole cohort had required admission to hospital for chest problems. Nevertheless, there was a difference of almost nine percentage points with regard to lung function results below the tenth centile in favour of the HFO group. Respiratory reserve in childhood may explain why there was no increase in respiratory morbidity in the CV group as documented by parent reports, but the CV group's poorer lung function may make them more vulnerable to lung function insults such as smoking.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

The results of our subset, who were also measured at 1 year of age, suggest that their small airway function has deteriorated, as they had greater evidence of gas trapping when assessed at 11–14 years of age than when they were assessed at 1 year corrected age. Those results are in keeping with the decline in small airway function seen in the first year after birth in moderately prematurely born infants and extremely prematurely born infants initially supported by CV. Thus, it will be very important to reassess all of the children to determine whether or not their lung function deteriorates further with increasing age and they become symptomatic.

We were concerned that any respiratory benefit associated with use of HFO might have been associated with adverse neurodevelopmental outcomes as, in some trials, HFO has been associated with increases in severe intracranial haemorrhage and periventricular leukomalacia. Those adverse outcomes could be the result of lung overdistension compromising cardiac output and cerebral perfusion and/or hypocarbia. However, no significant differences between the groups were seen regarding the majority of assessments of functional outcomes. A significantly greater proportion of the HFO children recorded that they had emotional symptoms on the SDQ questionnaire, but this difference was not found by the parents or teachers. There were significant differences between the two groups in educational attainment with regard to art and design, IT, and design and technology, all favouring the HFO children. In addition, a borderline significantly greater proportion of the CV children were receiving SEN support at school.

Our results emphasise the importance of the long-term follow-up of children born very prematurely entered into randomised trials if the full impact of interventions delivered in infancy is to be robustly determined. Furthermore, a lack of a positive result in infancy may not mean the intervention had no effect, but rather it may become manifest later and hence it is not possible to predict whether that effect could be adverse or beneficial on the results of short-term outcomes. It is essential that very prematurely born children entered into randomised trials are repeatedly assessed so that any changes with increasing age can be determined and appropriate treatment given. The results of this long-term follow-up should encourage neonatologists to use prophylactic HFO in extremely prematurely born infants.

Trial registration

This trial is registered as ISRCTN98436149.

Funding

This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 18, No. 41. See the NIHR Journals Library website for further project information.

Chapter 1 Background

One in 200 infants in the UK are born extremely prematurely, that is before 29 weeks of gestation. Advances in neonatal care have meant that 75% of such babies survive, but many have long-term respiratory and/or functional problems; for example, up to 40% develop bronchopulmonary dysplasia (BPD).[1] Affected infants have frequent hospital admissions in the first 2 years, particularly for respiratory infections.[2] In one series, one-quarter of BPD infants had three or more readmissions.[2] Supplementary oxygen at home may be required for many months.[3] BPD infants who required home oxygen had greater health-care utilisation than those who did not, with an associated doubling of their cost of care throughout the preschool years;[4] the families' quality of life has also been reported to be poorer.[5] At preschool and school age, troublesome recurrent respiratory symptoms are common. In one cohort of children who had BPD, 28% coughed more than once per week and 7% wheezed more than once per week in the preschool years,[4] and in a cohort of 7- to 8-year-olds, whereas only 7% of term controls were wheezing, 30% of BPD children and 24% of prematurely born children without BPD were also affected.[6] Troublesome symptoms and lung function abnormalities are even seen in young adults who had BPD.[7,8] Nine per cent of very prematurely born infants have serious disability at 2 years of age.[9] At school age, BPD is associated with poor cognitive and academic achievement, which is the predominant problem leading to educational special needs support. This poor cognitive and academic achievement, together with motor, attention and behavioural problems, contribute to functional deficits that may persist to adult life.[9]

Infants born extremely prematurely usually require respiratory support which, although often life-saving, is frequently associated with lung damage which leads to the long-term respiratory problems described above. As a consequence, new ventilation modes, including high-frequency oscillation (HFO), have been developed with the hope of reducing that adverse outcome. During HFO, a constant pressure is applied to optimise oxygenation and volume delivery is minimised. Unfortunately, if used inappropriately, HFO can increase severe intracranial haemorrhage and periventricular leukomalacia, which lead to adverse neurodevelopmental outcomes, including cerebral palsy, with an associated high cost of care. It was, therefore, essential that HFO use was assessed in an appropriately designed randomised controlled trial and hence the United Kingdom Oscillation Study (UKOS) was performed.

United Kingdom Oscillation Study

The UKOS was a multicentre, randomised trial undertaken to determine whether or not use of HFO or conventional ventilation (CV) from within 1 hour of birth would reduce mortality and the incidence of BPD. (The earlier results of UKOS discussed below were published separately elsewhere.)[1,10,11]

Infants were eligible for the study if their gestational age was between 23 weeks and 28 weeks plus 6 days, they were born in a participating centre and they required endotracheal intubation from birth and ongoing intensive care. Infants were excluded if they had to be transferred to another hospital for intensive care shortly after birth or had a major congenital malformation.

A total of 25 centres participated in the study – 22 in the UK and one each in Australia, Ireland and Singapore. To ensure that each centre had adequate experience with high-frequency oscillatory ventilation (HFOV), we required participating centres to have used this type of ventilatory support in a minimum of 20 infants before the study began. The quality of collected data was monitored and the statistical analyses were performed at the co-ordinating centre (St. George's Hospital, London, UK). Both the South Thames Multicentre Research Ethics Committee, London, UK, and the Local Research Ethics Committee at each participating centre approved the protocol.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Women at high risk of delivering an infant before 29 weeks of gestation were invited, before delivery, to participate in the trial, and oral or written assent was obtained. Randomisation occurred either when delivery was imminent or immediately after the infant was born. Written confirmation of consent was obtained from one or both parents within 24 hours after the birth, as directed by the Multicentre Research Ethics Committee. If consent was refused, the infant was excluded and the mode of ventilation was left to the discretion of the clinician.

After assent or consent had been obtained, infants were randomly assigned, in blocks of four, to either CV or HFOV, with stratification according to gestational age (two strata) and according to centre (25 strata). Procedures were implemented to ensure balanced assignment within strata at each participating centre. Each centre kept a log of all eligible infants and reasons for non-recruitment.

Within 1 hour after birth, eligible infants were assigned to receive either CV or HFOV as their primary mode of respiratory support. Unless the infant could be extubated electively, switching from the assigned mode of ventilation was permitted only during the first 120 hours after birth, if the clinical condition for a minimum of 1 hour met the criteria for treatment failure. These criteria were a partial pressure of oxygen (PaO_2) of < 49 mmHg in an infant receiving a fraction of inspired oxygen (FiO_2) of 1.0 following changes in the mean airway pressure or peak inspiratory pressure, or a partial pressure of carbon dioxide ($PaCO_2$) of > 60 mmHg despite interventions to improve ventilation, or both. If the infant still required ventilation after 120 hours of age, clinicians were free to use whichever mode of ventilation they wished. No changes in clinical management except those indicated below were specified as part of the trial. Conventional ventilation was delivered by time-cycled, pressure-limited ventilators starting with a rate of 60 breaths per minute and an inspiratory time of 0.4 seconds. Subsequently, ventilator settings were adjusted at the discretion of the attending clinician to maintain a PaO_2 between 49 and 75 mmHg and a $PaCO_2$ between 34 and 53 mmHg. HFOV, with optimisation of lung volume, was delivered by one of three models of high-frequency oscillator [the Dräger Babylog 8000 (Dräger Medical, Lubeck, Germany), the SensorMedics 3100A (CareFusion, San Diego, CA, USA), or the SLE 2000HFO (SLE Ltd, South Croydon, UK)], all of which have been shown to have similar performance characteristics at the frequencies recommended in this trial. Ventilation was begun at a mean airway pressure of 6–8 cmH_2O and a frequency of 10 Hz, and the amplitude was increased until the infant's chest was seen to be 'bouncing'. The ratio of inspiration to expiration was fixed at either 1 : 1 (with the Dräger or SLE ventilator) or 1 : 2 (with the SensorMedics ventilator), in accordance with the manufacturers' recommendations. The FiO_2 was initially set to ensure adequate oxygenation ($PaO_2 > 48$ mmHg), and, when the FiO_2 was > 0.3, the mean airway pressure was increased by 0.5–1.0 cmH_2O every 10–15 minutes until it was possible to decrease the FiO_2. The FiO_2 was reduced to 0.3 before the mean airway pressure was decreased, provided that the lungs were not hyperinflated (a condition defined by the flattening of the diaphragm below the margin of the ninth rib on chest radiography). Settings were then adjusted to maintain a PaO_2 between 49 and 75 mmHg and a $PaCO_2$ between 34 and 53 mmHg. Oxygenation was managed by adjustment of the mean airway pressure and the FiO_2; $PaCO_2$ was managed by adjustment of the oscillatory amplitude, but if difficulties in the management of the $PaCO_2$ persisted after a change in the amplitude alone, the ventilator frequency was also adjusted. If pulmonary interstitial emphysema developed, the strategy was changed to one of low volume and high FiO_2 with the reduction in the mean airway pressure to the lowest level compatible with a PaO_2 of 49–75 mmHg, even if this strategy resulted in an increase in the FiO_2 to the range of 0.7–0.9. No simultaneous positive-pressure breathing was used. The protocol recommended that infants receive exogenous surfactant as soon as possible after birth. A subsequent dose (given approximately 12 hours later) was recommended for infants receiving CV if the FiO_2 was > 0.3 and for infants receiving HFOV if the mean airway pressure was > 10 cmH_2O.

Definition of outcomes and sample size calculations

The primary outcome measure was a composite of death or chronic lung disease (defined by a dependence on supplemental oxygen) at 36 weeks of postmenstrual age. Secondary outcome measures were the age at death, the age at hospital discharge, major abnormality on cranial ultrasonography, air leak, failure of treatment, failure on hearing testing, necrotising enterocolitis, patent ductus arteriosus requiring treatment, treatment with postnatal systemic corticosteroids, pulmonary haemorrhage, and retinopathy of prematurity. A sample of 800–1200 infants was needed, given the assumptions that 30% of the study population would have a gestational age of 23–25 weeks, 70% would have a gestational age of 26–28 weeks and that the incidence of the primary outcome would be 75% for the lower-gestational-age group and 48% for the higher-gestational-age group. With a sample of this size, the study had 90% power (at a significance level of 0.05) to detect a difference between treatment groups of 9–11 percentage points.

Statistical analysis

An independent committee reviewed statistical analyses performed 12 and 18 months after recruitment began and found no reason to stop the trial early. Analyses were adjusted to preserve an overall level of significance of 0.05. For the secondary outcomes (both main effects and interactions), we used the Bonferroni method to correct for multiple testing, which resulted in the use of a *p*-value of 0.004 to indicate significance. All reported *p*-values are uncorrected unless otherwise stated.

Unadjusted relative risks or hazard ratios, as appropriate, with 95% confidence intervals (CIs) were calculated to estimate the relative effect of HFOV as compared with that of CV for all outcomes. Logistic regression or Cox regression was used to investigate treatment effects, with the use of gestational age (23–25 weeks or 26–28 weeks) and location (UK and Ireland, Australia or Singapore) as covariates. Interaction terms were fit in the model in order to assess differences in treatment effects according to gestational age and location. Baseline variables with the potential to be important prognostic factors were identified in advance of the analysis. We decided to include them in the model only if a clinically important imbalance was observed. All statistical analyses were performed according to the intention-to-treat principle, with the use of Stata software (StataCorp LP, College Station, TX, USA; version 12).

Between August 1998 and January 2001, 870 infants underwent randomisation; 804 were subsequently enrolled in the trial and data from 797 were analysed (*Figure 1*).

The two treatment groups were well balanced in terms of maternal characteristics. A total of 91% of the women received antenatal corticosteroids. The groups were also closely matched in terms of characteristics of the infants; 96% of infants were given surfactant replacement therapy at a median of 28 minutes after birth (range 0–1232 minutes).

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

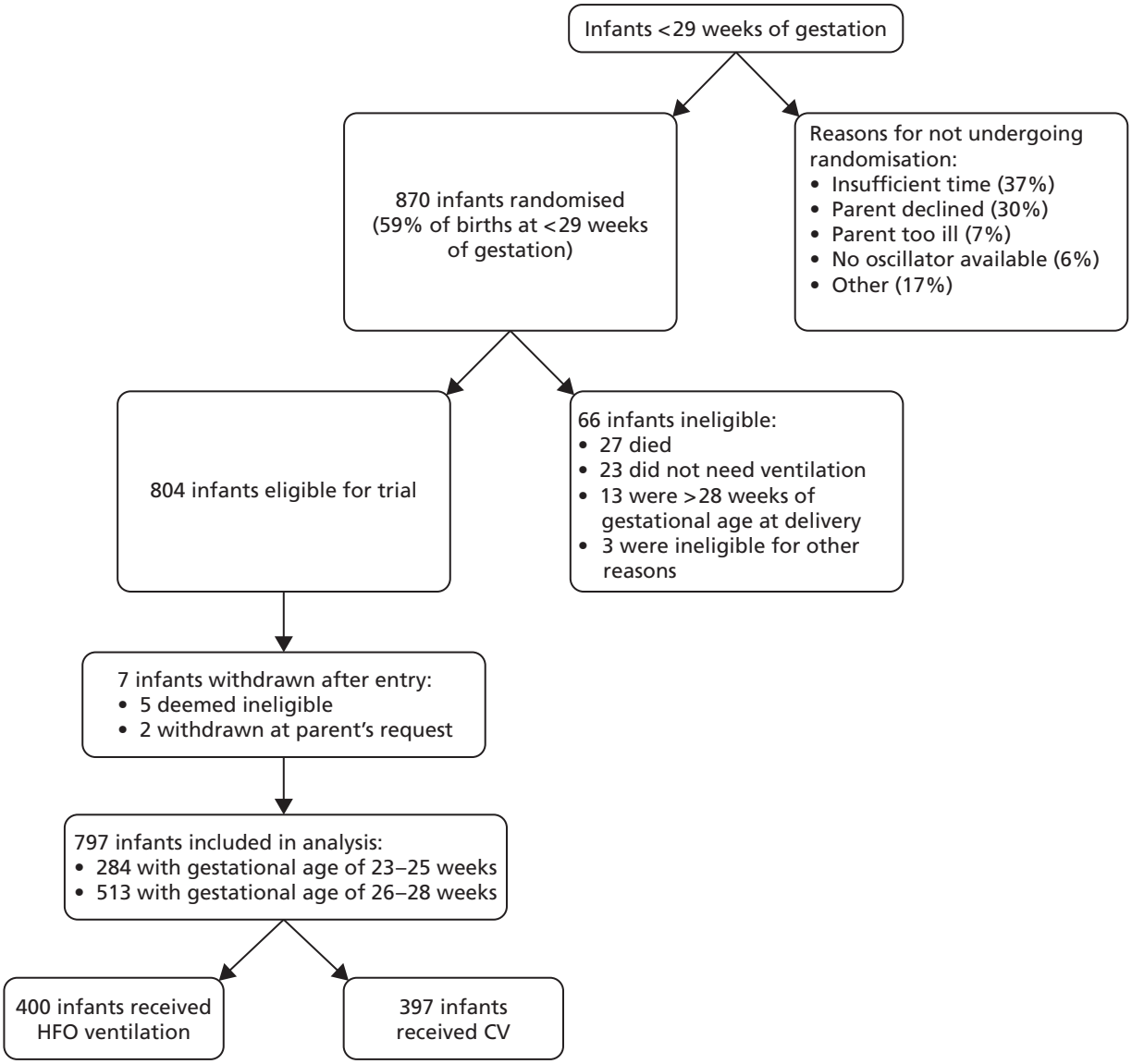


FIGURE 1 United Kingdom Oscillation Study Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Results

Primary outcome

The composite primary outcome of death or chronic lung disease (defined by dependence on supplemental oxygen at 36 weeks of postmenstrual age) occurred in 66% of infants assigned to HFO and 68% of those assigned to CV [relative risk (RR) 0.98 (95% CI 0.89 to 1.08), $p = 0.71$] (*Table 1*). Similar proportions of infants died (25% HFO vs. 26% CV) or had chronic lung disease (41% in each group). When the analysis was stratified according to gestational age, there were similar findings with respect to the primary outcome and the frequency of each component ($p = 0.46$ for the interaction between gestational age and mode of ventilation). Overall, 33% of the infants were alive without dependence on supplemental oxygen at 36 weeks of postmenstrual age: 12% of those who were born between 23 and 25 weeks gestational age and 45% of those who were born between 26 and 28 weeks gestational age. There were no significant differences in the secondary outcomes except regarding major cerebral abnormality, which was significantly lower in the HFO group (*Table 2*).

TABLE 1 Primary outcome to hospital discharge by mode of ventilation and by gestational age in UKOS[1]

	Number/total (%)		HFO/CV	
Infants by outcome	CV	HFO	RR	95% CI
All infants				
Died or O_2 dependent at 36 weeks CGA	268/397 (68)	265/400 (66)	0.98	0.89 to 1.08
Died	105/397 (26)	100/400 (25)		
Survived: O_2 dependent	163/397 (41)	165/400 (41)		
Survived: not O_2 dependent	129/397 (32)	135/400 (34)		
23–25 weeks				
Died or O_2 dependent at 36 weeks CGA	119/136 (88)	130/148 (88)	1.00	0.92 to 1.10
Died	60/136 (44)	61/148 (41)		
Survived: O_2 dependent	59/136 (43)	69/148 (47)		
Survived: not O_2 dependent	17/136 (13)	18/148 (12)		
26–28 weeks				
Died or O_2 dependent at 36 weeks CGA	149/261 (57)	135/252 (54)	0.94	0.80 to 1.10
Died	45/261 (17)	39/252 (15)		
Survived: O_2 dependent	104/261 (40)	96/252 (38)		
Survived: not O_2 dependent	112/261 (43)	117/252 (46)		

CGA, corrected gestational age.
From Johnson *et al.*[1] Copyright © Massachusetts Medical Society. Reprinted with permission.

TABLE 2 Secondary outcomes to hospital discharge in UKOS[1]

	Number/total (%) unless specified otherwise		HFO/CV	
Outcome	CV	HFO	RR	95% CI
Age at death (median, days, IQR)	6 (2–19)	6 (1–19)	0.85	0.64 to 1.13
Number of days in hospital for survivors [median, days (IQR)]	89 (70–112)	94 (73–114)		
Failure of treatment	41/397 (10)	41/400 (10)	0.99	0.66 to 1.50
Any air leak	72/395 (18)	64/399 (16)	0.88	0.65 to 1.20
Pulmonary haemorrhage (requiring change in ventilator settings)	55/390 (14)	44/395 (11)	0.79	0.55 to 1.14
Postnatal systemic steroids (any)	94/340 (28)	104/339 (31)	1.11	0.88 to 1.40
Patent ductus arteriosus requiring treatment	129/394 (33)	137/399 (34)	1.05	0.86 to 1.28
Any major cerebral abnormality	75/393 (19)	54/393 (14)	0.72	0.52 to 0.99
Retinopathy of prematurity (2+ or worse)	42/396 (11)	43/400 (11)	1.01	0.68 to 1.51
Failed hearing test	33/151 (22)	29/136 (21)	0.98	0.63 to 1.52
Necrotising enterocolitis	33/393 (8.4)	47/394 (12)	1.42	0.93 to 2.17

IQR, interquartile range.
From Johnson *et al.*[1] Copyright © Massachusetts Medical Society. Reprinted with permission.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Overall, those results do not provide evidence of a difference in the outcomes of infants supported by HFO or CV. The possible adverse effect of HFO on neurological outcomes, however, was not observed and indeed the proportion of infants with major cerebral abnormalities was significantly lower in the HFO group.[1]

Pulmonary function at follow-up of very preterm infants from the United Kingdom Oscillation Study

There were similar rates of chronic lung disease, defined as oxygen dependency at 36 weeks postmenstrual age (BPD), in the two ventilator groups of UKOS,[1] as reported above. A diagnosis of BPD, however, has been poorly associated with long-term respiratory outcome. Potential differences in lung function between the groups could become apparent as the infants grew older. Indeed, it has been reported that airway function may deteriorate during the first year after birth in prematurely born infants, regardless of whether or not they had initial lung disease.[12,13] A previous randomised study[14] had included respiratory follow-up and measurement of pulmonary function in infancy.[15] No differences in lung function in infancy were found.[15] Infants in that study, however, were relatively mature compared with those recruited into UKOS; in addition, they did not receive antenatal steroids or exogenous surfactant and no strategies to optimise lung volume on HFO were employed.[16] The aim, therefore, of this study[10] was to test the hypothesis that infants who had been exposed to antenatal steroids and exogenous surfactant and randomised to HFO in the UKOS trial would have superior pulmonary function at follow-up to those ventilated conventionally.

Pulmonary function assessments at 1 year corrected age were performed at a single centre in London, UK [King's College Hospital (KCH)], and a subgroup of trial infants was recruited from the participating centres that were within reasonable travelling distance from that centre. Informed written consent from infants' parents was obtained before testing, and the study was approved by both the South Thames Multicentre Research Ethics Committee and the Local Research Ethics Committee of KCH NHS Trust.

Infants were tested between the ages of 11 and 14 months corrected age. Before their appointment, parents were asked to complete a 2-week respiratory symptom diary card. Appointments were deferred if the infant developed symptoms of a respiratory tract infection during this period. All infants were seen in the paediatric respiratory laboratory at KCH. On arrival, a history was taken, and each infant was weighed, measured and examined. Parents were asked not to reveal the mode of ventilation to which their child had been initially assigned. The testing procedure consisted of measurement of tidal breathing parameters, functional residual capacity (FRC) by whole-body plethysmography (FRC_{pleth}), inspiratory and expiratory airway resistance (R_{aw}), and FRC by helium gas dilution (FRC_{He}). Additional detail on the method for making these measurements is provided in the online supplement.

Pulmonary function testing methodology

Infants were sedated with 80–120 mg/kg chloral hydrate, and monitored by pulse oximetry (Datex-Ohmeda 3800, Hatfield, UK) throughout the pulmonary function testing and afterwards until they were awake. Once asleep, the infant was laid supine in the plethysmograph (Department of Medical Engineering, Hammersmith Hospital, London, UK), which had a total volume of 90 l and included a heated, humidified rebreathing system. The infant breathed through an appropriately sized Rendell-Baker facemask, sealed around the nose and mouth with silicone putty. Pressure at the airway opening (*P*ao) was measured using a differential pressure transducer (range $\pm$ 5 kPa, MP45, Validyne Engineering Corporation, Northridge, CA, USA) connected to a port in the mask support. The mask support also incorporated a thermistor measuring airway temperature and was connected to a heated pneumotachograph (Fleisch, Switzerland) to measure airflow. The pneumotachograph was attached to a differential pressure transducer (range $\pm$ 0.2 kPa, MP 45, Validyne Engineering Corporation, Northridge, CA, USA). Pressure changes within the plethysmograph were measured using a differential pressure transducer (range $\pm$ 0.2 kPa, MP45, Validyne Engineering Corporation, Northridge CA, USA). All signals were amplified (CD18 carrier

amplifiers, Validyne Engineering Corporation, Northridge, CA, USA) and the flow signal integrated electrically to give tidal volume (FV 156 integrator, Validyne Engineering Corporation, Northridge, CA, USA). The resultant four channels of data were acquired, analysed and displayed in real time on a personal computer (Gateway GP7–500, Dublin, Ireland) running a computer program custom designed using LabWindows software (National Instruments, Austin, TX, USA) with analogue-to-digital sampling at 200 Hz (PC-LPM-16PnP, National Instruments, Austin, TX, USA). All channels were calibrated prior to each patient test, as previously described.[17]

Following application of the facemask, a minimum of 20 breaths were recorded for analysis of tidal breathing, including calculation of the time taken to achieve peak expiratory flow, expressed as a proportion of expiratory time (tPTEF : tE), and respiratory rate. FRC_{pleth} was then calculated from a minimum of three end-inspiratory occlusions.[18,19] A time-based trace of all four data channels and an *x*/*y* plot of plethysmographic volume shift during airway occlusion (V_{pleth})/*P*ao during each occlusion were displayed by the computer. Occlusions were considered acceptable if V_{pleth} and *P*ao were in phase and no airflow was evident.[20] The infant was then switched to the rebreathing bag. Individual breaths acquired during periods of rebreathing were displayed as *x*/*y* plots of V_{pleth}/flow by the computer. Only technically acceptable breaths, that is the loop was closed or nearly closed at points of zero flow, were used in the analysis.[21] R_{aw} was calculated electronically using an established formula[20] by applying a regression line to the selected portion of the loop. R_{aw} was calculated during initial inspiration between 0% and 50% maximal inspiratory flow, and during expiration between 0% and 50% maximal expiratory flow.[17] During all R_{aw} measurements, the computer calculated the apparatus resistance of the selected portion of the individual breath by relating *P*ao to flow and then subtracting this value from the total measured resistance.[22]

On completion of the plethysmographic measurements, FRC_{He} was measured while the infant lay undisturbed on the base of the plethysmograph, using the same mask with silicone putty. During the initial stages of the study, FRC_{He} was determined using a water-sealed spirometer (Pulmonet III, Gould, Bilthoven, the Netherlands), as described previously.[23] Most infants were tested using the EBS 2615 system (Equilibrated Bio Systems, New York, NY, USA), which consisted of a 500-ml rebreathing bag in a closed heliox circuit. The system was modified to produce a time-based display of flow and tidal volume, allowing accurate switching into the circuit at end expiration.[24] An online display of the helium dilution curve allowed precise determination of gas equilibration. For both FRC_{He} techniques, the mean of two recordings that were within 10% of each other was taken.[25] The FRC_{He} of 12 infants was measured using both devices in order to assess comparability, with a median difference of 4.8% (range 0.3–11.4%) between devices.

Sample size

A pulmonary function subset sample size of 100 infants had been calculated when the UKOS trial was designed, based on previously determined variability of pulmonary function measurements and a clinically relevant difference between the two groups that we wished to be able to detect. This sample size would have enabled detection of a difference of 0.56 standard deviations (SDs) between the groups, with 80% power at the 5% significance level. The actual sample size fell below this target (discussed later here) and, allowing for the unequal group sizes, enabled detection of 0.65 SDs between the groups.

Statistical analysis

Mean values with 95% CIs for the differences between groups were calculated for all data. The pulmonary function data did not follow a normal distribution and logarithmic transformation did not correct the skewness. However, the group sizes were over 30, and the SDs were similar in the two groups. In this situation, the *t*-test is fairly robust to slight deviations from normality and, thus, we chose to present 95% CIs for differences between means based on the *t* method. To check the robustness of the *t*-test and CI method, we also calculated *p*-values using the Mann–Whitney rank test. These *p*-values were virtually identical to those calculated using the *t*-test, and statistical significance (or non significance) was entirely consistent. Statistical analysis was performed using Stata software.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Results

Subjects

From the 12 centres that participated in this follow-up study, 185 infants were eligible for pulmonary function testing. From these, parents of 149 infants were invited to attend for testing. The remaining 36 infants either were living too far away from London or had been lost to follow-up. The parents of 90 infants agreed to participate in the follow-up study. However, 10 failed to attend their appointments, three (one CV and two HFOV) were repeatedly unwell or remained dependent on supplemental oxygen, and one could not be successfully sedated. This left 76 infants who formed the study group.

The studied infants had slightly lower mean birthweight and gestational age than the remainder of the trial survivors, as indicated by 95% CIs that excluded zero but were otherwise similar with respect to a range of sociodemographic and clinical parameters. Follow-up data were not available for all 592 survivors of the trial. The follow-up data were obtained exclusively from standardised respiratory questionnaires completed at 6 and 12 months' corrected age by each infant's own paediatrician.

When split according to randomised mode of ventilation, the two pulmonary function groups were well matched for a range of baseline characteristics, with no statistically significant differences. At follow-up, data were obtained when each infant attended for pulmonary function testing.

Pulmonary function

Most infants had complete pulmonary function results. On some occasions, technically acceptable recordings were not obtained, or the infant woke before measurements were complete. Measurements of FRC_{pleth} were missing for two infants (one in each group) and of FRC_{He} for four infants (one CV and three HFOV). One or other type of FRC measurement was available for all infants. Airway resistance measurements were missing for six infants (three in each group) and tidal breathing parameters for five infants (three CV and two HFOV).

Results

The study was conducted in a subset of 76 UKOS infants whose parents were willing to participate and were able to travel to KCH. There were no statistically significant differences in pulmonary function between the two groups (*Table 3*).

TABLE 3 Lung function at 1 year of age in a subset of UKOS infants[10]

Lung function method	CV ($n = 34$) Mean (SD), median	HFO ($n = 42$) Mean (SD), median	Difference in means (HFO – CV)	95% CI for difference in means	*p*-value
FRC_{pleth} (ml/kg)	26.9 (6.3), 25.4	26.5 (6.4), 25.8	–0.4	–3.4 to 2.5	0.76
FRC_{He} (ml/kg)	24.1 (5.4), 23.0	23.5 (5.7), 22.2	–0.6	–3.2 to 2.1	0.67
$FRC_{He} : FRC_{pleth}$	0.90 (0.11), 0.90	0.90 (0.13), 0.91	0.0	–0.06 to 0.06	0.93
Inspiratory R_{aw} [kPa/(l/s)]	3.3 (1.3), 3.0	3.4 (1.6), 3.0	0.1	–0.6 to 0.8	0.72
Expiratory R_{aw} [kPa/(l/s)]	4.4 (2.8), 3.3	4.1 (2.5), 3.3	–0.3	–1.6 to 1.1	0.66
$t_{PTEF} : t_E$	0.21 (0.07), 0.22	0.24 (0.06), 0.22	0.03	–0.01 to 0.06	0.15
Respiratory rate (breaths/minute)	31.2 (6.0), 30.8	33.9 (8.0), 33.1	2.7	–0.7 to 6.1	0.12

Reprinted from Thomas *et al.*[10] with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society.

These results do not provide evidence that lung function at follow-up is influenced by neonatal ventilation support for extremely prematurely born infants. It is important, however, to note that small airway function was only assessed by measurement of gas trapping and it would be important to assess the UKOS graduates when they are old enough to perform more comprehensive lung function assessments.

Respiratory and neurological outcomes at 2 years of age of infants from the United Kingdom Oscillation Study[11]

In this study,[11] the outcome for surviving infants up to 2 years of age corrected for prematurity who had been entered into UKOS was assessed to determine whether ventilatory modality was associated with either increased longer-term respiratory or neurodevelopmental morbidity.

Study population

Of the 592 surviving infants who were entered into the study and discharged home, seven subsequently died, no outcome forms were returned for 164, and outcome information was available for 428 from 22 centres in the UK and one each from Australia, Ireland and Singapore. Infants were followed by their local paediatrician until 2 years of age corrected for prematurity. Questionnaires were mailed to the local paediatrician responsible for follow-up when each infant reached 21 months post-term age, with a request that the child be evaluated as close to 24 months post-term age as possible and within the 'window' of 22–28 months. Up to two reminders were sent to paediatricians when questionnaires had not been returned to the co-ordinating centre by 25 months post-term age. If questionnaires were still not returned, in the UK, the child's local health visitor was telephoned and asked to complete the forms.

Paediatricians were asked to complete two forms. A respiratory questionnaire requested details about frequency of cough and wheeze and their relationship to infection, use of respiratory drugs, home oxygen, and hospital admissions (for both respiratory and other reasons). Social and demographic information, including family history of smoking and atopy, was also recorded. A neurodevelopmental questionnaire recorded information on health status and anthropometry.

In addition, parents were separately mailed a questionnaire that included questions in three areas: non-verbal cognitive development (derived from items in the Bayley scales of infant development[26]) and vocabulary and language (derived from the MacArthur language scales[27]). The original questionnaire was validated in a term population and modified for this study to incorporate better sensitivity at lower developmental scores.[28] A total score of 49 achieved 81% sensitivity and 81% specificity for a Bayley scale mental development index of 70 (more than two SDs below the mean).[28]

Statistical methods

The original trial was powered to detect a 12% difference in disability rates (estimated rate 17%) or a 14% difference in respiratory symptoms (estimates: 50% during first year; 33% during second year). We compared baseline infant, maternal and socioeconomic variables between the two randomisation groups, to confirm that deaths or loss of children to follow-up had not affected the balance. To investigate any potential bias due to the omission of subjects with missing data or data obtained outside the specified window, we compared important neonatal outcomes in the three possible groups of subjects: (1) those whose questionnaires were completed within the specified window (22–28 months post term); (2) those whose questionnaires were completed outside the window; and (3) those whose questionnaires had not been returned. Analysis was on an intention-to-treat basis using the follow-up data obtained exclusively within the 22–28-month window.

Results

Respiratory and neurodevelopmental questionnaires completed by paediatricians were returned for 428 (73%) children, of which 373 (87% of those returned) were within the specified age window. Parents returned developmental questionnaires within the specified age window for 288 children (49% of

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

survivors to discharge) The proportion of infants with oxygen dependency at 36 weeks postmenstrual age, supplemental oxygen at discharge, or major abnormality on cranial ultrasound scanning did not differ significantly between those infants with information returned inside the follow-up window, outside the window or those without follow-up data. There was a good balance in infant and maternal characteristics between the two ventilation groups among children with follow-up data. Specifically, they were well matched in terms of the major determinants of outcome: birthweight, gestational age, sex of infant or major abnormality on cranial ultrasound scan.

The frequency of reported respiratory symptoms was high: half of parents reported that their child suffered from coughing, of whom 31% coughed frequently (more than once a week); and 37% reported wheezing, of whom 30% wheezed frequently. Overall, 41% had received inhaled medication (*Table 4*). There were no significant differences in respiratory outcomes between the two groups, although there were trends favouring the HFO group in respiratory morbidity (see *Table 4*), but not in hospital admissions (*Table 5*).

Overall, 9% of children had severe disability and 38% had other disabilities at 2 years of age. There were no significant differences in neurological outcomes between the two ventilation groups (*Table 6*).

TABLE 4 Respiratory outcomes at 2 years of age in UKOS children[11]

	CV	HFO	HFO/CV	
Respiratory outcomes	**Number/total (%)**	**Number/total (%)**	**RR**	**95% CI**
Chest symptoms				
Suffer from coughing	98/194 (51)	84/172 (49)	0.97	0.79 to 1.19
Coughs > once a week	33/97 (34)	21/81 (26)	0.76	0.48 to 1.21
Coughs once a week, > once a month	15/97 (15)	17/81 (21)		
Coughs once a month or less	49/97 (51)	43/81 (53)		
Coughs with exercise	28/76 (37)	15/61 (25)	0.67	0.39 to 1.13
Coughs with infection	88/98 (90)	68/81 (84)	0.93	0.83 to 1.05
Suffer from wheezing	75/187 (40)	56/167 (34)	0.84	0.63 to 1.10
Wheezes > once a week	21/72 (29)	16/53 (30)	1.04	0.60 to 1.79
Wheezes once a week, > once a month	12/72 (17)	6/53 (11)		
Wheezes once a month or less	39/72 (54)	31/53 (58)		
Wheezes with exercise	26/60 (43)	13/42 (31)	0.71	0.42 to 1.22
Wheezes with infection	66/73 (90)	50/56 (89)	0.99	0.88 to 1.11
Chest medicines				
Chest medicine in the last 12 months	115/192 (60)	94/171 (55)	0.92	0.77 to 1.10
Bronchodilators	82/192 (43)	63/171 (37)	0.86	0.67 to 1.11
Inhaled steroids	50/192 (26)	36/171 (21)	0.81	0.56 to 1.18
Other				
On home oxygen now	4/194 (2.1)	2/173 (1.2)	0.56	0.10 to 3.02

Reproduced from Marlow *et al.*[11] with permission from BMJ Publishing Group Ltd.

TABLE 5 Respiratory admissions from birth to 2 years of age in UKOS children[11]

Outcome	CV		HFO		RR HFO/CV	95% CI or *p*-value
	Number/total or mean (SD)	% or range	Number/total or mean (SD)	% or range		
Respiratory admission ever	112/264	42	118/276	43	1.01	0.83 to 1.23
Mean (SD) range[a]	2.4 (2.3)	1–14	2.3 (2.3)	1–14		$p = 0.65$
Respiratory admission in last 12 months	27/179	15	24/157	15	1.01	0.61 to 1.68
Mean (SD) range[a]	1.3 (0.6)	1–3	1.4 (1.0)	1–5		$p = 0.81$
Surgical admission ever	59/264	22	59/276	21	0.96	0.70 to 1.32
Mean (SD) range[a]	1.4 (0.7)	1–4	1.5 (1.1)	1–7		$p = 0.82$
ICU admission ever	25/264	9.5	23/276	8.3	0.88	0.51 to 1.51
Mean (SD) range[a]	1.3 (0.6)	1–3	1.1 (0.5)	1–3		$p = 0.13$

a Mean number of admissions among those who had had an admission.
Reproduced from Marlow *et al.*[11] with permission from BMJ Publishing Group Ltd.

TABLE 6 Neurological outcomes at 2 years of age in UKOS children who survived[11]

Outcome	CV	HFO	RR (HFO/CV) or difference in means	95% CI
	Number/total (%)	Number/total (%)		
Neuromotor				
No or poor head control	1/189 (0.5)	0/170 (0.0)	SD	
Unable to sit unsupported	3/185 (1.6)	4/168 (2.4)	1.47	0.33 to 6.46
Unable to stand, requires support	14/189 (7.4)	12/168 (7.1)	0.96	0.46 to 2.03
Unable to walk, non-fluent gait	23/190 (12.0)	16/169 (9.5)	0.78	0.43 to 1.43
Unable to use left hand, not pincer grip	7/179 (3.9)	10/165 (6.1)	1.55	0.60 to 3.98
Unable to use right hand, not pincer grip	6/185 (3.2)	6/167 (3.6)	1.11	0.36 to 3.37
Unable to do/difficulty with bimanual tasks	7/188 (3.7)	14/168 (8.3)	2.24	0.93 to 5.41
Has convulsions (± treatment)	6/189 (3.2)	14/167 (8.4)	2.64	1.04 to 6.72
Vision				
Squint	23/189 (12.0)	22/171 (13.0)	1.06	0.61 to 1.83
Parent report – reduced vision	14/189 (7.4)	5/163 (3.1)	0.41	0.15 to 1.12
Parent report – abnormal eye movements	7/188 (3.7)	8/165 (4.8)	1.30	0.48 to 3.51
Hearing				
Hearing loss (± aids)	15/188 (8.0)	11/170 (6.4)	0.81	0.38 to 1.72

continued

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

TABLE 6 Neurological outcomes at 2 years of age in UKOS children who survived[11] (*continued*)

Outcome	CV Number/total (%)	HFO Number/total (%)	RR (HFO/CV) or difference in means	95% CI
Other domains				
Does not understands signs or words	0/185 (0.0)	3/168 (1.8)	n/a	
Tube feeding	4/191 (2.1)	1/172 (0.6)	0.28	0.03 to 2.46
Overall disability grading				
Severe disability[a]	16/191 (8.4)	15/172 (8.7)	0.93	0.74 to 1.16
Other disability	76/191 (40.0)	62/172 (36.0)		
No disability	99/191 (52.0)	95/172 (55.0)		
Any disability				
23–25 weeks' gestation	25/47 (54)	24/51 (47)	0.88	0.60 to 1.31
26–28 weeks' gestation	67/144 (46)	53/121 (44)	0.94	0.72 to 1.23
Cognitive development				
Parent report composite score < 49	40/151 (26)	41/137 (30)	1.13	0.78 to 1.63
Parent report composite mean (SD)[b]	76 (37)	75 (38)	–1.7	–10.40 to 7.00
Growth *23–25 weeks' gestation*				
Height SDS mean (SD)	–0.67 (0.98)	–0.76 (1.03)	–0.09	–0.50 to 0.33
Weight SDS mean (SD)	–0.80 (1.41)	–0.90 (1.16)	–0.10	–0.63 to 0.43
Head circumference SDS mean (SD)	–1.59 (1.44)	–1.46 (1.28)	0.13	–0.45 to 0.70
26–28 weeks' gestation				
Height SDS mean (SD)	–0.53 (1.10)	–0.40 (1.09)	0.13	–0.16 to 0.42
Weight SDS mean (SD)	–0.73 (1.24)	–0.54 (1.26)	0.19	–0.13 to 0.51
Head circumference SDS mean (SD)	–1.28 (1.50)	–1.14 (1.42)	0.15	–0.25 to 0.54

n/a, not applicable; SDS, standard deviation score.

a 'Severe disability' is at least one extreme response in one of the following clinical domains: neuromotor, vision, hearing, communication or other physical disabilities. 'No disability' is a normal (or missing) response to all clinical domains.

b Parental questionnaire composite score of non-verbal development, sentence complexity, and vocabulary; 49 is the cut-off for cognitive delay equivalent to Bayley Mental Development Index < 70.

Reproduced from Marlow *et al.*[11] with permission from BMJ Publishing Group Ltd.

Chapter 2 United Kingdom Oscillation Study follow-up study

Introduction

Recent meta-analyses of randomised trials of new modes of ventilation have demonstrated that only HFO use was associated with a significant reduction in BPD, but the effect was modest.[29] In that meta-analysis of 15 trials, overall, there were no significant differences in severe intracranial haemorrhage or periventricular leukomalacia rates, but the effects were inconsistent across the trials. Following the adverse results of one trial,[30] a type of oscillator was withdrawn. Nevertheless, a survey showed that 40% of UK neonatal units regularly ventilating babies use HFO in addition to, or in place of, CV.[31] Before even more neonatal units adopt HFO into their routine practice, it is essential to determine, using clinically meaningful assessments, that is respiratory and neurodevelopmental status at school age, whether or not HFO is at least as safe and efficacious as CV techniques. Only if similar or better outcomes are found would it be appropriate to continue to use HFO.

The clinical implications of the systematic review[29] are difficult to interpret, as the diagnosis of BPD does not correlate well with long-term pulmonary outcomes in prematurely born children. A better predictive measure is lung function assessment at follow-up, but this has rarely been incorporated into randomised trials of HFO. At school age, the data on lung function are limited and conflicting. Small airway function may decline over the first year after birth in prematurely born infants.[12] Whether or not there is catch-up growth has not been examined, but the results of a non-randomised study suggested that the decline does not occur if prematurely born infants are initially supported by high-volume HFO rather than CV.[13] Thus, it is important to determine whether or not the use of high-volume HFO in a randomised trial in infants at highest risk for adverse long-term respiratory outcomes, that is those born very prematurely, is associated with better lung function, particularly small airway function and other respiratory outcomes at school age. Longitudinal assessment of lung function is also required to determine if the use of HFO from birth influences catch-up growth in lung function.

Although, the meta-analysis of HFO trials demonstrated no significant excess of neurodevelopmental abnormalities,[29] in some studies HFO has been associated with increases in severe intracranial haemorrhage and periventricular leukomalacia. The associations are biologically plausible as high-volume HFO could cause lung overdistension compromising cardiac output and cerebral perfusion. In addition, HFO could increase hypocarbia, which can also result in less severe, but clinically important, degrees of brain injury. Thus, it is important when assessing long-term respiratory outcomes of infants entered into randomised trials of HFO to also determine their long-term neurodevelopmental outcomes. Such data are essential to determine if HFO should continue to be used and be introduced even further into clinical practice or, conversely, its use be discontinued for very prematurely born infants, even if there are favourable respiratory outcomes.

Pulmonary hypertension (PH) complicates severe BPD, but even raised pulmonary vascular resistance (PVR), which can be present in older patients with BPD, can result in morbidity. There is some evidence that the degree of PVR may also depend on ventilator strategy, as it may be lower if fast rates and low tidal volumes rather than slow rates and high tidal volumes are used. Thus, it was important to determine if HFO use in very prematurely born infants might reduce the risk of PVR at school age. Diagnosis of PH is often difficult because the symptoms may be subtle and masked by coexisting respiratory problems.[32] Doppler echocardiography is commonly used to screen for PH in clinical practice and has been used to screen for PH in other groups of patients such as those with sickle cell disease.[33] The children in this study were assessed using Doppler echocardiography, which is an accurate and non-invasive technique.[33,34]

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Although tricuspid regurgitation is seen in only about 33% of normal children, if there is PH, 80% of patients will have tricuspid regurgitation which can be quantified by Doppler.[35]

The aim of this follow-up study was to determine the long-term outcomes of children who had been recruited into UKOS and, in particular, to test the hypothesis that use of HFO in the newborn period would be associated with superior small airway function at school age. In addition, we wished to assess the effects of HFO compared with CV on a broad range of respiratory health and educational outcomes at age 11–14 years in children born very prematurely. The results of those follow-up assessments of children from the randomised trial would robustly inform the true risk–benefit ratio of use of HFO in very prematurely born infants. A null (no difference) finding would be as important clinically as any difference that might be observed, as it would resolve the uncertainty surrounding the long-term effects of HFO and CV and determine whether or not HFO could be safely used to support very prematurely born infants. A subsidiary aim was to track the lung function in the subset of children previously assessed at 1 year, as those results would highlight whether or not changes in lung function over time differed according to ventilation mode.

Study design

Comprehensive lung function and cardiac assessments were undertaken when the children were 11–14 years of age at KCH NHS Foundation Trust, London, UK. All assessments were made by a research fellow and research nurse blind to the child's randomised mode of ventilation. Respiratory, health-related quality of life and functional assessment questionnaires were completed (see *Appendix 1*). Parents and their children who were unable to attend the London centre completed the questionnaires only.

Recruitment of children into the study and parent input

The UKOS children were followed to 2 years of age. Since then we have maintained contact with the families by sending birthday cards to the UK-based children. This included an information sheet, a stamped-addressed envelope and a request to inform us of any change in contact details. We also provided information about the study on our website. Families have spontaneously kept in touch with us and many have informed us of changes in their contact details. When funding for the follow-up at age 11–14 years was obtained, a newsletter was sent to all families. A mother of a UKOS child has been involved in the study design and its conduct as a member of the steering committee. Her input has been invaluable in advising us on recruitment strategies and communication with families.

Assessments

Respiratory function and atopy assessment

Airway function was assessed by spirometry [forced expiratory flow at 75%, 50% or 25% vital capacity (FEF_{75}, FEF_{50} or FEF_{25}), forced expiratory flow at one minute (FEV_1) and peak expiratory flow (PEF)], to generate information on the larger airways (specifically PEF) and smaller airways (specifically FEF_{25}). A minimum of three flow–volume loops with results 10% of each other were recorded, and the flow–volume loop with the highest FEV_1 analysed. As those techniques indirectly measure airway resistance and are effort dependent, direct assessment was also made by impulse oscillometry, which is not effort dependent. In addition, inhomogeneity of ventilation distribution, a sensitive index of small airway abnormalities, was assessed by a multiple breath technique, measuring indices of gas mixing including the lung clearance index (LCI). Lung volumes were assessed by measurements of FRC_{He} and FVC. Plethysmographic assessment of FRC_{pleth}, total lung capacity (TLC) and residual volume (RV) were made and gas trapping assessed by calculating the FRC_{He} to FRC_{pleth} ratio and, hence, small airway abnormalities further identified. Measurements were made at least twice and mean values within 10% of each other were recorded. Total lung gas transfer, alveolar volume (VA) and gas transfer per unit volume were assessed using the single

breath gas transfer technique. All lung function results were standardised for sex and height using the reference ranges of Rosenthal *et al.*[36,37] and Nowowiejska *et al.*[38] Airway hyperreactivity was assessed by a bronchial challenge tailored to the child's baseline lung function. Children with a baseline $FEV_1 \leq 70\%$ of predicted received a bronchodilator and their FEV_1 and FRC were remeasured. Children with a $FEV_1 > 70\%$ of that predicted underwent a cold-air challenge. This involved the child breathing through a face mask, supplied with subfreezing air (–15 °C), for 4 minutes at 60% of their maximum voluntary ventilation, as measured by a target ventilation meter. FEV_1 was measured prior to, and then every, 2 minutes for 12 minutes after the cold-air challenge had finished.[39] A response to the challenge was a change in FEV_1 of at least 10%.

The fraction of exhaled nitric oxide (*F*eNO) was measured with an online computerised system (HypAir™*F*eNO system, running ExpAir software version 1.29; Medisoft, Sorinnes, Belgium) following American Thoracic Society recommendations.[40] Subjects inhaled NO-free air through the mouth to TLC and exhaled through an expiratory resistor to maintain an expiratory pressure of 20 cmH_2O and target flow of 50 ml/second for at least 6–7 seconds.[41] The *F*eNO was calculated as the mean of three measurements that agreed to within 10% of the mean value.

Atopy was assessed by skin-prick testing and from the family history. Skin-prick testing was undertaken to a panel of common inhalant allergens including mixed grass pollen, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, dog and cat. A positive (histamine) and a negative control were used. The skin-prick tests were considered positive if the wheal reaction was 3 mm greater than the negative control.

Pulmonary hypertension

The children were assessed using Doppler echocardiography, PH was defined as the mean pulmonary artery pressure (mPAP) > 25 mmHg.[41] The mPAP was calculated as mean right ventricular (RVENT) minus the right atrial (RA) pressure plus the estimated RA pressure. Continuous-wave Doppler was used to determine the peak velocity of the tricuspid regurgitation jet and the time velocity integral was traced to obtain the mean RVENT–RA gradient. All results were reported as the average of three measurements.

Other data collected

Height, weight, blood pressure and demographic details at assessment were collected. Hospital admissions were determined from parental report. Admissions before 2 years of age had already been recorded in the UKOS database. Urine samples were analysed for cotinine levels.

Questionnaires (see Appendix 1*)*

The Health Utilities Index version 3 (HUI-3) was completed and questions were also asked of respiratory health, symptoms, medicine usage and neurological illnesses such as seizures. Parents were additionally asked whether or not their child had previous hospital admissions (hospital admissions up to 2 years of age had already been included on the UKOS database). The parents and child completed the questionnaires independently. The Strengths and Difficulties Questionnaire (SDQ) was completed by the child, their parent and their teacher. School performance over a range of subjects was determined by a questionnaire completed by the child's teacher, as was special needs support requirement.

Sample size

The primary outcome was small airway function. A sample size of 320 allowed a difference of 0.36 SDs in the mean lung function results to be detected with 90% power at the 5% significance level. Differences in lung function of ≥1.00 SD have been demonstrated in children with and without adverse respiratory outcomes; thus, our sample size allowed detection of a clinically important difference in lung function. Secondary outcomes were other aspects of lung function, respiratory health and symptoms, multiattribute health status as assessed by HUI-3, the results of the SDQ, special educational needs (SEN) support and subject-specific educational attainment.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Statistical analysis

The study was analysed as a two parallel-group study in keeping with the original design. The general modelling approach was to use a mixed model for both continuous and binary outcomes with the mother/pregnancy as the random effect to allow for clustering due to the relatively high proportion of multiple births common in very preterm populations. Methodological work involving simulations by one of the UKOS investigators (JP) and colleagues has shown that for data sets with a similar structure to UKOS, that is with most children being singleton births (i.e. a cluster of size one), but with a proportion of children who are twins, triplets or quads, the best estimates are obtained from using a mixed model, even if the proportions of multiples is relatively low.[42] For the binary data, the Laplace method was used within Stata as our ongoing simulations have indicated that this method gives the most reliable estimates. All study outcome analyses were adjusted for observed baseline imbalances between the two ventilation groups by incorporating the unbalanced factors as fixed effects in the multifactorial model. Unadjusted and adjusted analyses have been presented to show the effects of adjustment as estimates with 95% CIs. As we had a clearly predefined single primary outcome, FEF_{75}, we have not adjusted for multiple testing of the secondary outcomes. In a few cases with very small proportions for secondary outcomes, for example, cerebral palsy, affecting 30 children overall, the mixed model with covariates would not converge and so a one-level logistic model was used with the clustering allowed for by obtaining a robust standard error. Where numbers of a binary event were very small, an adjusted analysis was impossible using any method and so, in such cases, a simple chi-squared test was used to provide an indicative *p*-value.

Neonatal baseline data were compared for the children recruited and not recruited at age 11–14 years to determine the representativeness of the group with follow-up data. Neonatal and follow-up data in the sample recruited for follow-up were compared by ventilation group to check for imbalance by group due to differential recruitment.

The primary analysis was to compare FEF_{75} *z*-score by mode of ventilation at birth. The *z*-scores normalised lung function for the sex and height of the child using standard formulae incorporated into the lung function measuring equipment.

As some lung function results had a skewed distribution, those data were transformed, most frequently using a logarithmic transformation. A further sensitivity analysis was performed to adjust lung function for cotinine level and pubertal stage regardless of their statistical significance. This was done as cotinine is an indicator of exposure to environmental tobacco smoke and thus potentially affects respiratory function and pubertal stage is linked to growth rate. A further sensitivity analysis was performed on key secondary outcomes derived from the questionnaire data to include only those children with both lung function and questionnaire data as, as anticipated, some families were only able to complete questionnaires by mail and not able to attend for assessment.

Differences in mean lung function are often difficult to interpret clinically and, so, for the primary outcome we also calculated the proportions of children in each ventilator group who had results below the tenth centile as a criterion for 'poor' lung function. This was possible because the lung function *z*-scores follow a normal distribution. The fuller rationale and methods for this are given in Peacock *et al.*[43]

Dealing with missing data

Some children were unable to complete all lung function tests and, so, multiple imputation using chained equations was used to impute missing data. The following variables, in addition to all lung function variables, were used in the imputation: ventilation group, birthweight, gestational age group, use of surfactant, multiple birth, mother's ethnicity, child's current height, a binary health indicator (any report of the following wheeze, antibiotics, chest medicine, hospital admission, seizure, diabetes, cerebral palsy, hydrocephalus, gastrostomy, bowel stoma indicating 'yes') and attention deficit hyperactivity disorder

(ADHD) inattention score. Fifty data sets were imputed, and the imputation assumed that given these covariates, the data were missing at random. A further sensitivity analysis of the primary outcome was performed adjusting for the factors related to non-recruitment, namely ethnicity, Index of Multiple Deprivation (IMD) and maternal smoking during pregnancy.[44]

Intraclass correlation coefficients

These have been calculated to aid other researchers.

Software

An online data collection system for clinical studies (MedSciNet; MedSciNet AB, Stockholm, Sweden) was used for data collection and data management. Statistical analysis was conducted using Stata.

Results

Recruitment

Seven hundred and ninety-seven infants were recruited into UKOS from 25 centres; 22 were in England, Scotland or Wales and one in each of Australia, Ireland and Singapore. Infants from the 22 UK centres were followed up at the age of 6, 12 and 24 months and a subset of 76 UK-based children, who were able to travel to KCH, underwent lung function assessment at age 12 months.

The target group for the current study included all 538 children in England, Scotland, Wales and Ireland surviving to hospital discharge (*Figure 2*). Fifteen children had subsequently died and 57, despite vigorous

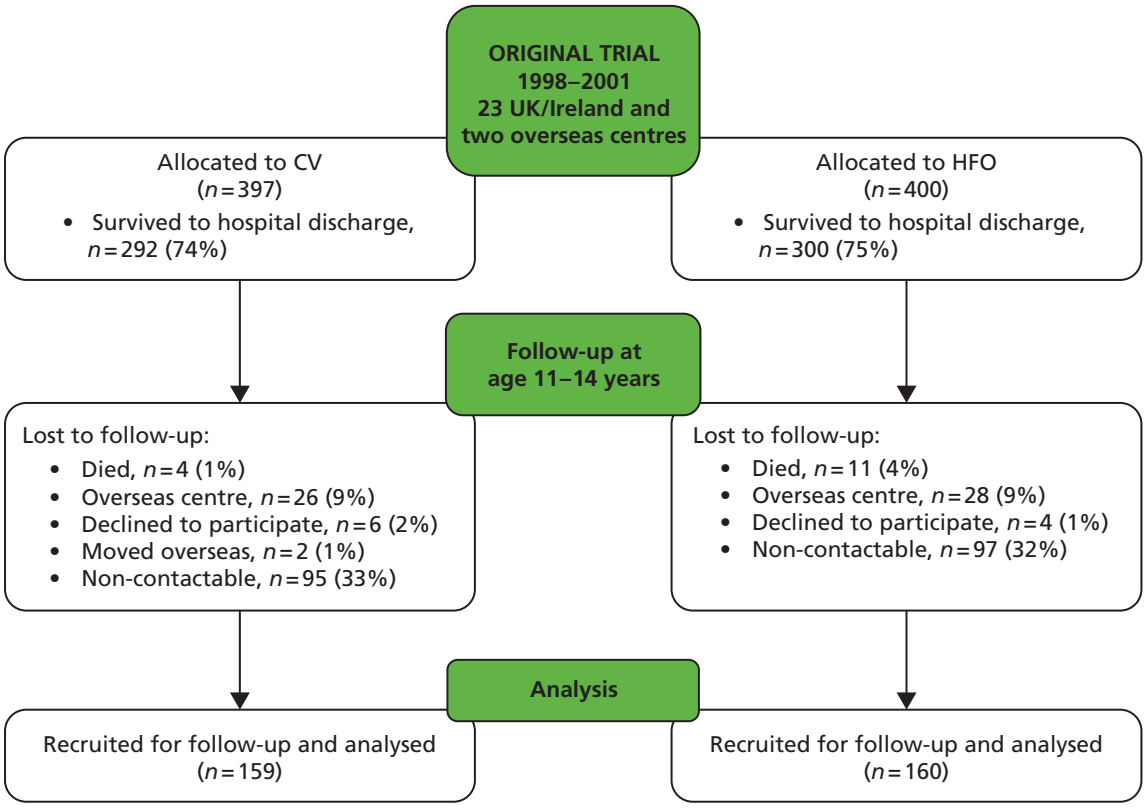


FIGURE 2 United Kingdom Oscillation Study Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

efforts, could not be traced, and so the maximum available sample was 466. One hundred and forty-eight children either declined follow-up or failed to reply to multiple letters and telephone calls. A total of 319 children are the subject of this report. The planned sample size was 320 children completing all elements of the study. However, while our total was virtually at target ($n = 319$), only 256 of these completed full lung function tests as well as completing questionnaires, leaving 59 who took part by completing the detailed questionnaires but not the assessments, and four who completed the assessments but did not return the questionnaires. Comparison of the baseline characteristics of those who were and were not recruited demonstrated significant differences with regard to only the mother's ethnic group, children who were recruited were more likely to have a Caucasian mother and less likely to have a mother who smoked during pregnancy (24% vs. 38%) (*Table 7*). Differences in the birthweight *z*-score were of borderline significance; recruited children had on average a lower *z*-score than those not recruited (mean $z = -0.59$ vs. -0.41).

TABLE 7 Comparison of baseline characteristics between children recruited and not recruited. The data are presented as the mean (SD) or number/total number (%) unless specified

Baseline characteristics	Recruited	Not recruited	*p*-value
N	319	204	
Male sex	162/319 (51)	109/204 (53)	0.550
Mother's ethnicity			
White	285/318 (90.0)	149/203 (73.0)	< 0.001 overall
Black	21/318 (6.6)	35/203 (17.0)	
Other	12/318 (3.8)	19/203 (9.3)	
IMD median (range)[a]	15.2 (1.0–68.1)	28.2 (1.1–70.0)	< 0.001
Birthweight (g)	895 (209)	914 (204)	0.310
Birthweight *z*-score (range)	–0.59 (–3.45 to 2.41)	–0.41 (–3.28 to 2.17)	0.050
Gestational age (weeks)	26.9 (1.33)	26.7 (1.39)	0.350
Multiple birth	76/319 (24)	45/204 (22)	0.640
Surfactant given	310/319 (97)	203/204 (99)	0.097
Mother smoked during pregnancy	69/292 (24)	72/188 (38)	0.001
Postnatal steroids	84/314 (27)	61/203 (30)	0.420
Oxygen dependency at 36 weeks postmenstrual age	183/319 (57)	121/204 (59)	0.660
Oxygen dependency at 28 days	262/319 (82)	164/204 (80)	0.620
Oxygen dependent at discharge	71/315 (23)	44/204 (22)	0.800

a IMD for those not recruited is based on last known address postcode. Higher values for IMD indicate greater deprivation. IMD is a UK measure of deprivation and, so, cannot be calculated for children from the three non-UK centres.

Baseline characteristics

There were four maternal and neonatal characteristics factors that differed significantly between the two ventilation groups: the CV group had a higher mean birthweight (923 g vs. 867 g), were born slightly later (mean gestational age 27.0 weeks vs. 26.7 weeks), included a greater proportion who were born at 26–28 weeks of gestation (81% vs. 68%) and included a greater proportion who received surfactant (99% vs. 95%) (*Table 8*).

There were no significant differences between the two groups in their characteristics when they were assessed at 11–14 years of age (*Table 9*).

TABLE 8 Maternal and neonatal characteristics of the children according to ventilation group. The data are presented as the mean (SD) or number/total number (%) unless specified

Maternal and neonatal characteristics	Mode of ventilation		*p*-value
	CV	HFO	
N	159	160	
Male sex	85/159 (53)	77/160 (48)	0.340
Mother's ethnic group			
White	142/158 (90.0)	143/160 (89.0)	
Black	11/158 (7.0)	10/160 (6.3)	
Other	5/158 (3.2)	7/160 (4.4)	0.920 overall
At birth			
Birthweight (g)	923 (206)	867 (209)	0.016
Birthweight *z*-score (range)	–0.55 (–2.94 to 1.73)	–0.62 (–3.45 to 2.41)	0.520
Gestational age, weeks	27.0 (1.18)	26.7 (1.45)	0.043
Gestational group			
Born at 23–25 weeks of gestation	30/159 (19)	52/160 (33)	
Born at 26–28 weeks of gestation	129/159 (81)	108/160 (68)	0.005
Multiple birth	39/159 (25)	37/160 (23)	0.770
Surfactant given	158/159 (99)	152/160 (95)	0.036
Mother smoked during pregnancy	31/146 (21)	38/146 (26)	0.340
Postnatal steroids	36/157 (23)	48/157 (31)	0.130
Oxygen dependency at 36 weeks postmenstual age	95/159 (60)	88/160 (55)	0.390
Oxygen dependency at 28 days	131/159 (82)	131/160 (82)	0.900
Oxygen dependent at discharge	34/156 (22)	37/159 (23)	0.750

There were no missing data for birthweight and gestational age.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

TABLE 9 Characteristics of the children at age 11–14 years according to ventilation group. The data are presented as the mean (SD) or number/total number (%) unless specified

Characteristics	Mode of ventilation				*p*-value
	CV		HFO		
For those who completed full assessment[a]					
Age (years)	121	12.5 (0.60)	129	12.6 (0.62)	0.660
Range		11.2–14.4		11.5–14.4	
Weight (kg) (range)	121	44.4 (23.4–102.0)	129	44.9 (19.0–86.7)	0.530
Boy		45.4 (25.0–102.0)		43.3 (19.0–86.7)	0.650
Girl		43.1 (23.4–57.0)		46.5 (29.0–72.0)	0.100
Height (cm) (range)	121	153 (129–173)	129	151 (124–172)	0.260
Boy		153 (138–173)		151 (124–172)	0.120
Girl		152 (129–169)		152 (137–164)	0.850
BMI median (kg/m^2) (range)	121	17.8 (12.8–34.5)	121	18.9 (11.9–30.6)	0.150
Boy		17.7 (12.8–34.5)		17.8 (11.9–29.3)	0.760
Girl		19.0 (14.1–23.6)		19.3 (14.4–30.6)	0.068
Haemoglobin (g/dl)	118	12.7 (1.25)	124	12.7 (1.13)	0.980
Oxygen saturation (%)	119	98.3 (1.11)	127	98.3 (1.21)	0.970
Blood pressure systolic (mmHg)	89	118.4 (9.18)	98	118.0 (10.80)	0.820
Blood pressure diastolic (mmHg)	89	74.5 (8.79)	98	74.4 (9.40)	0.940
Current smoking exposure					
Cotinine range (ng/ml)	116	< 10, 154	115	< 10, 168	
Undetectable (< 10 ng/ml)		86/106 (80)		92/115 (80)	0.840 overall
Passive smoker (10–15 ng/ml)		4/106 (4)		3/115 (3)	
Active smoker (> 15 ng/ml)		17/106 (16)		20/115 (17)	
For those who completed questionnaires only					
Pubertal status[b]	148		155		
Reached stage 3 in physical or hair development		109/146 (75)		110/152 (72)	0.740
Do not know		5/146 (3.4)		8/152 (5.3)	
Family smoke	148	44/149 (30)	153	51/152 (34)	0.450
House has problems with damp or mould	148	10/150 (6.7)	155	13/154 (8.4)	0.560
Family has asthma	149	76/150 (51)	155	72/154 (47)	0.500
Home owner	147	105/148 (71)	155	114/154 (74)	0.550
IMD median (range)[c]	114	15.4 (2.6–68.0)	123	14.8 (1.0–67.9)	0.660

a Ten were excluded from analysis because of scoliosis (one CV, two HFO), severe cerebral palsy (three CV, two HFO), severe autism (one CV) or having one hypoplastic lung (one HFO).
b Data from child self-assessed questionnaire; 303 returned with 49% from CV group. Puberty was defined as those who had reached stage 3 in either physical development or hair development (self-assessed).
c Higher value for IMD indicates greater deprivation. IMD is a UK measure of deprivation and so cannot be calculated for children from three non-UK centres (36 from CV and 32 from HFO).

Lung function and allergy assessment results

There was a statistically significant difference in the primary outcome small airway function, FEF_{75}; the *z*-score was higher in the HFO group (mean FEF_{75} *z*-score was –1.19 vs. –0.97) (*Table 10*). This difference was significant in both the unadjusted model that allowed for multiple births, but did not include any covariates, and in the fully adjusted model which additionally adjusted for the baseline neonatal factors that had shown imbalance between the groups. The adjusted difference in mean *z*-scores was 0.23 (95% CI 0.02 to 0.45). The percentage of children with lung function below the tenth centile was 46% in the CV compared with 37% in the HFO group. There were similar differences in mean lung function between the groups for both FEF_{50} and FEF_{25}. The histograms for FEF_{75} shows that the two groups had a similar shape distribution and the CV distribution is simply shifted downwards, that is to say there was a reduction in FEF_{75} in all children (*Figure 3*).

TABLE 10 Lung function and allergy testing results by ventilation group. Results are presented as the difference of means (HFO – CV) or odds ratio[a] (HFO/CV), unadjusted and adjusted for birthweight, gestational age groups and whether surfactant was given before birth

Lung function tests		CV	HFO	Unadjusted difference or OR[a] (95% CI)	Adjusted difference or OR[a] (95% CI)	*p*-value for adjusted analysis
N		121	129			
FEF_{75} *z*-score	248	–1.19 (0.80)	–0.97 (0.95)	0.21 (0.00 to 0.42)	0.23 (0.02 to 0.45)	0.035
FEF_{50} *z*-score	248	–1.37 (0.85)	–1.07 (0.93)	0.28 (0.07 to 0.49)	0.30 (0.09 to 0.52)	0.006
FEF_{25} *z*-score	248	–1.16 (0.95)	–0.84 (0.90)	0.27 (0.05 to 0.49)	0.29 (0.07 to 0.51)	0.011
$FEF_{25–75}$ *z*-score	231	–1.58 (1.05)	–1.34 (1.09)	0.18 (–0.07 to 0.44)	0.21 (–0.04 to 0.47)	0.100
FEV_1 *z*-score	248	–0.95 (1.02)	–0.60 (1.08)	0.31 (0.06 to 0.56)	0.35 (0.09 to 0.60)	0.008
FVC *z*-score	248	–0.44 (0.89)	–0.29 (1.05)	0.11 (–0.12 to 0.35)	0.13 (–0.10 to 0.37)	0.270
FEV_1/FVC *z*-score	248	–1.75 (1.78)	–1.16 (1.75)	0.54 (0.12 to 0.95)	0.58 (0.16 to 0.99)	0.007
PEF % predicted	247	80.3 (15.0)	86.3 (15.5)	5.58 (1.97 to 9.18)	5.85 (2.21 to 9.49)	0.002
Gas transfer						
$D_{L,CO}$ *z*-score	210	–1.10 (0.92)	–0.81 (1.19)	0.30 (0.02 to 0.57)	0.31 (0.04 to 0.58)	0.023
VA (l)	210	3.44 (0.66)	3.40 (0.59)	–0.05 (–0.19 to 0.10)	–0.05 (–0.20 to 0.09)	0.480
$D_{L,CO}$/VA (mmol/minute/kPa/l)	210	1.73 (0.20)	1.76 (0.21)	0.04 (–0.01 to 0.09)	0.04 (–0.01 to 0.09)	0.110
RV *z*-score	211	0.46 (1.19)	0.31 (1.35)	–0.05 (–0.38 to 0.27)	–0.09 (–0.42 to 0.24)	0.600
TLC *z*-score	213	0.20 (1.00)	0.36 (1.13)	0.16 (–0.11 to 0.44)	0.16 (–0.12 to 0.43)	0.260
FRC_{pleth} *z*-score	218	–0.07 (1.26)	–0.11 (1.28)	–0.10 (–0.42 to 0.23)	–0.08 (–0.41 to 0.25)	0.630
VC_{max} *z*-score	213	–0.50 (0.88)	–0.17 (1.09)	0.29 (0.03 to 0.55)	0.31 (0.05 to 0.57)	0.020

continued

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

TABLE 10 Lung function and allergy testing results by ventilation group. Results are presented as the difference of means (HFO – CV) or odds ratio[a] (HFO/CV), unadjusted and adjusted for birthweight, gestational age groups and whether surfactant was given before birth (*continued*)

Lung function tests			CV	HFO	Unadjusted difference or OR[a] (95% CI)	Adjusted difference or OR[a] (95% CI)	*p*-value for adjusted analysis
FRC_{He} *z*-score		229	–0.62 (1.10)	–0.75 (1.05)	–0.15 (–0.41 to 0.10)	–0.18 (–0.44 to 0.08)	0.190
LCI		155	7.50 (1.18)	7.62 (1.39)	0.16 (–0.21 to 0.53)	0.17 (–0.21 to 0.54)	0.390
FRC_{SF6} (l)		163	1.77 (0.43)	1.73 (0.42)	–0.04 (–0.16 to 0.08)	–0.04 (–0.16 to 0.08)	0.530
R5Hz % predicted		237	99.6 (23)	92.5 (21)	–7.02 (–12.30 to –1.70)	–7.13 (–12.50 to –1.76)	0.009
R20Hz % predicted		237	95.5 (24)	90.2 (22)	–5.65 (–11.20 to –0.08)	–5.22 (–10.70 to 0.24)	0.061
Airways reactivity							
Cold air challenge, positive response		193	24/95 (25%)	20/98 (20%)	0.76 (0.39 to 1.49)[a]	0.76 (0.38 to 1.53)[a]	0.450
Bronchodilator, positive response		37	7/21 (33%)	716 (44%)	1.56 (0.41 to 5.99)[a]	1.75 (0.38 to 7.98)[a]	0.470
*Fe*NO (p.p.b.)[b]		207	15.4 (1.88)	14.7 (1.91)	0.96 (0.80 to 1.14)	0.98 (0.83 to 1.17)	0.840
Skin-prick test, positive		188	9/92 (9.8%)	11/96 (11.5%)	1.19 (0.43 to 3.28)	1.34 (0.45 to 3.99)	0.600
Number of positives	1		5/9	8/11			
	2		4/9	2/11			
	3		0/9	1/11			

$D_{L,CO}$, diffusing capacity of the lung for carbon monoxide; FRC_{SF6}, functional residual capacity derived from LCI measurement using sulphur hexafluoride as the tracer gas; p.p.b., parts per billion; R5Hz, respiratory resistance at 5 Hz.
a Odds ratios.
b Estimates based on log-transformed *Fe*NO. Differences are the ratio of geometric means.

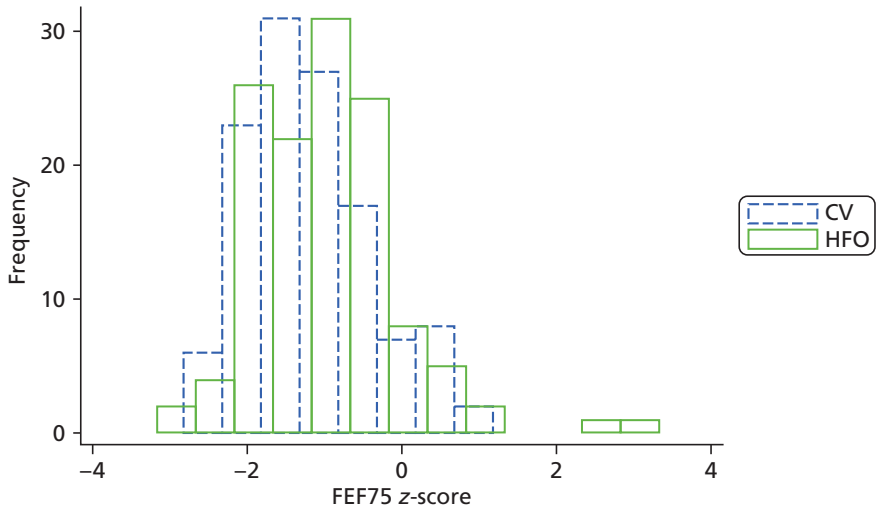


FIGURE 3 Distribution of FEF_{75} *z*-score by ventilation group. Dotted blue line indicates CV group. Solid green line indicates HFO group.

There were significant differences between the ventilation groups with regard to a number of the other lung function results: FEV_1 (difference = 0.35 SDs), FEV_1 : FVC (0.58 SDs), PEF (5.85% points), diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) (0.31 SDs), VC_{max} (0.31 SDs) and respiratory resistance at 5 Hz (R5Hz) (7.13% points) (see *Table 10*).

The results were all worse on average in the CV group. There were no significant differences with regard to airway hyper-reactivity and exhaled nitric oxide between the two groups.

Sensitivity analyses were performed on the lung function measurement results; pubertal stage and cotinine levels were added to the fully adjusted model (*Table 11*). This further analysis demonstrated findings consistent with the previous analysis, with significant differences in the primary outcome and the above secondary outcomes with similar effect sizes. The results of multiple imputation used to address the incomplete lung function data demonstrated similar effect sizes between the HFO and CV groups (*Table 12*), and the further analysis that adjusted for differences in the sample assessed and those not follow-up also gave almost identical effect sizes (*Table 13*, sensitivity analysis 2).

TABLE 11 Sensitivity analysis of the lung function data, adjusting additionally for pubertal stage and cotinine level

	Basic model[a]		Sensitivity analysis[b]	
Lung function test	Adjusted difference (95% CI)	*p*-value	Adjusted difference (95% CI)	*p*-value
FEF_{75} *z*-score	0.23 (0.02 to 0.45)	0.035	0.30 (0.06 to 0.53)	0.013
FEF_{50} *z*-score	0.30 (0.09 to 0.52)	0.006	0.30 (0.06 to 0.53)	0.013
FEF_{25} *z*-score	0.29 (0.07 to 0.51)	0.011	0.25 (0.02 to 0.49)	0.034
$FEF_{25–75}$ *z*-score	0.21 (–0.04 to 0.47)	0.100	0.17 (–0.11 to 0.45)	0.240
FEV_1 *z*-score	0.35 (0.09 to 0.60)	0.008	0.32 (0.04 to 0.61)	0.027
FVC *z*-score	0.13 (–0.10 to 0.37)	0.270	0.10 (–0.16 to 0.36)	0.460
FEV_1/FVC *z*-score	0.58 (0.16 to 0.99)	0.007	0.45 (0.02 to 0.88)	0.041
PEF (% predicted)	5.85 (2.21 to 9.49)	0.002	6.88 (2.77 to 11.0)	0.001
$D_{L,CO}$ *z*-score	0.31 (0.04 to 0.58)	0.023	0.35 (0.04 to 0.65)	0.028
VA (l)	–0.05 (–0.20 to 0.09)	0.480	–0.07 (–0.21 to 0.08)	0.360
$D_{L,CO}$/VA (mmol/minute/kPa/l)	0.04 (–0.01 to 0.09)	0.110	0.03 (–0.03 to 0.08)	0.330
RV *z*-score	–0.09 (–0.42 to 0.24)	0.600	–0.03 (–0.37 to 0.31)	0.850
FRC_{pleth} *z*-score	–0.08 (–0.41 to 0.25)	0.630	–0.09 (–0.44 to 0.26)	0.620
VC_{max} *z*-score	0.31 (0.05 to 0.57)	0.020	0.31 (0.02 to 0.60)	0.037
FRC_{He} z-score	–0.18 (–0.44 to 0.08)	0.190	–0.22 (–0.51 to 0.08)	0.150
LCI	0.17 (–0.21 to 0.54)	0.390	0.13 (–0.33 to 0.58)	0.580
FRC_{SF6} (l)	–0.04 (–0.16 to 0.08)	0.530	–0.06 (–0.18 to 0.07)	0.370
R5Hz (% predicted)	–7.13 (–12.5 0 to –1.76)	0.009	–7.45 (–13.40 to –1.50)	0.014
R20Hz (% predicted)	–5.22 (–10.70 to 0.24)	0.061	–5.42 (–11.30 to 0.43)	0.069
*Fe*NO (p.p.b.)[c]	0.98 (0.83 to 1.17)	0.84 0	0.94 (0.78 to 1.14)	0.550

p.p.b., parts per billion; R20Hz, respiratory resistance at 20 Hz.
a Basic model: adjusted for birthweight, gestational age groups and whether surfactant was given before birth.
b Sensitivity analysis: adjusted for birthweight, gestational age groups, whether surfactant was given before birth, puberty status (having reached stage 3 or not) and cotinine level (undetectable, passive smoker or active smoker).
c Estimates based on log-transformed *Fe*NO. Differences are the ratio of geometric means.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

TABLE 12 Multiple imputation on missing lung function data

Lung function test	Available data	Imputed data	Complete cases (basic model[a]) adjusted difference (95% CI)	*p*-value	Imputed data[b] adjusted difference (95% CI)	*p*-value
FEF_{75} *z*-score	248	–	0.23 (0.02 to 0.45)	0.035	–	–
FEF_{50} *z*-score	248	–	0.30 (0.09 to 0.52)	0.006	–	–
FEF_{25} *z*-score	248	–	0.29 (0.07 to 0.51)	0.011	–	–
$FEF_{25–75}$ *z*-score	231	17	0.21 (–0.04 to 0.47)	0.100	0.20 (–0.05 to 0.45)	0.12
FEV_1 *z*-score	248	–	0.35 (0.09 to 0.60)	0.008	–	–
FVC *z*-score	248	–	0.13 (–0.10 to 0.37)	0.270	–	–
FEV_1/FVC *z*-score	248	–	0.58 (0.16 to 0.99)	0.007	–	–
PEF (% predicted)	247	1	5.85 (2.21 to 9.49)	0.002	5.85 (2.22 to 9.48)	0.002
$D_{L,CO}$ *z*-score	209	39	0.31 (0.04 to 0.58)	0.023	0.29 (0.02 to 0.56)	0.037
VA (l)	209	39	–0.05 (–0.20 to 0.09)	0.480	–0.08 (–0.21 to 0.06)	0.280
$D_{L,CO}$/VA (mmol/minute/kPa/l)	210	Not imputed	0.04 (–0.01 to 0.09)	0.110	–	–
RV *z*-score	211	37	–0.09 (–0.42 to 0.24)	0.600	–0.20 (–0.53 to 0.13)	0.240
TLC *z*-score	212	36	0.16 (–0.12 to 0.43)	0.260	0.11 (–0.16 to 0.37)	0.430
FRC_{pleth} *z*-score	217	31	–0.08 (–0.41 to 0.25)	0.630	–0.11 (–0.43 to 0.21)	0.500
VC_{max} *z*-score	212	36	0.31 (0.05 to 0.57)	0.020	0.25 (0.00 to 0.50)	0.046
FRC_{He} *z*-score	228	20	–0.18 (–0.44 to 0.08)	0.190	–0.16 (–0.42 to 0.10)	0.230
LCI	153	95	0.17 (–0.21 to 0.54)	0.390	0.04 (–0.41 to 0.49)	0.870
FRC_{SF6} (l)	161	87	–0.04 (–0.16 to 0.08)	0.530	–0.08 (–0.20 to 0.04)	0.180
R5Hz (% predicted)	235	13	–7.13 (–12.50 to –1.76)	0.009	–7.63 (–13.10 to –2.14)	0.006
R20Hz (% predicted)	235	13	–5.22 (–10.70 to 0.24)	0.061	–5.49 (–11.20 to 0.23)	0.060
*F*eNO (p.p.b.)[c]	206	42	0.98 (0.83 to 1.17)	0.840	0.99 (0.83 to 1.19)	0.940

p.p.b., parts per billion; R20Hz, respiratory resistance at 20 Hz.

a Basic model (on complete data): adjusted for birthweight, gestational age groups and whether surfactant was given before birth.

b Imputed values only given where data set was incomplete for that particular lung function measurement.

c Estimates based on log-transformed *F*eNO. Differences are ratio of geometric means.

TABLE 13 Additional sensitivity analyses of the lung function data, adjusting additionally for (1) pubertal stage, cotinine levels and oxygen dependency at 36 weeks; (2) ethnicity, IMD, mother smoked during pregnancy

Lung function test	Basic model adjusted difference (95% CI)	*p*-value	Sensitivity analysis 1 adjusted difference (95% CI)	*p*-value	Sensitivity analysis 2 adjusted difference (95% CI)	*p*-value
FEF_{75} *z*-score	0.23 (0.02 to 0.45)	0.035	0.27 (0.04 to 0.50)	0.0230	0.27 (0.04 to 0.50)	0.022
FEF_{50} *z*-score	0.30 (0.09 to 0.52)	0.006	0.26 (0.03 to 0.49)	0.027	0.34 (0.11 to 0.57)	0.004
FEF_{25} *z*-score	0.29 (0.07 to 0.51)	0.011	0.21 (–0.02 to 0.44)	0.070	0.34 (0.11 to 0.58)	0.005
$FEF_{25–75}$ *z*-score	0.21 (–0.04 to 0.47)	0.100	0.14 (–0.13 to 0.41)	0.300	0.29 (0.02 to 0.57)	0.034
FEV_1 *z*-score	0.35 (0.09 to 0.60)	0.008	0.28 (0.00 to 0.56)	0.053	0.41 (0.14 to 0.67)	0.003
FVC *z*-score	0.13 (–0.10 to 0.37)	0.270	0.08 (–0.18 to 0.34)	0.550	0.17 (–0.07 to 0.41)	0.170
FEV_1/FVC *z*-score	0.58 (0.16 to 0.99)	0.007	0.40 (–0.02 to 0.83)	0.062	0.69 (0.24 to 1.14)	0.003
PEF (% predicted)	5.85 (2.21 to 9.49)	0.002	6.54 (2.44 to 10.60)	0.002	6.64 (2.73 to 10.5)	0.001
$D_{L,CO}$ *z*-score	0.31 (0.04 to 0.58)	0.023	0.34 (0.03 to 0.65)	0.030	0.34 (0.05 to 0.62)	0.021
VA (l)	–0.05 (–0.20 to 0.09)	0.480	–0.06 (–0.21 to 0.08)	0.410	–0.02 (–0.17 to 0.14)	0.820
$D_{L,CO}$/VA (mmol/minute/kPa/l)	0.04 (–0.01 to 0.09)	0.110	0.02 (–0.03 to 0.08)	0.410	0.05 (0.00 to 0.11)	0.069
RV *z*-score	–0.09 (–0.42 to 0.24)	0.600	0.01 (–0.32 to 0.34)	0.950	–0.09 (–0.44 to 0.26)	0.620
TLC *z*-score	0.16 (–0.12 to 0.43)	0.260	0.20 (–0.10 to 0.49)	0.200	0.17 (–0.12 to 0.45)	0.250
FRC_{pleth} *z*-score	–0.08 (–0.41 to 0.25)	0.630	–0.07 (–0.42 to 0.28)	0.700	–0.10 (–0.45 to 0.24)	0.560
VC_{max} *z*-score	0.31 (0.05 to 0.57)	0.020	0.30 (0.01 to 0.59)	0.043	0.36 (0.10 to 0.61)	0.007
FRC_{He} z-score	–0.18 (–0.44 to 0.08)	0.190	–0.20 (–0.50 to 0.09)	0.170	–0.21 (–0.48 to 0.07)	0.140
LCI	0.17 (–0.21 to 0.54)	0.390	0.21 (–0.22 to 0.65)	0.340	0.29 (–0.10 to 0.68)	0.140
FRC_{SF6} (l)	–0.04 (–0.16 to 0.08)	0.530	–0.06 (–0.19 to 0.06)	0.340	–0.05 (–0.18 to 0.08)	0.450
R5Hz (% predicted)	–7.13 (–12.50 to –1.76)	0.009	–7.23 (–13.20 to –1.29)	0.017	–8.28 (–14.10 to –2.46)	0.005
R20Hz (% predicted)	–5.22 (–10.70 to 0.24)	0.061	–5.36 (–11.20 to 0.51)	0.073	–5.88 (–11.90 to 0.17)	0.057
*Fe*NO (p.p.b.)	0.98 (0.83 to 1.17)[a]	0.840[a]	0.92 (0.76 to 1.11)[a]	0.390	0.99 (0.81 to 1.20)[a]	0.890

p.p.b., parts per billion; R20Hz, respiratory resistance at 20 Hz.
a Estimates based on log-transformed *Fe*NO. Differences are the ratio of geometric means.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Analysis of the lung function results of children who had also been assessed at 1 year demonstrated that their small airway function had deteriorated, as demonstrated by an increase in gas trapping.

Further details of the imputation modelling

The following variables, in addition to all lung function variables, were used in the imputation: ventilation group, birthweight, gestational age group, use of surfactant, multiple birth, mother's ethnicity, child's current height, a binary health indicator (any report of the following: wheeze, antibiotics, chest medicine, hospital admission, seizure, diabetes, cerebral palsy, hydrocephalus, gastrostomy, bowel stoma indicating 'yes') and ADHD inattention score. Fifty data sets were imputed and the imputation assumed that, given these covariates, the data were missing at random.

Respiratory morbidity in the past 12 months and health problems

There were no significant differences between ventilation groups with regard to respiratory morbidity in the last 12 months or health problems as documented by the parent-completed questionnaire and the effect sizes were nearly all very close to 1 (*Table 14*). The reasons why the child was admitted to hospital are given in *Table 15* and the reasons why the child was under the care of a doctor are given in *Table 16*.

TABLE 14 Respiratory morbidity in the past 12 months as documented by the parent questionnaires. The results are presented as *n* (%) and the odds ratio (HFO/CV), unadjusted and adjusted for birthweight, gestational age groups and whether surfactant was given

Respiratory morbidity in past 12 months	CV	HFO	Unadjusted OR (HFO/CV) (95% CI)	Adjusted OR (HFO/CV) (95% CI)	*p*-value for adjusted analysis
Wheeze	22/150 (15)	23/154 (15)	1.02 (0.55 to 1.89)	1.01 (0.53 to 1.90)	0.98
Number of wheeze attacks[a]					
Daily	1/22 (4.6)	5/22 (23)			0.76 overall[b]
Weekly	1/22 (4.6)	2/22 (9.1)			
Monthly	4/22 (18)	4/22 (18)			
< monthly	16/22 (73)	11/22 (50)			
If wheeze, sleep disturbed by wheeze					
Never woken with wheeze	15/22 (68)	14/23 (61)			
Seldom wakes (< 1 night/week)	6/22 (27)	6/23 (26)			
Frequently wakes (≥ 1 night/week)	1/22 (4.6)	3/23 (13)			
Antibiotics for chest problems					
Yes	22/150 (15)	18/154 (12)	0.76 (0.38 to 1.54)	0.69 (0.34 to 1.43)	0.32[c]
No	123/150 (82)	132/154 (86)			
Do not know	5/150 (3.3)	4/154 (2.6)			
If yes, number of courses of antibiotics[d]					
One course of antibiotics	11/21 (52)	11/15 (73)			
Two courses of antibiotics	6/21 (29)	1/15 (6.7)			
Two or more courses of antibiotics	4/21 (19)	3/15 (20)			

TABLE 14 Respiratory morbidity in the past 12 months as documented by the parent questionnaires. The results are presented as *n* (%) and the odds ratio (HFO/CV), unadjusted and adjusted for birthweight, gestational age groups and whether surfactant was given (*continued*)

Respiratory morbidity in past 12 months	CV	HFO	Unadjusted OR (HFO/CV) (95% CI)	Adjusted OR (HFO/CV) (95% CI)	*p*-value for adjusted analysis
Other medicines for chest problems					
Yes	24/150 (16)	23/152 (15)	0.94 (0.51 to 1.75)	0.94 (0.50 to 1.77)	0.85[c]
No	125/150 (83)	127/152 (84)			
Do not know	1/150 (0.7)	2/152 (1.3)			
Admission to hospital (see *Table 15*)	15/150 (10)	18/152 (12)	1.21 (0.60 to 2.44)	0.95 (0.45 to 1.99)	0.89
Chest problems	4	0			
Number of admissions (range)	1–6	–			
Surgery	8	13			
Number of admissions (range)	1–2	1–2			
Other	8	5			
Number of admissions (range)	1–3	1			
Child's health					
Had fits, seizures and convulsions	10/147 (6.8)	15/153 (9.8)	1.49 (0.67 to 3.29)	1.41 (0.65 to 3.07)	0.38
If yes[c]					
Not on prescribed medicine for seizures	5/10	9/14			
On prescribed treatment with no seizure	3/10	2/14			
On prescribed treatment with < 1 seizure/month	0	2/14			
On prescribed treatment with ≥ 1 seizure/month	2/10	1/14			
Diabetes	0	0			
Cerebral palsy	13	18	1.39 (0.66 to 2.94)		0.38[e]
Hydrocephalus with shunt	2	3	1.46 (0.24 to 8.99)		0.68[e]
Gastrostomy	2	1	0.48 (0.04 to 5.35)		0.55[e]
Any other bowel stoma	3	2	0.64 (0.07 to 6.25)		0.70[e]
Any other problem which child is under care of doctor (see *Table 16*)	38/144 (26)	47/144 (33)	1.38 (0.78 to 2.45)	1.30 (0.72 to 2.34)	0.38

a One missing value in the HFO group.
b *p*-value based on ordinal logistic regression and is only approximate as numbers are too small; those with no wheeze attacks were included in the model. Pearson correlation coefficient is 0.42.
c Analysis on yes responses vs. no responses.
d One missing response in the CV group, three missing in the HFO group.
e Analysis assumed non-responders as not having the particular health problem. Estimates are unadjusted due to small numbers.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

TABLE 15 List of reasons why the child was admitted to the hospital in the past 12 months, from parental questionnaire

Hospital admission diagnosis	CV	HFOV
Chest problems	1	
Chest infection	1	
Breathing problems	1	
Back operation		1
Knee surgery		1
Hand surgery	1	
Foot surgery		1
Testicle operation	1	1
Ear operation		1
Eye operation		1
Botox in eyes	1	
Botox	2	3
Grommet insertion		1
Adenoids removed		2
Broken bone(s)	1	
Dislocated hip		1
Soft tissue damage	1	
Tooth removed		2
Seizure		1
Fainting	1	
Scoliosis		1
ADHD	1	
Abdominal pain	3	
Constipation		1
Temperature	1	
Inactive TB	1	
Sleep study		1

TB, tuberculosis.

TABLE 16 List of reasons why the child was under the care of a doctor, from parental questionnaire

Doctor diagnosis	CV	HFOV
Asthma	5	10
Other chest/breathing issues (not asthma)	2	3
Allergies	3	4
Hearing issues	2	6
Eyesight issues	2	1
Eczema	1	2
Skin issues (not eczema)	3	5
Heart pain	1	
Spinal abnormalities	1	4
Hip dislocation		1
Cleft lip	1	
Kidney stones		1
Stomach issues	2	2
Constipation	2	3
Bowel issues		5
Incontinence/urinary problems	2	2
Vitamin deficiency		1
Eating difficulties	2	1
Weight issues		1
Hypermobility	1	2
Period pain		1
Premature puberty		1
Growth issues	2	
Autism	3	
ADHD	2	3
OCD		1
DCD		1

DCD, developmental co-ordination disorder; OCD, obsessive–compulsive disorder.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Health-related quality of life and Strengths and Difficulties Questionnaire scores

The HUI-3 was completed separately by the child and their parent(s); there were no significant differences by ventilation group (*Table 17*). The SDQ was completed by the child, their parent and/or their teacher; there were no significant differences between the ventilation groups (see *Table 15*). When the SDQ scores were dichotomised, the only significant difference between the two groups was for the children's report of emotional symptoms with a higher proportion in the HFO group, odds ratio (OR) 2.50 (1.13 to 5.56) (*Table 18*).

TABLE 17 Health Utilities Index version 3 and SDQ results by mode of ventilation. Results are presented as mean (SD), differences of the means (HFO – CV) unadjusted and adjusted for birthweight, gestational age groups and whether surfactant was given before birth

HUI-3/child self-assessed SDQ results	*n*	CV	HFO	Unadjusted difference (95% CI)	Adjusted difference (95% CI)	*p*-value for adjusted analysis
HUI-3 overall utility score						
Child self-assessed HUI-3	286	0.80 (0.29)	0.80 (0.27)	–0.01 (–0.07 to 0.06)	0.00 (–0.06 to 0.07)	0.930
Median (range)		0.93 (–0.30 to 1.00)	0.91 (–0.20 to 1.00)			
Parent-assessed HUI-3	289	0.79 (0.30)	0.78 (0.28)	–0.01 (–0.07 to 0.06)	0.00 (–0.06 to 0.07)	0.900
Median (range)		0.93 (–0.30 to 1.00)	0.89 (–0.25 to 1.00)			
Child self-assessed SDQ						
Total difficulties	293	9.79 (6.01)	10.2 (6.31)	0.68 (–0.63 to 2.00)	0.46 (–0.87 to 1.79)	0.520[a]
Emotional symptoms	295	2.55 (1.91)	3.08 (2.27)	0.51 (0.05 to 0.97)	0.48 (0.02 to 0.95)	0.110[a]
Conduct problems	294	1.58 (1.65)	1.50 (1.71)	–0.09 (–0.45 to 0.28)	–0.11 (–0.48 to 0.26)	0.550
Hyperactivity	294	3.65 (2.57)	3.64 (2.60)	0.02 (–0.56 to 0.61)	–0.06 (–0.65 to 0.53)	0.840
Peer problems	295	2.01 (1.92)	2.08 (1.93)	0.09 (–0.35 to 0.52)	–0.03 (–0.47 to 0.40)	0.890
Pro-social behaviour	297	8.47 (2.01)	8.42 (1.78)	–0.10 (–0.51 to 0.31)	–0.07 (–0.49 to 0.35)	0.750
Impact score	301	0.62 (1.53)	0.60 (1.42)	–0.02 (–0.35 to 0.31)	–0.05 (–0.39 to 0.29)	0.770

TABLE 17 Health Utilities Index version 3 and SDQ results by mode of ventilation. Results are presented as mean (SD), differences of the means (HFO – CV) unadjusted and adjusted for birthweight, gestational age groups and whether surfactant was given before birth (*continued*)

HUI-3/child self-assessed SDQ results	*n*	CV	HFO	Unadjusted difference (95% CI)	Adjusted difference (95% CI)	*p*-value for adjusted analysis
Parent-assessed SDQ						
Total difficulties	302	9.74 (6.92)	10.2 (7.36)	0.97 (–0.49 to 2.44)	0.76 (–0.72 to 2.25)	0.580[a]
Emotional symptoms	303	2.13 (2.24)	2.55 (2.41)	0.29 (–0.17 to 0.75)	0.22 (–0.23 to 0.68)	0.340
Conduct problems	302	1.34 (1.69)	1.49 (1.89)	0.17 (–0.23 to 0.56)	0.18 (–0.23 to 0.58)	0.390
Hyperactivity	302	4.03 (2.92)	3.93 (3.01)	–0.01 (–0.66 to 0.64)	–0.06 (–0.72 to 0.60)	0.870
Peer problems	303	2.23 (2.24)	2.36 (2.34)	0.18 (–0.32 to 0.69)	0.05 (–0.45 to 0.55)	0.860
Pro-social behaviour	303	8.46 (2.10)	8.32 (2.07)	–0.18 (–0.63 to 0.27)	–0.17 (–0.63 to 0.30)	0.480
Impact score	303	0.96 (1.99)	1.05 (1.79)	0.21 (–0.16 to 0.58)	0.14 (–0.22 to 0.51)	0.430
Teacher-assessed SDQ						
Total difficulties	221	7.99 (6.85)	7.53 (5.94)	–0.43 (–2.03 to 1.18)	–0.70 (–2.32 to 0.91)	0.770[a]
Emotional symptoms	222	2.27 (2.31)	2.27 (2.16)	0.00 (–0.57 to 0.58)	–0.10 (–0.68 to 0.49)	0.750
Conduct problems	223	0.71 (1.49)	0.55 (1.34)	–0.05 (–0.35 to 0.25)	–0.07 (–0.37 to 0.23)	0.650
Hyperactivity	223	2.86 (2.79)	2.95 (2.87)	0.07 (–0.60 to 0.75)	–0.06 (–0.73 to 0.60)	0.850
Peer problems	223	2.16 (2.31)	1.86 (2.03)	–0.28 (–0.83 to 0.27)	–0.32 (–0.87 to 0.24)	0.260
Pro-social behaviour	223	7.49 (2.65)	7.68 (2.40)	0.15 (–0.47 to 0.78)	0.22 (–0.41 to 0.86)	0.490
Impact score	222	0.74 (1.31)	0.51 (1.05)	–0.20 (–0.47 to 0.07)	–0.25 (–0.53 to 0.02)	0.069
ADHD						
Total score	216	8.20 (10.9)	8.19 (10.1)	–0.05 (–2.68 to 2.59)	–0.76 (–3.38 to 1.86)	0.570
Inattention score	218	1.35 (2.38)	1.13 (2.16)	–0.21 (–0.79 to 0.37)	–0.42 (–0.99 to 0.15)	0.150
Hyperactivity–impulsivity score	220	0.64 (1.77)	0.67 (1.54)	0.00 (–0.42 to 0.41)	–0.09 (–0.51 to 0.33)	0.680

a Distribution for all scores are skewed, transformation does not improve distribution unless indicated by [a]. Means and differences of means are presented using non-transformed scores. *p*-values for those indicated by [a] are from models using square root of the score.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

TABLE 18 Strength and Difficulties Questionnaire scores by ventilation group. Questionnaires scores are dichotomised into normal and abnormal/borderline categories and the results are presented as *n* (%) and unadjusted and adjusted odds ratios

SDQ results	Cut-off point[a]	*n*	CV	HFO	Unadjusted OR (HFO/CV) (95% CI)	Adjusted OR (95% CI)	*p*-value for adjusted analysis
Child self-assessed SDQ							
Total difficulties	> 15	293	25/145 (17)	28/148 (19)	1.12 (0.62 to 2.03)	1.03 (0.56 to 1.90)	0.930
Emotional symptoms	> 5	295	10/146 (7)	24/149 (16)	2.61 (1.20 to 5.67)	2.50 (1.13 to 5.56)	0.024
Conduct problems	> 3	294	23/145 (16)	17/149 (11)	0.68 (0.34 to 1.36)	0.66 (0.33 to 1.34)	0.260
Hyperactivity	> 5	294	37/146 (25)	35/148 (24)	0.91 (0.54 to 1.55)	0.88 (0.51 to 1.52)	0.640
Peer problems	> 3	295	29/146 (20)	36/149 (24)	1.39 (0.72 to 2.71)	1.15 (0.59 to 2.22)	0.690
Pro-social behaviour	< 6	297	15/146 (10)	13/151 (8.6)	0.82 (0.37 to 1.84)	0.89 (0.39 to 2.02)	0.780
Impact score	> 0	301	35/148 (24)	34/153 (22)	0.92 (0.51 to 1.69)	0.82 (0.44 to 1.54)	0.540
Parent-assessed SDQ							
Total difficulties	> 13	302	39/149 (26)	48/153 (31)	1.33 (0.76 to 2.35)	1.14 (0.63 to 2.07)	0.660
Emotional symptoms	> 3	303	41/149 (28)	48/154 (31)	1.19 (0.73 to 1.96)	1.04 (0.57 to 1.89)	0.910
Conduct problems	> 2	302	33/149 (22)	38/153 (25)	1.17 (0.65 to 2.10)	1.17 (0.64 to 2.13)	0.610
Hyperactivity	> 5	302	49/149 (33)	45/153 (29)	0.85 (0.51 to 1.41)	0.80 (0.47 to 1.37)	0.420
Peer problems	> 2	303	53/149 (36)	62/154 (40)	1.24 (0.76 to 2.01)	1.03 (0.62 to 1.71)	0.920
Pro-social behaviour	< 6	303	14/149 (9)	14/154 (9)	0.96 (0.43 to 2.14)	0.99 (0.44 to 2.22)	0.990
Impact score	> 0	303	45/149 (30)	56/154 (36)	1.34 (0.81 to 2.24)	1.17 (0.69 to 1.99)	0.550

TABLE 18 Strength and Difficulties Questionnaire scores by ventilation group. Questionnaires scores are dichotomised into normal and abnormal/borderline categories and the results are presented as *n* (%) and unadjusted and adjusted odds ratios (*continued*)

SDQ results	Cut-off point[a]	*n*	CV	HFO	Unadjusted OR (HFO/CV) (95% CI)	Adjusted OR (95% CI)	*p*-value for adjusted analysis
Teacher-assessed SDQ							
Total difficulties	> 11	221	26/109 (24)	27/112 (24)	1.01 (0.56 to 1.84)	0.94 (0.51 to 1.72)	0.84
Emotional symptoms	> 4	222	20/109 (18)	18/113 (16)	0.84 (0.41 to 1.72)	0.80 (0.39 to 1.65)	0.55
Conduct problems	>2	223	11/109 (10)	8/114 (7.0)	0.67 0.26 to 1.74)	0.55 (0.21 to 1.44)	0.22
Hyperactivity	> 5	223	22/109 (20)	25/114 (22)	1.12 (0.56 to 2.24)	1.01 (0.49 to 2.08)	0.99
Peer problems	> 3	223	29/109 (27)	24/114 (21)	0.71 (0.35 to 1.43)	0.66 (0.32 to 1.38)	0.27
Pro-social behaviour	< 6	223	24/109 (22)	23/114 (20)	0.89 (0.45 to 1.78)	0.87 (0.43 to 1.77)	0.70
Impact score	> 0	222	33/107 (31)	29/115 (25)	0.74 (0.38 to 1.43)	0.61 (0.30 to 1.24)	0.17

a Scores higher or lower than the cut off point indicate children who are considered borderline and abnormal cases with mental health disorders. These are 'rough guidelines' provided by www.sdqinfo.com (last accessed 3 June 2014).

Educational attainment and provision and attention deficit hyperactivity disorder

Two hundred and twenty-four teachers completed questionnaires regarding the children's educational attainment and provision and returned them directly to the researchers. There were statistically significant differences in attainment in three subjects: art and design, information technology (IT) and design and technology. The attainment was better in the HFO group (*Table 19*). A smaller proportion of the HFO group than the CV group (41% vs. 53%) were receiving SEN support (OR 0.56; 95% CI 0.32 to 1.00), but this was not quite statistically significant. When the analysis was restricted to children who had completed the assessments at KCH, that result was no longer statistically significant but the size of the estimate was unchanged (*Table 20*). The results of the teacher rating scale for ADHD did not differ significantly by ventilation group (see *Table 17*).

Echocardiography

There were no significantly different results by ventilation group (*Table 21*).

Intraclass correlation coefficients

These are reported for in *Table 22*.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

TABLE 19 Education attainment and educational provision by ventilation group. The results are presented as mean (SD) or *n* (%) unless specified, with unadjusted and adjusted difference (HFO – CV) or odds ratio (HFO/CV)

	n	CV	HFO	Unadjusted difference (95% CI)	Adjusted difference (95% CI)	*p*-value for adjusted difference
Area of study[a]						
English/literacy	219	2.81 (1.04)	2.92 (0.91)	0.07 (–0.17 to 0.32)	0.12 (–0.13 to 0.37)	0.350
Mathematics	218	2.76 (1.03)	2.76 (1.01)	0.00 (–0.27 to 0.26)	0.04 (–0.22 to 0.31)	0.750
Art and design	208	2.76 (0.89)	3.00 (0.79)	0.24 (0.01 to 0.47)	0.31 (0.09 to 0.54)	0.006
Geography	206	2.79 (0.91)	2.88 (0.77)	0.07 (–0.13 to 0.27)	0.11 (–0.09 to 0.32)	0.270
History	205	2.81 (0.89)	2.92 (0.84)	0.10 (–0.13 to 0.33)	0.18 (–0.06 to 0.41)	0.140
IT	204	2.82 (0.80)	3.00 (0.78)	0.18 (–0.03 to 0.39)	0.24 (0.03 to 0.45)	0.023
Science	215	2.83 (0.99)	2.96 (0.83)	0.12 (–0.12 to 0.36)	0.19 (–0.05 to 0.43)	0.120
Design and technology	197	2.80 (0.88)	3.04 (0.75)	0.24 (0.02 to 0.46)	0.27 (0.05 to 0.49)	0.017
Educational provision						
School type and support	*301*					
Mainstream school		88/148 (59)	85/153 (56)	0.84 (0.51 to 1.38)	0.90 (0.54 to 1.49)	0.690
Mainstream school with learning support or help		41/148 (28)	54/153 (35)			
Special class or unit		2/148 (1.4)	4/153 (2.6)			
Special school or pupil referral unit (PRU)		14/148 (9.5)	10/153 (6.5)			
Home or hospital tuition		2/148 (1.4)	0			
Other		1/148 (1)	0			

TABLE 19 Education attainment and educational provision by ventilation group. The results are presented as mean (SD) or *n* (%) unless specified, with unadjusted and adjusted difference (HFO – CV) or odds ratio (HFO/CV) (*continued*)

	n	CV	HFO	Unadjusted difference (95% CI)	Adjusted difference (95% CI)	*p*-value for adjusted difference
Requires SEN	*224*	*57/108 (53)*	*60/116 (52)*	*0.96 (0.57 to 1.62)*	*0.94 (0.54 to 1.64)*	*0.830*
Area of need[b]						
Specific learning difficulty		16	13	0.75 (0.34 to 1.64)[c]	0.58 (0.26 to 1.30)[c]	0.190
Moderate learning difficulty		19	19	0.95 (0.47 to 1.90)[c]	0.89 (0.45 to 1.79)[c]	0.750
Severe learning difficulty		1	3	2.92 (0.30 to 28.50)[c]		0.360[d]
Profound and multiple learning difficulty		2	0			
Behaviour, emotional and social difficulty		10	5	0.45 (0.15 to 1.38)[c]		0.160[d]
Speech, language and communication needs		14	14	0.95 (0.43 to 2.01)[c]	0.95 (0.41 to 2.20)[c]	0.900
Autistic spectrum disorder		5	3	0.56 (0.13 to 2.41)[c]		0.440[d]
Hearing impairment		8	10	1.21 (0.46 to 3.20)[c]	1.33 (0.49 to 3.65)[c]	0.570
Visual impairment		8	6	0.70 (0.24 to 2.09)[c]	0.59 (0.18 to 1.93)[c]	0.380
Multisensory impairment		0	0			
Physical disability		7	14	2.04 (0.79 to 5.26)[c]	2.36 (0.89 to 6.26)[c]	0.085
Other SEN		7	8	1.10 (0.39 to 3.14)[c]	1.03 (0.34 to 3.18)[c]	0.960
On special needs register	*223*	*52/108 (48)*	*57/115 (50)*	*1.06 (0.63 to 1.79)*	*1.04 (0.60 to 1.82)*	*0.880*
Stage of special needs register						
School Action		21/52 (40)	18/56 (32)			
School Action Plus		14/52 (27)	15/56 (27)			
Statement of Special Education Needs		17/52 (33)	24/56 (43)			

continued

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

TABLE 19 Education attainment and educational provision by ventilation group. The results are presented as mean (SD) or *n* (%) unless specified, with unadjusted and adjusted difference (HFO – CV) or odds ratio (HFO/CV) (*continued*)

	n	CV	HFO	Unadjusted difference (95% CI)	Adjusted difference (95% CI)	*p*-value for adjusted difference
Receives SEN support in school[b]	*216*	*56/106 (53)*	*45/111 (41)*	*0.61 (0.36 to 1.04)*	*0.56 (0.32 to 1.00)*	*0.051*
Individual educational/ behaviour plan		23	24			
Median hours/week (range)		5 (1–40)	20 (1–30)			
One-to-one special needs provision		17	22			
Median hours/week (range)		1.5 (1–20)	4 (1–40)			
Small group special needs provision		44	34			
Median hours/week (range)		3 (1–33)	3 (1–30)			
Seeing the following professionals in school[b]						
Outreach teacher		7	4			
Educational psychologist		19	12			
Clinical psychologist		2	1			
Physiotherapist		6	11			
Speech/language therapist		16	16			
Occupational therapist		14	13			
Child requires extra support according to teacher's opinion	219	22/108 (20)	16/111 (14)	0.66 (0.32 to 1.34)	0.57 (0.27 to 1.21)	0.150

a Rating scale for area of study: 1, very below average; 2, below average; 3, average; 4, above average; and 5, very above average.
b Some children require more than one area of SEN, SEN support or professional help in school (responders could tick more than one box).
c All non-responses were assumed not to have the particular area of need.
d *p*-value unadjusted due to small numbers; all non-responses were assumed not to have the particular area of need.
All data derived from teacher's questionnaire except for school type and support, which comes from parental questionnaire. There were 227 returned teacher's questionnaires (111 in CV group and 116 in HFO group) and 305 parental questionnaires returned (150 in CV group and 155 in HFO group).

TABLE 20 Sensitivity analysis on educational attainment data. This analysis was undertaken on results from those who came to assessment and had their teacher's questionnaire completed. Difference is calculated by HFO – CV

	Adjusted difference (95% CI)	*p*-value	Sensitivity analysis: adjusted difference (95% CI)	*p*-value
Area of study				
English/literacy	0.12 (–0.13 to 0.37)	0.350	0.11 (–0.15 to 0.38)	0.410
Mathematics	0.04 (–0.22 to 0.31)	0.750	0.03 (–0.25 to 0.32)	0.820
Art and design	0.31 (0.09 to 0.54)	0.006	0.27 (0.05 to 0.50)	0.019
Geography	0.11 (–0.09 to 0.32)	0.270	0.08 (–0.14 to 0.29)	0.470
History	0.18 (–0.06 to 0.41)	0.140	0.15 (–0.09 to 0.40)	0.220
IT	0.24 (0.03 to 0.45)	0.023	0.26 (0.04 to 0.48)	0.019
Science	0.19 (–0.05 to 0.43)	0.120	0.13 (–0.12 to 0.39)	0.310
Design and technology	0.27 (0.05 to 0.49)	0.017	0.23 (0.01 to 0.46)	0.042
Educational provision				
Mainstream school	0.90 (0.54 to 1.49)	0.690	0.81 (0.46 to 1.43)	0.470
Requires SEN	0.94 (0.54 to 1.64)	0.830	1.00 (0.56 to 1.81)	0.990
On special needs register	1.04 (0.60 to 1.82)	0.880	1.13 (0.62 to 2.06)	0.680
Receives SEN support in school	0.56 (0.32 to 1.00)	0.051	0.59 (0.32 to 1.10)	0.095
Child requires extra support according to teacher's opinion	0.57 (0.27 to 1.21)	0.150	0.48 (0.21 to 1.12)	0.090

One hundred and ninety-seven had came to assessment and had teacher questionnaire completed. Two hundred and forty-two had came to assessment and had parental questionnaire completed.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

TABLE 21 Echocardiogram results by ventilation group. The results are presented as the means (SD) and difference of means (HFO – CV), unadjusted and adjusted for birthweight, gestational age groups and whether surfactant was given before birth. The data are presented as the mean (SD)

Echocardiographic measurements	*n*	CV	HFO	Unadjusted difference (95% CI)	Adjusted difference (95% CI)	*p*-value for adjusted analysis
N		97	101			
maxPG (mmHg)	136	19.80 (3.77)	19.70 (4.27)	–0.15 (–1.50 to 1.20)	–0.26 (–1.62 to 1.11)	0.71
TR peak velocity (m/second)	138	2.22 (0.21)	2.20 (0.25)	–0.02 (–0.10 to 0.05)	–0.03 (–0.11 to 0.05)	0.44
EDIVS *z*-score	189	–0.15 (0.74)	–0.15 (0.65)	–0.01 (–0.20 to 0.19)	–0.01 (–0.20 to 0.19)	0.94
TAPSE *z*-score	178	0.19 (1.85)	–0.11 (1.99)	–0.34 (–0.88 to 0.21)	–0.41 (–0.94 to 0.12)	0.13
LVEF% predicted	190	68.40 (8.25)	68.80 (7.64)	0.21 (–1.95 to 2.36)	0.12 (–2.02 to 2.27)	0.91
LA (cm^2)	195	11.60 (1.83)	11.90 (1.82)	0.24 (–0.26 to 0.73)	0.22 (–0.28 to 0.71)	0.39
Ev (cm/second)	185	99.70 (13.70)	100.00 (14.40)	0.81 (–3.04 to 4.66)	0.97 (–2.87 to 4.80)	0.62
Av (cm/second)	184	58.10 (11.50)	58.80 (11.90)	–0.45 (–3.39 to 2.50)	–0.59 (–3.42 to 2.24)	0.68
E/A	184	1.73 (1.16)[a]	1.72 (1.15)[a]	0.99 (0.95 to 1.04)[a]	0.99 (0.95 to 1.04)[a]	0.81

Av, atrial filling velocity of the left ventricle; E/A, differences are the ratio of geometric means; EDIVS, end-diastolic diameter of the interventricular septum; Ev, early filling velocity of the left ventricle; LA, left atrial diameter; LVEF, left ventricle ejection fraction; maxPG, peak pressure gradient between right atrium and right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation jet velocity.
a Estimates based on log-transformed.

TABLE 22 Intraclass correlation coefficient from mixed models in unadjusted and adjusted analyses

Outcome	Range of intraclass correlation coefficient
Lung function	0.33–0.68
Child self-assessed SDQ	0.18–0.47
Parent- and teacher-assessed SDQ	0.24–0.85
ADHD	0.44–0.56
Area of school study	0.20–0.73

Longitudinal study of lung function

Small airway function of prematurely born infants may deteriorate over the first year after birth. A subset of the 42 children had detailed pulmonary function measurements at 1 and 12 years of age. The aim was to determine whether or not small airway function, assessed by measuring the degree of gas trapping, changed between 1 and 12 years of age and whether or not any changes were affected by neonatal factors. Lung volumes were assessed by FRC_{pleth} and FRC_{he}; the degree of gas trapping was calculated as the FRC_{He} to FRC_{pleth} ratio. Changes in the FRC_{He} to FRC_{pleth} ratios and the effects of gestation, sex, and oxygen dependency at 36 weeks postmenstrual age (BPD_{36}) were analysed using mixed models. Nineteen of the infants were born between 23 and 25 weeks' gestation and 23 between 26 and 28 weeks; 24 (57%) had BPD_{36}. The mean (SD) FRC_{He} : FRC_{pleth} at 1 and 12 years of age was 0.90 (0.12) and 0.84 (0.12), respectively. For those with BPD_{36}, the mean ratios was 0.87 (0.13) at age 1 year and 0.81 (0.13) at age 12 years; for those without BPD_{36}, they were 0.94 (0.11) and 0.87 (0.10), respectively. Overall, there was a reduction in FRC_{He} : FRC_{pleth} of 5.9% (95% CI 0.70% to 11%; $p = 0.026$) between ages 1 and 12 years after adjusting for birthweight, gestational age, sex and BPD_{36}. There was no significant difference in the degree of deterioration between the children who had and did not have BPD_{36}. These results suggest that small airway function deteriorates between 1 and 12 years in children born very prematurely.

Discussion

We have demonstrated that schoolchildren born extremely prematurely who were supported by HFO in the neonatal period had an increase in mean lung function of 0.23 SDs on average compared with those supported by CV. The proportion of children with lung function results below the tenth centile was eight percentage points lower in the HFO group than in the CV group. Specifically, the HFO group had better small airway function (FEF_{75}), as we had hypothesised and, in addition, they also had superior large airway function. Those latter results are particularly compelling as there were similar findings from different assessments of large airway function (FEV_1, FEF_{50}, FEF_{25}), including from the non-volitional test impulse oscillometry. In addition, the HFO group had better $D_{L,CO}$ results, suggesting they had a greater lung surface area for gas exchange. The groups did differ at baseline in mean birthweight, gestational age and administration of surfactant, but all differences favoured the CV group and adjustment for these factors had no effect on the differences in mean lung function that were observed. The difference in the mean FEF_{75} results between the two groups was due to a shift in the entire CV group's distribution downwards, rather than an effect only in certain children (see *Figure 3*). It was a whole-population effect, as first described by Rose,[45] and arises when there is a small effect on each subject. Thus, these data suggest that the use of HFO would benefit all extremely prematurely born infants.

The differences in lung function, although statistically significant, were relatively small: on average, approximately 0.30 *z*-scores. This small effect and the respiratory reserve in childhood explain why there was no associated increase in respiratory morbidity, as documented by symptom status and need for medication on the parent-completed questionnaires. In addition, there was no significant difference in the number of hospital admissions between the two groups, but only three of the whole cohort had required admission to hospital for chest problems. The greater proportion of the CV group than the HFO group with small airway function results below the tenth percentile, however, may make them more vulnerable to subsequent lung function insults such as smoking. There were no significant differences in the echocardiographic results between the two groups; whether or not this reflects that few of the children had PH in the neonatal period is not known, as the centres did not undertake routine screening. It may be, however, that both groups have clinically important abnormalities in PVR. To address that question, a cohort of term-born children is currently being assessed.

The results of our subset who were also measured at 1 year suggests that their small airway function may have deteriorated, as they had greater evidence of gas trapping when assessed at 11–14 years of age than when they were assessed at 1 year corrected age. Those results are in keeping with the decline in small airway function seen in the first year after birth in moderately prematurely born infants[12] and extremely

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

prematurely born infants initially supported by CV.[13] Thus, it will be very important to reassess all the children to determine whether or not their lung function deteriorates further still with increasing age and they become symptomatic.

We did not recruit 320 children for full assessment, but recruited 319 overall and 256 children for lung function assessment. Maternal smoking was higher than found among mothers of a Swedish cohort of schoolchildren[46] and likely reflects the lower socioeconomic class of prematurely born infants. Maternal smoking also differed between those who were and were not recruited. The lung function group's results, however, showed consistent and statistically differences which were unchanged by any of the many adjustments we employed and so we are fully confident in our findings.

We were concerned that any respiratory benefit associated with use of HFO might have been associated with adverse neurodevelopmental outcomes as, in some trials, HFO has been associated with increases in severe intracranial haemorrhage and periventricular leukomalacia. Those adverse outcomes could be the result of lung over-distension compromising cardiac output and cerebral perfusion and/or hypocarbia. There were, however, no significant differences between the groups regarding the majority of assessments of functional outcomes. A significantly greater proportion of the HFO children recorded that they had emotional symptoms on the SDQ, but this difference was not found by either the parents or teachers and is probably a type 1 error. Indeed, there were significant differences between the two groups in educational attainment with regard to art and design, IT and design and technology, all favouring the HFO children. In addition, a borderline significantly greater proportion of the CV children were receiving SEN support at school.

There are now 17 trials of elective HFO compared with CV for acute pulmonary dysfunction in preterm infants included in the systematic review in the Cochrane database.[47] HFO use remained associated with a reduction in BPD, although the effect was of borderline significance, it was also associated with a significantly lower incidence of retinopathy of prematurity. HFO use was also associated with a significantly increased incidence of pneumothorax, but, overall, there was no significant difference according to ventilation mode with regard to short-term neurological morbidity.[47] The authors of the systematic review concluded that there was no clear evidence that elective HFO offers any important advantages over CV when used as the initial ventilation strategy to support preterm infants and future trials should target those infants at highest risk of BPD, extremely prematurely born infants and report important long-term neurodevelopmental outcomes.[47]

We have undertaken a large randomised trial of HFO (UKOS) in extremely prematurely born infants, all born before 29 weeks of gestational age.[1] There were no significant differences in the short-term outcomes[1] or at the 2-year follow-up,[11] although certain respiratory outcomes favoured the HFO group.[11] It is, then, perhaps not surprising in retrospect that we now have identified clinically important differences in respiratory function favouring the HFO group compared with the CV group when they were assessed at 11–14 years of age.

Our results demonstrate the importance of long-term follow-up of children born very prematurely entered into randomised trials if the full impact of interventions delivered in infancy is to be robustly determined. A lack of a significant positive result in infancy may not mean the intervention had no effect, but rather it may become manifest later in childhood.

Recommendations for future research in this area

Very prematurely born children entered into other randomised trials comparing HFO with CV should be assessed at school age to determine whether or not the positive effects of HFO we demonstrate are specific to our study design or are found in other trials. Those results would have important implications for how elective HFO is used going forward. Studies should be undertaken incorporating serial assessments to determine if HFO is associated with a persistent reduction in lung function decline.

Conclusion

The follow-up of extremely prematurely born infants at 11–14 years of age entered into a randomised trial of HFO compared with CV has demonstrated significant differences in lung function in favour of HFO. There was no evidence that this was offset by poorer functional outcomes; indeed, HFO children did better in some school subjects.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Acknowledgements

Three students have been involved in the assessments as part of their BSc in Physiology: Fred Thomas, Thomas De'ath and Jodie Nguyen.

Additional funding was received from the South London CLRN to support an administrator to facilitate recruitment.

Ms Rupa Odedra (administrator) assisted in making travel arrangements for the children and their families.

Mr Bolaji Coker (database manager) designed and managed the database.

Contributions of authors

Professors Anne Greenough and **Professor Janet Peacock** designed the overall study.

Professor Neil Marlow was responsible for which functional assessments were used and **Dr Sandy Calvert** was the principal investigator for UKOS.

All the above contributed to the ongoing monitoring of this study and interpretation of the results.

The UKOS follow-up team additionally consisted of:

Dr Sanja Zivanovic (research fellow) who was primarily responsible for the follow-up assessments and will be writing up this study as her PhD thesis.

Mrs Mireia Alcazar-Paris (research nurse) who assisted Dr Sanja Zivanovic to undertake the assessments, she also was responsible for contacting the parents and data entry.

Ms Jessica Lo (statistician) who was responsible for checking the data and for all data analysis overseen by Professor Peacock.

United Kingdom Oscillation Study steering committee

The external steering group was chaired by Professor Henry Halliday, Honorary Professor of Child Health, and included clinical experts, a senior statistician and a UKOS parent (see below). The steering committee met on two occasions during the study. The external members provided invaluable advice about the conduct of the study, particularly regarding contacting families and maximising the response rate. The external steering committee also commented on the data accrual in terms of completed visits and on the statistics analysis plan.

The other members were:

Professor John Henderson, University of Bristol, Professor of Paediatric Respiratory Medicine: independent member.

Dr Steve Cunningham, University of Edinburgh, Consultant and Honorary Reader in Paediatric Respiratory Medicine: independent member.

Mrs Sally Kerry, Queen Mary University of London, Reader in Medical Statistics: independent member.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Mrs Janie Dromgoole: UKOS parent representative.

Professor Anne Greenough, King's College London, Professor of Neonatology and Respiratory Physiology: joint principal investigator.

Professor Janet Peacock, King's College London, Professor of Medical Statistics: joint principal investigator.

Professor Neil Marlow, University College London, Professor of Neonatology: co-investigator.

Dr Sandra Calvert, St George's University of London, Consultant Neonatologist: co-investigator.

Publications

Zivanovic S, Peacock J, Alcazar-Paris M, Lo JW, Lunt A, Marlow N, *et al.* United Kingdom Oscillation Study Group. Late outcomes of a randomised trial of high frequency oscillation in neonates. *N Engl J Med* 2014;**370**:1121–30.

References

1. Johnson AH, Peacock JL, Greenough A, Marlow N, Limb ES, Marston L, *et al.* High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. *New Engl J Med* 2002;**347**:633–42. http://dx.doi.org/10.1056/NEJMoa020432
2. Greenough A, Cox S, Alexander J, Lenney W, Turnbull F, Burgess S, *et al.* Health care utilisation of infants with chronic lung disease, related to hospitalisation for RSV infection. *Arch Dis Child* 2001;**85**:463–8. http://dx.doi.org/10.1136/adc.85.6.463
3. Greenough A, Alexander J, Burgess S, Chetcuti PA, Cox S, Lenney W, *et al.* Home oxygen status and rehospitalisation and primary care requirements of infants with chronic lung disease. *Arch Dis Child* 2002;**86**:40–3. http://dx.doi.org/10.1136/adc.86.1.40
4. Greenough A, Alexander J, Burgess S, Bytham J, Chetcuti PA, Hagan J, *et al.* Preschool health care utilisation related to home oxygen status. *Arch Dis Child Fetal Neonatal Ed* 2006;**91**:F337–41. http://dx.doi.org/10.1136/adc.2005.088823
5. McLean A, Townsend A, Clark J, Sawyer MG, Baghurst P, Haslam R, *et al.* Quality of life of mothers and families caring for preterm infants requiring home oxygen therapy: a brief report. *J Pediatr Child Health* 2000;**36**:440–4. http://dx.doi.org/10.1046/j.1440-1754.2000.00561.x
6. Gross SJ, Iannuzzi DM, Kveselis DA, Anbar RD. Effect of preterm birth on pulmonary function at school age: a prospective controlled study. *J Pediatr* 1998;**133**:188–92. http://dx.doi.org/10.1016/S0022-3476(98)70219-7
7. Vrijlandt EJ, Gerritsen J, Boezen HM, Duiverman EJ, Dutch POPS-19 Collaborative Study Group. Gender differences in respiratory symptoms in 19-year-old adults born preterm. *Respir Res* 2005;**6**:177. http://dx.doi.org/10.1186/1465-9921-6-117
8. Vrijlandt EJ, Gerritsen J, Boezen HM, Grevink RG, Duiverman EJ. Lung function and exercise capacity in young adults born prematurely. *Am J Respir Crit Care Med* 2006;**173**:890–6. http://dx.doi.org/10.1164/rccm.200507-1140OC
9. Marlow N. Neurocognitive outcome after very preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F224–8. http://dx.doi.org/10.1136/adc.2002.019752
10. Thomas MR, Rafferty GF, Limb ES, Peacock JL, Calvert SA, Marlow N, *et al.* Pulmonary function at follow-up of very preterm infants from the United Kingdom oscillation study. *Am J Respir Crit Care Med* 2004;**169**:868–72. http://dx.doi.org/10.1164/rccm.200310-1425OC
11. Marlow N, Greenough A, Peacock JL, Marston L, Limb ES, Johnson AH, *et al.* Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;**91**:F320–6. http://dx.doi.org/10.1136/adc.2005.079632
12. Hoo AF, Dezateux C, Henschen M, Costeloe K, Stocks J. Development of airway function in infancy after preterm delivery. *J Pediatr* 2002;**141**:652–8. http://dx.doi.org/10.1067/mpd.2002.128114
13. Hofhuis W, Huysman MW, van der Wiel EC, Holland WP, Hop WC, Brinkhorst G, *et al.* Worsening of V'_{max}FRC in infants with chronic lung disease in the first year of life: a more favorable outcome after high-frequency oscillation ventilation. *Am J Respir Crit Care Med* 2002;**166**:1539–43. http://dx.doi.org/10.1164/rccm.2202046
14. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. *N Engl J Med* 1989;**320**:88–93. http://dx.doi.org/10.1056/NEJM198901123200204

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

15. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants: assessment of pulmonary function at 9 months of corrected age. *J Pediatr* 1990;**116**:933–41. http://dx.doi.org/10.1016/S0022-3476(05)80657-2

16. Bryan AC, Froese AB. Reflections on the HIFI trial. *Pediatrics* 1991;**87**:565–7.

17. Thomas M, Greenough A, Blowes R, Rafferty GF, Calvert S, Marlow N, *et al.* Airway resistance estimation by best fit analysis in very premature infants. *Physiol Meas* 2002;**23**:279–85. http://dx.doi.org/10.1088/0967-3334/23/2/304

18. Dubois AB, Botelho SY, Bedell GN, Marshall R, Comroe JH Jr. A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. *J Clin Invest* 1956;**35**:322–6. http://dx.doi.org/10.1172/JCI103281

19. Yüksel B, Greenough A. Measurement of thoracic gas volume in patients born prematurely: should occlusion be made at end-inspiration or end-expiration? *Pediatr Pulmonol* 1994;**18**:295–8. http://dx.doi.org/10.1002/ppul.1950180506

20. Stocks J, Marchal F, Kraemer R, Gutkowski P, Bar-Yishay E, Godfrey S. Plethysmographic Assessment of Functional Residual Capacity and Airway Resistance. In Stocks SPJ, Tepper RS, Morgan WJ, editors. *Infant Respiratory Function Testing*. New York, NY: John Wiley & Sons, Inc.; 1996. pp. 190–240.

21. Stocks J, Levy NM, Godfrey S. A new apparatus for the accurate measurement of airway resistance in infancy. *J App Physiol Respir Envron Exerc Physiol* 1977;**43**:155–9.

22. Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R. Plethysmographic measurements of lung volume and airway resistance. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/American Thoracic Society. *Eur Respir J* 2001;**17**:302–12. http://dx.doi.org/10.1183/09031936.01.17203020

23. Yüksel B, Greenough A. Functional residual capacity to thoracic gas volume (FRC:TGV) ratio in healthy neonates. *Resp Med* 1995;**89**:429–33. http://dx.doi.org/10.1016/0954-6111(95)90212-0

24. Tepper RS, Merth IT, Newth CJ, Gerhardt T. Measurement of Functional Residual Capacity in Infants by Helium Dilution and Nitrogen Washout Techniques. In Stocks SJ, Tepper RS, Morgan WJ, editors. *Infant Respiratory Function Testing*. New York, NY: John Wiley & Sons, Inc.; 1996. pp. 165–89.

25. Morris MG, Gustafsson P, Tepper R, Gappa M, Stocks J. The bias flow nitrogen washout technique for measuring the functional residual capacity in infants. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. *Eur Respir J* 2001;**17**:529–36. http://dx.doi.org/10.1183/09031936.01.17305290

26. Bayley N. *Bayley Scales of Infant Development*. 2nd edn. San Antonio, TX: The Psychological Corporation; 1993.

27. Fenson L, Pethick S, Renda C, Cox JL. Short-form versions of the MacArthur Communicative Development Inventories. *Appl Psycholinguist* 2000;**21**:95–115. http://dx.doi.org/10.1017/S0142716400001053

28. Johnson S, Marlow N, Wolke D, Davidson L, Marston L, O'Hare A, *et al.* Validation of a parent report measure of cognitive development in very preterm infants. *Dev Med Child Neurol* 2004;**46**:389–97. http://dx.doi.org/10.1017/S0012162204000635

29. Henderson-Smart DJ, Bhuta T, Cools F, Offringa M. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev* 2003;**4**:CD000104.

30. Moriette G, Paris-Llado J, Walti H, Escande B, Magny JF, Cambonie G, *et al.* Prospective randomized multicentre comparison of high-frequency oscillatory ventilation and conventional ventilation in preterm infants of less than 30 weeks with respiratory distress syndrome. *Pediatrics* 2001;**107**:363–72. http://dx.doi.org/10.1542/peds.107.2.363

31. Sharma A, Greenough A. Survey of neonatal respiratory support strategies. *Acta Paediatr* 2007;**96**:1115–17. http://dx.doi.org/10.1111/j.1651-2227.2007.00388.x

32. Mourani P, Sontag MK, Younoszai A, Ivy DD, Abman SH. Clinical utility of echocardiography for the diagnosis and management of pulmonary vascular disease in young children with chronic lung disease. *Pediatrics* 2008;**121**:317–25. http://dx.doi.org/10.1542/peds.2007-1583

33. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, *et al.* Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med* 2004;**350**:886–95. http://dx.doi.org/10.1056/NEJMoa035477

34. Arcasoy SM, Christie JD, Ferrari VA, Sutton MS, Zisman DA, Blumenthal NP, *et al.* Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med* 2003;**167**:735–40. http://dx.doi.org/10.1164/rccm.200210-1130OC

35. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. *J Am Coli Cardiol* 1985;**6**:359–65. http://dx.doi.org/10.1016/S0735-1097(85)80172-8

36. Rosenthal M, Bain SH, Cramer D, Helms P, Denison D, Bush A, *et al.* Lung function in white children aged 4 to 19 years: I-Spirometry. *Thorax* 1993;**48**:794–802. http://dx.doi.org/10.1136/thx.48.8.794

37. Rosenthal M, Cramer D, Bain SH, Denison D, Bush A, Warner JO. Lung function in white children aged 4 to 19 years: II-Single breath analysis and plethysmography. *Thorax* 1993;**48**:803–8. http://dx.doi.org/10.1136/thx.48.8.803

38. Nowowiejska B, Tomalak W, Radliński J, Siergiejko G, Latawiec W, Kaczmarski M. Transient reference values for impulse oscillometry for children aged 3–18 years. *Pediatr Pulmonol* 2008;**43**:1193–7. http://dx.doi.org/10.1002/ppul.20926

39. Sylvester KP, O'Connor BJ, Farebrother HM, Rafferty GF, Greenough A. Cold air and exercise challenge – influence of minute ventilation. *J Asthma* 2007;**44**:143–7. http://dx.doi.org/10.1080/02770900601182525

40. American Thoracic Society. Recommendations for standardized procedures for the on-line and off-line measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide in adults and children-1999. *Am J Respir Crit Care Med* 1999;**160**:2104–17. http://dx.doi.org/10.1164/ajrccm.160.6.ats8-99

41. Galiè N, Hoeper M, Humbert M, Torbicki A, Vachiery JL, Barbera JA, *et al.* Guidelines on diagnosis and treatment of pulmonary hypertension: the Task Force on Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;**30**:2493–537. http://dx.doi.org/10.1093/eurheartj/ehp297

42. Sauzet O, Wright K, Marston L, Brocklehurst P, Peacock JL. Modelling the hierarchical structure in data sets with very small clusters: a simulation study to explore the effect of the proportion of clusters when the outcome is continuous. *Stat Med* 2013;**32**:1429–38. http://dx.doi.org/10.1002/sim.5638

43. Peacock JL, Sauzet O, Ewings SM, Kerry SM. Dichotomizing continuous data while retaining statistical power using a distributional approach. *Stat Med* 2012;**31**:3089–103. http://dx.doi.org/10.1002/sim.5354

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

44. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. *BMJ* 2011;**342**:d40. http://dx.doi.org/10.1136/bmj.d40

45. Rose G. Sick individuals and sick populations. *Int J Epidemiol* 1985;**14**:32–8. http://dx.doi.org/10.1093/ije/14.1.32

46. Hedman L, Bjerg A, Sundberg S, Forsberg B, Rönmark E. Both environmental tobacco smoke and personal smoking is related to asthma and wheeze in teenagers. *Thorax* 2011;**66**:20–5. http://dx.doi.org/10.1136/thx.2010.143800

47. Cools F, Henderson-Smart DJ, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev* 2010;**1**:CD000104.

Appendix 1 Questionnaires

Trial number

UKOS

United Kingdom Oscillation Study

Follow-up at age 12-13 years

CONFIDENTIAL

Teacher Questionnaire

To be completed by the class teacher of children in the UKOS2 Study

KING'S College LONDON

St George's University of London

UCL

UKOS2 Teacher questionnaire v1 14.03.2011

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Instructions for completing this questionnaire

Dear Teacher,

Re: Child's name: ..... **Child's Date of Birth:** .....

This child is taking part in the UKOS follow-up study – a follow-up of children born extremely prematurely who took part in the United Kingdom Oscillation Study (UKOS) when they were first born. We have obtained permission from this child's parent/guardian to ask you for some information about his/her classroom behaviour and school performance during the current academic year. We would be very grateful if you would complete this questionnaire.

How to complete this questionnaire:

Please answer all questions as best you can, even if the question doesn't seem very relevant to this child. We have included a section at the end of the questionnaire for you to make any additional comments about this child's school performance or to provide any relevant information that you feel is not covered elsewhere in the questionnaire. We will treat all the information in the **strictest confidence**. Parents will not have access to this information and we will not divulge it to anyone outside the study. The questionnaire will be destroyed when we have finished with it.

How to return the questionnaire:

Please complete the questionnaire and seal it in the envelope provided and post it to us using the self-addressed envelope provided.

For further information:

If you have any questions or would like any further information about the UKOS Study, please telephone the UKOS Study office at King's College London 020 3299 3037, or email us at ukos@kcl.ac.uk

Thank you for completing this questionnaire and helping with this important study.
Your contribution is greatly appreciated.

Section A: Educational Provision

A1. Does this child have any special educational needs? yes ☐ no ☐

If yes, please specify the child's area of need(s) from the list below.

Please tick all that apply.

- Specific learning difficulty (SpLD) ☐
- Moderate learning difficulty (MLD) ☐
- Severe learning difficulty (SLD) ☐
- Profound and multiple learning difficulty (PMLD) ☐
- Behaviour, emotional and social difficulty (BESD) ☐
- Speech, language and communication needs (SLCN) ☐
- Autistic Spectrum Disorder (ASD) ☐
- Hearing impairment (HI) ☐
- Visual impairment (VI) ☐
- Multi-sensory impairment (MSI) ☐
- Physical disability (PD) ☐
- Other – please specify ..... ☐

A2. Is this child currently on the special needs register? yes ☐ no ☐

If yes, please specify which stage the child is at:

Please tick one.

- School Action ☐
- School Action Plus ☐
- Statement of Special Educational Needs ☐

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

A4. If this child has a Statement of SEN, does this include specific hours of support? yes ☐ no ☐

If yes, please tell us how many hours: ☐

A5. Does this child receive SEN support in school? yes ☐ no ☐

If yes, please specify the type(s) of support received **and** the number of hours of each type of support received using the list below.

Please complete all that apply.

	Tick if received	Enter hours per week
Individual Education/Behaviour Plan	☐	☐
One-to-one special needs provision	☐	☐
Small group special needs provision	☐	☐

A6. If the child receives one-to-one special needs provision, please specify who provides this

	Tick all that apply
Teacher	☐
Teaching Assistant	☐
Other – please specify	☐

A7. If the child receives small group special needs provision, please specify who provides this

	Tick all that apply
Teacher	☐
Teaching Assistant	☐
Other – please specify	☐

A8. Has this child ever seen any of the following professionals in school?

Please tick all that apply:

- Outreach Teacher ☐
- Educational Psychologist ☐
- Clinical Psychologist ☐
- Physiotherapist ☐
- Speech/Language Therapist ☐
- Occupational Therapist ☐

A9. In your professional opinion, does this child need extra support (in addition to that which is currently provided)? yes ☐ no ☐

If yes, please give details of the type of support you feel this child would benefit from:

.....

.....

.....

.....

.....

.....

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Section B. Academic Attainment

Please rate the child's ability in relation to the average level expected of his/her class in each of the following subjects during the current academic year. Please cross out any subjects not received by, or not applicable, to this child.

	Very below average	Below average	Average	Above average	Very above average
English/Literacy	☐	☐	☐	☐	☐
Mathematics	☐	☐	☐	☐	☐
Art & Design	☐	☐	☐	☐	☐
Geography	☐	☐	☐	☐	☐
History	☐	☐	☐	☐	☐
I.T.	☐	☐	☐	☐	☐
Science	☐	☐	☐	☐	☐
Design & Technology	☐	☐	☐	☐	☐

Section C. Strengths and Difficulties

For each question, please tick the most appropriate box. Please answer all the questions even if they don't seem very relevant to this child. Please given your answers on the basis of the child's behaviour over the last 6 months or this school year.

	Not true	Somewhat true	Certainly true
C1. Considerate of other people's feelings	☐	☐	☐
C2. Restless, overactive, cannot stay still for long	☐	☐	☐
C3. Often complains of headaches, stomach aches or sickness	☐	☐	☐
C4. Shares readily with other children (treats, toys, pencils etc)	☐	☐	☐
C5. Often has temper tantrums or hot tempers	☐	☐	☐
C6. Rather solitary, tends to play alone	☐	☐	☐
C7. Generally obedient, usually does what adults request	☐	☐	☐
C8. Many worries, often seems worried	☐	☐	☐
C9. Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
C10. Constantly fidgeting or squirming	☐	☐	☐
C11. Has at least one good friend	☐	☐	☐
C12. Often fights with other children or bullies them	☐	☐	☐
C13. Often unhappy, down-hearted or tearful	☐	☐	☐
C14. Generally liked by other children	☐	☐	☐
C15. Easily distracted, concentration wanders	☐	☐	☐
C16. Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
C17. Kind to younger children	☐	☐	☐
C18. Often lies or cheats	☐	☐	☐
C19. Picked on or bullied by other children	☐	☐	☐
C20. Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
C21. Thinks things out before acting	☐	☐	☐
C22. Steals from home, school or elsewhere	☐	☐	☐
C23. Gets on better with adults than other children	☐	☐	☐
C24. Many fears, easily scared	☐	☐	☐
C25. Sees tasks through to the end, good attention span	☐	☐	☐

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

C26. Overall, do you think that this child has difficulties in one or more of the following areas: emotions, concentration behaviour or being able to get on with other people?

- No → If no, please go to Section D
- Yes, minor difficulties → If you have ticked any of these 'yes' options, please answer the rest of the questions in this section
- Yes, definite difficulties
- Yes, severe difficulties

C27. How long have these difficulties been present?

- Less than a month
- 1-5 months
- 6-12 months
- Over a year

C28. Do these difficulties upset or distress the child?

- Not at all
- Only a little
- Quite a lot
- A great deal

C29. Do the difficulties interfere with the child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
Peer relationships				
Classroom learning				

C30. Do the difficulties put a burden on you or the class as a whole?

- Not at all
- Only a little
- Quite a lot
- A great deal

Section D. Activity and Attention

This section asks about activity and attention. For each question, please tick the box that best describes this child's school behaviour over the last six months or this school year. Please answer all the questions as best you can, even if you are not absolutely certain.

	Never or rarely	Sometimes	Often	Very often
D1. Fails to give close attention to details or makes careless mistakes in schoolwork	☐	☐	☐	☐
D2. Fidgets with hands or feet or squirms in seat	☐	☐	☐	☐
D3. Has difficulty sustaining attention in tasks or play activities	☐	☐	☐	☐
D4. Leaves seat in class or other situations in which remaining seated is expected	☐	☐	☐	☐
D5. Does not seem to listen when spoken to directly	☐	☐	☐	☐
D6. Runs about or climbs excessively in situations in which it is inappropriate	☐	☐	☐	☐
D7. Doesn't follow through on instructions and fails to finish work	☐	☐	☐	☐
D8. Has difficulty playing or engaging in leisure activities quietly	☐	☐	☐	☐
D9. Has difficulty organising tasks and activities	☐	☐	☐	☐
D10. Is "on the go" or acts as if "driven by a motor"	☐	☐	☐	☐
D11. Avoids tasks (e.g., schoolwork, homework) that require sustained effort	☐	☐	☐	☐
D12. Talks excessively	☐	☐	☐	☐
D13. Loses things necessary for tasks or activities	☐	☐	☐	☐
D14. Blurts out answers before questions have been completed	☐	☐	☐	☐
D15. Is easily distracted	☐	☐	☐	☐
D16. Has difficulty awaiting turn	☐	☐	☐	☐
D17. Is forgetful in daily activities	☐	☐	☐	☐
D18. Interrupts or intrudes on others	☐	☐	☐	☐

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Section E. School attendance

E1. Please tell us how many days this child has been absent from school this academic year.

Number of days there have been in the school year so far ☐

Number of days this child has been absent ☐

E2. Please tell us how many days this child was absent from school in the previous academic year.

Number of days in the previous academic year ☐

Number of days this child was absent ☐

E3. Please tell us what school year this child is in.

	Please tick
Year 7	☐
Year 8	☐
Year 9	☐

Additional information

Would you like to tell us anything else about this child? If so, please write your comments in the box below.

Finally, please complete the following details:

Your name: .....

Your relationship to the child:
E.g., head teacher, class teacher
.....

Today's date: .....

Signature: .....

Thank you for completing this questionnaire,

your time is greatly appreciated.

Please seal the questionnaire in the stamped-addressed envelope provided and post to the UKOS office

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

UKOS

United Kingdom Oscillation Study

Follow-up at age 12-13 years

Parent's Questionnaire

Please tell us your name: _____

What is your relationship to the child: _____

The questions in this form ask about your child's usual health and usual ability to do things. Please do not report temporary or occasional problems. For example we are interested in how well your child is usually able to get around, talk and see. We will be asking about other things too, like emotions, and ability to learn and remember, as well as questions about your child's health.

You may think that some of the things we ask don't apply to your child, but we are interested in the overall health of a large group of children. Therefore we need to ask the same questions for each child. If you need any help filling this in do ring us on 020 3299 3037 or email queries to ukos@kcl.ac.uk

There are no right and wrong answers! All we want is your opinion about your child's health. Can you please tick the relevant boxes on the following pages.

Trial Number ☐☐☐☐☐

Part One: Your child's ability

1*. Which one of the following best describes your child's usual ability to see well enough to read ordinary newsprint?

- ☐ Able to see well enough without glasses or contact lenses
- ☐ Able to see well enough with glasses or contact lenses
- ☐ Unable to see well enough with glasses or contact lenses
- ☐ Unable to see at all

If your child has a problem with seeing, do you know the cause?

☐ Yes ☐ No

If yes, can you please tell us what it is? _____

_____

2*. Which one of the following best describes your child's usual ability to see well enough to recognise a friend on the other side of the street?

- ☐ Able to see well enough without glasses or contact lenses
- ☐ Able to see well enough with glasses or contact lenses
- ☐ Unable to see well enough with glasses or contact lenses
- ☐ Unable to see at all

3*. Which one of the following best describes your child's usual ability to hear what is said in a group conversation with at least three other people?

- ☐ Able to hear what is said without a hearing aid
- ☐ Able to hear what is said with a hearing aid
- ☐ Unable to hear what is said even with a hearing aid
- ☐ Unable to hear what is said, but do not wear a hearing aid
- ☐ Unable to hear at all

If your child has a problem with hearing, do you know the cause?

☐ Yes ☐ No

If yes, can you please tell us what it is? _____

_____

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

4*. Which one of the following best describes your child's usual ability to hear what is said in a conversation with one other person in a quiet room?

- ☐ Able to hear what is said without a hearing aid
- ☐ Able to hear what is said with a hearing aid
- ☐ Unable to hear what is said even with a hearing aid
- ☐ Unable to hear what is said, but do not wear a hearing aid
- ☐ Unable to hear at all

5*. Which one of the following best describes your child's usual ability to be understood when speaking his/her own language with people who do not know them?

- ☐ Able to be understood completely
- ☐ Able to be understood partially
- ☐ Unable to be understood
- ☐ Unable to speak at all

6*. Which one of the following best describes your child's usual ability to be understood when speaking with people who know him/her well?

- ☐ Able to be understood completely
- ☐ Able to be understood partially
- ☐ Unable to be understood
- ☐ Unable to speak at all

7*. Which one of the following best describes how your child usually feels?

- ☐ Happy and interested in life
- ☐ Somewhat happy
- ☐ Somewhat unhappy
- ☐ Very unhappy
- ☐ So unhappy that life is not worthwhile

8*. Which one of the following best describes your child's usual level of pain and discomfort?

- ☐ Free of pain and discomfort
- ☐ Mild to moderate pain or discomfort that prevents no activities
- ☐ Moderate pain or discomfort that prevents a few activities
- ☐ Moderate to severe pain or discomfort that prevents some activities
- ☐ Severe pain or discomfort that prevents most activities

* Copyright Health Utilities Inc. (HUInc), 2000

9*. Which one of the following best describes your child's usual ability to walk?

Note: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.

- ☐ Able to walk around the neighbourhood without difficulty, and without equipment
- ☐ Able to walk around the neighbourhood with difficulty, but does not require walking equipment or the help of another person
- ☐ Able to walk around the neighbourhood with walking equipment, but without the help of another person
- ☐ Able to walk only short distances with walking equipment, and requires a wheel chair to get around the neighbourhood
- ☐ Unable to walk alone, even with walking equipment. Able to walk short distance with the help of another person, and requires a wheelchair to get around the neighbourhood
- ☐ Unable to walk at all

If your child has a problem with getting around, do you know the cause?

☐ Yes ☐ No

If yes, can you please tell us what it is?_____

_____

10*. Which one of the following best describes your child's usual ability to use hands and fingers?

Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands or fingers.

- ☐ Full use of two hands and ten fingers
- ☐ Limitations in the use of hands or fingers, but does not require special tools or the help of another person
- ☐ Limitations in the use of hands or fingers, independent with use of special tools (does not require the help of another person)
- ☐ Limitations in the use of hands and fingers, requires the help of another person for some tasks (not independent even with use of special tools)
- ☐ Limitations in the use of hands or fingers, requires the help of another person for most tasks (not independent even with use of special tools)
- ☐ Limitations in the use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools)

11*. Which one of the following best describes your child's usual ability to remember things?

- ☐ Able to remember most things
- ☐ Somewhat forgetful
- ☐ Very forgetful
- ☐ Unable to remember anything at all

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

12*. Which one of the following best describes your child's usual ability to think and solve day to day problems?

- ☐ Able to think clearly and solve day to day problems
- ☐ Has a little difficulty when trying to think and solve day to day problems
- ☐ Has some difficulty when trying to think and solve day to day problems
- ☐ Has great difficulty when trying to think and solve day to day problems
- ☐ Unable to think or solve day to day problems

13*. Which one of the following best describes your child's usual ability to perform basic activities?

- ☐ Eats, bathes, dresses and uses the toilet normally
- ☐ Eats, bathes, dresses and uses the toilet independently with difficulty
- ☐ Requires mechanical equipment to eat, bathe, dress or use the toilet independently
- ☐ Requires the help of another person to eat, bathe, dress or use the toilet

14*. Which one of the following best describes how your child usually feels?

- ☐ Generally happy and free from worry
- ☐ Occasionally fretful, angry, irritable, anxious or depressed
- ☐ Often fretful, angry, irritable, anxious or depressed
- ☐ Almost always fretful, angry, irritable, anxious or depressed
- ☐ Extremely fretful, angry, irritable, anxious or depressed; to the point of needing professional help

15*. Which one of the following best describes your child's usual level of pain or discomfort?

- ☐ Free of pain and discomfort
- ☐ Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities
- ☐ Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities
- ☐ Frequent pain or discomfort; frequent disruption of normal activities. Discomfort requires prescription narcotics for relief
- ☐ Severe pain or discomfort. Pain not relieved by drugs and constantly disrupts normal activities

* Copyright Health Utilities Inc. (HUInc), 2000

Part Two: Your child's general development

16*. For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of your child's recent behaviour over the last month.

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Has many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

17*. Do you have other comments or concerns relating to your child's general development?_____

_____

_____

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

18*. Over the last month, has your child had difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

- ☐ No
- ☐ Yes minor difficulties
- ☐ Yes definite difficulties
- ☐ Yes severe difficulties

If you have answered "yes", please answer the following questions about these difficulties. If "no" then go to question 19.

a*. Do the difficulties upset or distress your child?

- ☐ Not at all
- ☐ Only a little
- ☐ Quite a lot
- ☐ A great deal

b*. Do the difficulties interfere with your child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
Home life	☐	☐	☐	☐
Friendships	☐	☐	☐	☐
Classroom learning	☐	☐	☐	☐
Leisure activities	☐	☐	☐	☐

c*. Do the difficulties put a burden on you or the family as a whole?

- ☐ Not at all
- ☐ Only a little
- ☐ Quite a lot
- ☐ A great deal

*Goodman R 1997. Copyright material reproduced with kind permission of Dr R Goodman

19. Your child's school.
Which of the following best describes the sort of school your child is in and type of support they receive? *(Please tick one box)*

- ☐ My child is in a mainstream school
- ☐ My child is in a mainstream school with some learning support or additional help
- ☐ My child is in a special class or unit
- ☐ My child is in a special school or pupil referral unit (PRU)
- ☐ My child has home or hospital tuition
- ☐ None of these

Please can you describe what best describes the sort of school your child is in:_____

_____

Part Three: Your child's health

This part asks particularly about whether your child has any wheezing/asthma, hospital admissions, seizures and some particular problems your child may have. Don't be alarmed by any of these questions. The likelihood is that your child will not have or develop any of these serious problems.

20. In the last 12 months, has your child had any attacks of wheezing?

☐ Yes ☐ No If no, go to question 22

If yes, can you tell us approximately how frequently?

- ☐ Daily
- ☐ Weekly
- ☐ Monthly
- ☐ Less than monthly

21. In the last 12 months, has your child's sleep been disturbed due to wheezing?

- ☐ Never woken with wheezing
- ☐ Seldom wakes (less than one night per week)
- ☐ Frequently wakes (one or more nights per week)

22. In the last 12 months has your child been given any courses of antibiotics for chest problems?

☐ Yes ☐ Don't know ☐ No

If yes, can you tell us approximately how many? ☐

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

23. In the last 12 months has your child been given any other medicines (not antibiotics) for chest problems?

☐ Yes ☐ Don't know ☐ No If no go to question 24

If yes, can you tell us what they are from the list below?

		In the last 12 months
Prednisolone		☐
Oxygen		☐
Inhalers: "Relievers"	Ventolin (blue)	☐
	Bricanyl (blue)	☐
	Atrovent (green)	☐
	Salmeterol (green)	☐
	Others	☐
	please tell us which: _____	
"Preventers"	Becotide (brown)	☐
	Pulmicort (brown)	☐
	Flixotide (orange)	☐
	Others	☐
	please tell us which: _____	

24. In the last 12 months has your child been admitted to hospital for any reason?

☐ Yes ☐ No If no go to question 25

If yes, can you tell us the reason and number of admissions?

Reason	**Number of admissions**
Chest problems	☐
Surgery	☐
Anything else	☐

Can you tell us briefly what these were for?

_____

_____

_____

25. Has your child ever had any fits, seizures and convulsions?

☐ Yes ☐ No If no go to question 26

Please tick one answer which best describes your child's seizures/convulsions now:

☐ Not on prescribed medicines for seizures
☐ On prescribed treatment with no seizures
☐ On prescribed treatment with less than 1 seizure per month
☐ On prescribed treatment with 1 seizure per month or more

26. Please tick if your child has any of the following conditions?

☐ Diabetes
☐ Cerebral palsy
☐ Hydrocephalus with shunt
☐ Gastronomy
☐ Hydrocephalus with shunt
☐ Any other bowel stoma

27. Any other problem for which he/she is under the care of a doctor?

☐ Yes ☐ No

If yes, can you tell us about this problem and give us the diagnosis if you know it?

_____
_____
_____

Part Four: You and home environment

We need to know a little about you and your circumstances and have taken some of these questions from the 2001 census. You may need to tick more than one box.

Home environment

These questions apply to the family at home; by this we mean mum, dad or partner, and brothers and sisters.

28. Does anyone in the family smoke?

☐ Yes ☐ No

29. Does your house have problems with damp or mould?

☐ Yes ☐ No

30. Has a doctor ever said that any member of your family has asthma?

☐ Yes ☐ No

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Your home

31. Do you rent or own your accommodation?

- ☐ Owner (mortgage)
- ☐ Council rented
- ☐ Private rented (furnished)
- ☐ Private rented (unfurnished)
- ☐ Housing association
- ☐ Tied to occupation
- ☐ Other (please describe below)

Reason: _____

_____

32. What is your ethnic group?

Choose ONE section from A to E, then tick the appropriate box to indicate your cultural background.

A White

- ☐ British
- ☐ Irish
- ☐ Any other White background (please specify) _____

B Mixed

- ☐ White and Black Caribbean
- ☐ White and Black African
- ☐ White and Asian
- ☐ Any other Mixed background (please specify) _____

C Asian or Asian British

- ☐ Indian
- ☐ Pakistani
- ☐ Bangladeshi
- ☐ Any other Asian background (please specify) _____

D Black or Black British

- ☐ Caribbean
- ☐ African
- ☐ Any other Black background (please specify) _____

E Chinese or other ethnic group

- ☐ Chinese
- ☐ Any other (please specify) _____

If there is anything else you would like to tell us about your child's health, please tell us here:

Thank you very much for completing the questionnaire.

Please can you check carefully that you have completed every section.

If you would like a summary of the study findings please tick this box:

☐

Please return it in the prepaid envelope provided to:

NIHR United Kingdom Oscillation Study (UKOS)

King's College London
King's College Hospital
Neonatal Intensive Care Unit 4th Floor
Golden Jubilee Wing
Denmark Hill
London SE5 9RS

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

UKOS

United Kingdom Oscillation Study

Follow-up at age 12-13 years

Questionnaire for girls

Please tell us your name:

The questions in this form ask about your usual health and your usual ability to do things. Please do not report temporary or occasional problems. For example we are interested in how well you are usually able to get around, talk and see. We will be asking about other things too, like emotions, and ability to learn and remember, as well as questions about your health. Finally we will ask some questions about the changes that start to happen to a girl's body as they grow up. If you have any difficulty answering any of the questions, please ask your parents to help.

There are no right and wrong answers! All we want is your opinion about your health. Can you please tick the relevant boxes on the following pages.

Trial Number

Part One: Your ability

1*. Which one of the following best describes your usual ability to see well enough to read ordinary newsprint?

- ☐ Able to see well enough without glasses or contact lenses
- ☐ Able to see well enough with glasses or contact lenses
- ☐ Unable to see well enough with glasses or contact lenses
- ☐ Unable to see at all

If you have a problem with seeing, do you know the cause?

☐ Yes ☐ No

If yes, can you please tell us what it is? _____

_____

2* Which one of the following best describes your usual ability to see well enough to recognise a friend on the other side of the street?

- ☐ Able to see well enough without glasses or contact lenses
- ☐ Able to see well enough with glasses or contact lenses
- ☐ Unable to see well enough with glasses or contact lenses
- ☐ Unable to see at all

3*. Which one of the following best describes your usual ability to hear what is said in a group conversation with at least three other people?

- ☐ Able to hear what is said without a hearing aid
- ☐ Able to hear what is said with a hearing aid
- ☐ Unable to hear what is said even with a hearing aid
- ☐ Unable to hear what is said, but do not wear a hearing aid
- ☐ Unable to hear at all

If you have a problem with hearing, do you know the cause?

☐ Yes ☐ No

If yes, can you please tell us what it is? _____

_____

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

4*. Which one of the following best describes your usual ability to hear what is said in a conversation with one other person in a quiet room?

- ☐ Able to hear what is said without a hearing aid
- ☐ Able to hear what is said with a hearing aid
- ☐ Unable to hear what is said even with a hearing aid
- ☐ Unable to hear what is said, but do not wear a hearing aid
- ☐ Unable to hear at all

5*. Which one of the following best describes your usual ability to be understood when speaking your own language with people who do not know you?

- ☐ Able to be understood completely
- ☐ Able to be understood partially
- ☐ Unable to be understood
- ☐ Unable to speak at all

6*. Which one of the following best describes your usual ability to be understood when speaking with people you know well?

- ☐ Able to be understood completely
- ☐ Able to be understood partially
- ☐ Unable to be understood
- ☐ Unable to speak at all

7*. Which one of the following best describes how you usually feel?

- ☐ Happy and interested in life
- ☐ Somewhat happy
- ☐ Somewhat unhappy
- ☐ Very unhappy
- ☐ So unhappy that life is not worthwhile

8*. Which one of the following best describes your usual level of pain and discomfort?

- ☐ Free from pain and discomfort
- ☐ Mild to moderate pain or discomfort that prevents no activities
- ☐ Moderate pain or discomfort that prevents a few activities
- ☐ Moderate to severe pain or discomfort that prevents some activities
- ☐ Severe pain or discomfort that prevents most activities

*Copyright Health Utilities Inc (HUInc) 2000

9*. Which one of the following best describes your usual ability to walk?
Note: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.

- ☐ Able to walk around the neighbourhood without difficulty, and without walking equipment
- ☐ Able to walk around the neighbourhood with difficulty, but do not require walking equipment or the help of another person
- ☐ Able to walk around the neighbourhood with walking equipment, but without the help of another person
- ☐ Able to walk only short distances with walking equipment, and require a wheel chair to get around the neighbourhood
- ☐ Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and require a wheelchair to get around the neighbourhood
- ☐ Unable to walk at all

If you have a problem with getting around, do you know the cause?

☐ Yes ☐ No

If yes, can you please tell us what it is? _____

_____

10*. Which one of the following best describes your usual ability to use your hands and fingers?
Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands or fingers.

- ☐ Full use of two hands and ten fingers
- ☐ Limitations in the use of hands or fingers, but do not require special tools or the help of another person
- ☐ Limitations in the use of hands or fingers, independent with use of special tools (do not require the help of another person)
- ☐ Limitations in the use of hands and fingers, require the help of another person for some tasks (not independent even with use of special tools)
- ☐ Limitations in the use of hands or fingers, require the help of another person for most tasks (not independent even with use of special tools)
- ☐ Limitations in the use of hands or fingers, require the help of another person for all tasks (not independent even with use of special tools)

11*. Which one of the following best describes your usual ability to remember things?

- ☐ Able to remember most things
- ☐ Somewhat forgetful
- ☐ Very forgetful
- ☐ Unable to remember anything at all

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

12*. Which one of the following best describes your usual ability to think and solve day to day problems?

- ☐ Able to think clearly and solve day to day problems
- ☐ Have a little difficulty when trying to think and solve day to day problems
- ☐ Have some difficulty when trying to think and solve day to day problems
- ☐ Have great difficulty when trying to think and solve day to day problems
- ☐ Unable to think or solve day to day problems

13* Which one of the following best describes your usual ability to Perform basic activities?

- ☐ Eat, bathe, dress and use the toilet normally
- ☐ Eat, bathe, dress and use the toilet independently with difficulty
- ☐ Require mechanical equipment to eat, bathe, dress or use the toilet independently
- ☐ Require the help of another person to eat, bathe, dress or use the toilet

14*. Which one of the following best describes how you usually feel?

- ☐ Generally happy and free from worry
- ☐ Occasionally fretful, angry, irritable, anxious or depressed
- ☐ Often fretful, angry, irritable, anxious or depressed
- ☐ Almost always fretful, angry, irritable, anxious or depressed
- ☐ Extremely fretful, angry, irritable, anxious or depressed; to the point of needing professional help

15*. Which one of the following best describes your usual level of pain or discomfort?

- ☐ Free of pain and discomfort
- ☐ Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities
- ☐ Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities
- ☐ Frequent pain or discomfort; frequent disruption of normal activities. Discomfort requires prescription narcotics for relief
- ☐ Severe pain or discomfort. Pain not relieved by drugs and constantly disrupts normal activities

* Copyright Health Utilities Inc (HUInc) 2000

Part Two: Your general development

16*. For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of how things have been for you over the last six months.

	Not True	Somewhat True	Certainly True
I try to be nice to other people. I care about their feelings	☐	☐	☐
I am restless, I cannot stay still for long	☐	☐	☐
I get a lot of headaches, stomach-aches or sickness	☐	☐	☐
I usually share with others (food, games, pens etc.)	☐	☐	☐
I get very angry and often lose my temper	☐	☐	☐
I am usually on my own. I generally play alone or keep to myself	☐	☐	☐
I usually do as I am told	☐	☐	☐
I worry a lot	☐	☐	☐
I am helpful if someone is hurt, upset or feeling ill	☐	☐	☐
I am constantly fidgeting or squirming	☐	☐	☐
I have one good friend or more	☐	☐	☐
I fight a lot. I can make other people do what I want	☐	☐	☐
I am often unhappy, down-hearted or tearful	☐	☐	☐
Other people my age generally like me	☐	☐	☐
I am easily distracted, I find it difficult to concentrate	☐	☐	☐
I am nervous in new situations. I easily lose confidence	☐	☐	☐
I am kind to younger children	☐	☐	☐
I am often accused of lying or cheating	☐	☐	☐
Other children or young people pick on me or bully me	☐	☐	☐
I often volunteer to help others (parents, teachers, children)	☐	☐	☐
I think before I do things	☐	☐	☐
I take things that are not mine from home, school or elsewhere	☐	☐	☐
I get on better with adults than with people my own age	☐	☐	☐
I have many fears, I am easily scared	☐	☐	☐
I finish the work I'm doing. My attention is good	☐	☐	☐

17*. Do you have any other comments or concerns?

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

18*. Overall, do you think that you have difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

- ☐ No
- ☐ Yes minor difficulties
- ☐ Yes definite difficulties
- ☐ Yes severe difficulties

If you have answered "yes", please answer the following questions about these difficulties. If "no" then go to question 19.

a* How long have these difficulties been present?

- ☐ Less than one month
- ☐ 1-5 months
- ☐ 6-12 months
- ☐ Over a year

b* Do the difficulties upset or distress you?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

c* Do the difficulties interfere with your everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
Home life	☐	☐	☐	☐
Friendships	☐	☐	☐	☐
Classroom learning	☐	☐	☐	☐
Leisure activities	☐	☐	☐	☐

d*. Do the difficulties put a burden on you or the family as a whole?

- ☐ Not at all
- ☐ Only a little
- ☐ Quite a lot
- ☐ A great deal

*Goodman R 1997. Copyright material reproduced with kind permission of Dr R Goodman

Part Three: About your body

There are important changes to a girl's body that can start as early as 6 years of age for some girls but can start much later in others, up to 16 years of age. In this questionnaire we ask you to describe what changes you have noticed up to now. We would like you to complete the questionnaire yourself but you might want to ask your parents for help if you have difficulty answering any of the questions.

All the information you give will be treated in the strictest confidence. This means that we will not show it to anyone outside the study, and no one outside the study will know who this questionnaire belongs to.

19. Firstly, could you tell us how active you are. In the last month, how often have you taken part in strong physical activity (such as running, dance, gymnastics, netball, swimming, aerobics)?

None	Less than once a week	1-3 times a week	4-6 times a week	Daily
☐	☐	☐	☐	☐

20. Have you started your periods yet?

Yes ☐ No ☐ if no please go to question 26

21. If you answered yes, when was your first period?

Month ☐☐ Year ☐☐☐☐ **OR** I was years ☐ old

22. a) In the last year, how many days of bleeding have you usually had during each of your periods?

Days ☐

b) If you don't know is it probably:

3 days or less	4-6 days	7 days or more
☐	☐	☐

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

23. In the last year, what was the usual length of your menstrual cycle? In other words, how many days were there from the first day of one period to the first day of the next period?

Days ☐ **OR** Tick if you don't know ☐

24. Have you ever had any of the following symptoms associated with your period?

a) Heavy bleeding or prolonged bleeding (bleeding for a long time)

Yes and I saw a doctor for this ☐

Yes but I didn't see a doctor for this ☐

No ☐

b) Severe muscle cramps (severe pain in the lower part of your tummy) while you were bleeding during your period?

Yes and I saw a doctor for this ☐

Yes but I didn't see a doctor for this ☐

No ☐

c) Period-type pains or pain in the lower part of your tummy for most days of the month even when you have not been bleeding?

Yes and I saw a doctor for this ☐

Yes but I didn't see a doctor for this ☐

No ☐

25. Sometimes, if girls have problems with their periods (eg heavy bleeding, irregular bleeding or severe cramps), their GP might prescribe the oral contraceptive pill (which can be called 'the pill', 'birth control pills' or 'oestrogen pills') to help. Have you taken oral contraceptives or birth control pills, for any reason during the last year?

Yes ☐ No ☐

26. Have you started to have hair growing in your armpits?

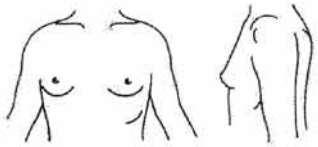
Yes ☐ No ☐

We would now like to know about the changes that are happening to your body. The pictures on the next 2 pages show different stages of development that are often used by doctors to assess girls' growth and development. Please answer questions 27 and 28 by reading the instructions and looking at the pictures carefully.

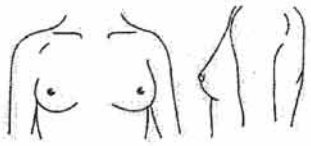
27. The pictures below show stages in the way breasts develop. Not all children follow the same pattern of development. A girl can go through each of the 5 stages shown below, although some girls might skip some stages. Please look at each of the drawings and read the descriptions carefully. Please put a tick in the box that is closest to your breast stage at the moment based on both the picture and the description.

☐ Stage 1. In this stage the nipple is raised a little. The rest of the breast is still flat.

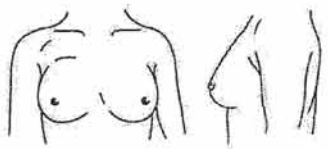
☐ Stage 2. This is called the breast bud stage. In this stage the nipple is raised more than Stage 1. The breast is a small round. The dark area around the nipple (called the areola) is larger than in Stage 1.



☐ Stage 3. The areola and the breast are both larger than in Stage 2. The areola does not stick out away from the breast.



☐ Stage 4. The areola and the nipple make up a mound that sticks up above the shape of the breast. (This stage might not happen at all for some girls. Some girls develop from Stage 3 to Stage 5 without Stage 4).

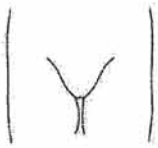


☐ Stage 5. This is the adult stage. The breasts are fully developed. Only the nipple sticks out in this stage. The areola has moved back in the general shape of the breast.

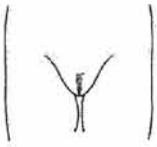
☐ Please tick this box if you are not sure

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

28. The pictures below show different amounts of pubic hair. Not all children follow the same pattern of development. Please look at each of the pictures and read the descriptions carefully. Please put a tick in the box that is closest to the amount of pubic hair you have at the moment based on both the picture and the description. (Your stage of pubic hair growth might not be the same as your stage of physical development.)



☐ Stage 1. There is no pubic hair at all.



☐ Stage 2. There is a little long, slightly coloured hair. This hair may be straight or a little curly.

☐ Stage 3. The hair is darker at this stage. It is coarser and more curly. It has spread out and thinly covers a bigger area.

☐ Stage 4. The hair is now dark, curly and coarse as that of an adult woman. But the area that the hair covers is not as large as that of an adult. The hair has not spread out to the legs yet.

☐ Stage 5. The hair is now like that of an adult woman. It also covers the same area as that of an adult woman. The hair usually forms a triangular pattern as it spreads out to the legs.

☐ Please tick this box if you are not sure

If there is anything else you would like to tell us about your health, please tell us here:

Thank you very much for completing the questionnaire.

Please can you check carefully that you have completed every section.

Please return it in the prepaid envelope provided to:

NIHR United Kingdom Oscillation Study (UKOS)

King's College London
King's College Hospital
Neonatal Intensive Care Unit 4th Floor
Golden Jubilee Wing
Denmark Hill
London SE5 9RS

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

UKOS

United Kingdom Oscillation Study

Follow-up at age 12-13 years

Questionnaire for boys

Please tell us your name: ☐

The questions in this form ask about your usual health and your usual ability to do things. Please do not report temporary or occasional problems. For example we are interested in how well you are usually able to get around, talk and see. We will be asking about other things too, like emotions, and ability to learn and remember as well as questions about your health. Finally we will ask some questions about the changes that start to happen to a boy's body as they grow up. If you have any difficulty answering any of the questions, please ask your parents to help.

There are no right and wrong answers! All we want is your opinion about your health. Can you please tick the relevant boxes on the following pages.

Trial Number ☐☐☐☐☐

Part One: Your ability

1*. Which one of the following best describes your usual ability to see well enough to read ordinary newsprint?

- ☐ Able to see well enough without glasses or contact lenses
- ☐ Able to see well enough with glasses or contact lenses
- ☐ Unable to see well enough with glasses or contact lenses
- ☐ Unable to see at all

If you have a problem with seeing, do you know the cause?

☐ Yes ☐ No

If yes, can you please tell us what it is? _____

_____

2*. Which one of the following best describes your usual ability to see well enough to recognise a friend on the other side of the street?

- ☐ Able to see well enough without glasses or contact lenses
- ☐ Able to see well enough with glasses or contact lenses
- ☐ Unable to see well enough with glasses or contact lenses
- ☐ Unable to see at all

3*. Which one of the following best describes your usual ability to hear what is said in a group conversation with at least three other people?

- ☐ Able to hear what is said without a hearing aid
- ☐ Able to hear what is said with a hearing aid
- ☐ Unable to hear what is said even with a hearing aid
- ☐ Unable to hear what is said, but do not wear a hearing aid
- ☐ Unable to hear at all

If you have a problem with hearing, do you know the cause?

☐ Yes ☐ No

If yes, can you please tell us what it is? _____

_____

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

4*. Which one of the following best describes your usual ability to hear what is said in a conversation with one other person in a quiet room?

- ☐ Able to hear what is said without a hearing aid
- ☐ Able to hear what is said with a hearing aid
- ☐ Unable to hear what is said even with a heating aid
- ☐ Unable to hear what is said, but do not wear a hearing aid
- ☐ Unable to hear at all

5*. Which one of the following best describes your usual ability to be understood when speaking your own language with people who do not know you?

- ☐ Able to be understood completely
- ☐ Able to be understood partially
- ☐ Unable to be understood
- ☐ Unable to speak at all

6*. Which one of the following best describes your usual ability to be understood when speaking with people you know well?

- ☐ Able to be understood completely
- ☐ Able to be understood partially
- ☐ Unable to be understood
- ☐ Unable to speak at all

7*. Which one of the following best describes how you usually feel?

- ☐ Happy and interested in life
- ☐ Somewhat happy
- ☐ Somewhat unhappy
- ☐ Very unhappy
- ☐ So unhappy that life is not worthwhile

8*. Which one of the following best describes your usual level of pain and discomfort?

- ☐ Free from pain and discomfort
- ☐ Mild to moderate pain or discomfort that prevents no activities
- ☐ Moderate pain or discomfort that prevents a few activities
- ☐ Moderate to severe pain or discomfort that prevents some activities
- ☐ Severe pain or discomfort that prevents most activities

* Copyright Health Utilities Inc. (HUInc) 2000

9*. Which one of the following best describes your usual ability to walk?
Note: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker

- ☐ Able to walk around the neighbourhood without difficulty, and without walking equipment
- ☐ Able to walk around the neighbourhood with difficulty, but do not require walking equipment or the help of another person
- ☐ Able to walk around the neighbourhood with walking equipment, but without the help of another person
- ☐ Able to walk only short distances with walking equipment, and require a wheel chair to get around the neighbourhood
- ☐ Unable to walk alone, even wth walking equipment. Able to walk short distances with the help of another person, and require a wheelchair to get around the neighbourhood
- ☐ Unable to walk at all

If you have a problem with getting around, do you know the cause?

☐ Yes ☐ No

If yes, can you please tell us what it is? _____

_____

10*. Which one of the following best describes your usual ability to use your hands and fingers?
Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands or fingers.

- ☐ Full use of two hands and ten fingers
- ☐ Limitations in the use of hands or fingers, but do not require special tools or the help of another person
- ☐ Limitations in the use of hands or fingers, independent with use of special tools (do not require the help of another person)
- ☐ Limitations in the use of hands and fingers, require the help of another person for some tasks (not independent even with use of special tools)
- ☐ Limitations in the use of hands or fingers, require the help of another person for most tasks (not independent even with use of special tools)
- ☐ Limitations in the use of hands or fingers, require the help of another person for all tasks (not independent even with use of special tools)

11*. Which one of the following best describes your usual ability to remember things?

- ☐ Able to remember most things
- ☐ Somewhat forgetful
- ☐ Very forgetful
- ☐ Unable to remember anything at all

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

12*. Which one of the following best describes your usual ability to think and solve day to day problems?

- ☐ Able to think clearly and solve day to day problems
- ☐ Have a little difficulty when trying to think and solve day to day problems
- ☐ Have some difficulty when trying to think and solve day to day problems
- ☐ Have great difficulty when trying to think and solve day to day problems
- ☐ Unable to think or solve day to day problems

13* Which one of the following best describes your usual ability to Perform basic activities?

- ☐ Eat, bathe, dress and use the toilet normally
- ☐ Eat, bathe, dress and use the toilet independently with difficulty
- ☐ Require mechanical equipment to eat, bathe, dress or use the toilet independently
- ☐ Require the help of another person to eat, bathe, dress or use the toilet

14*. Which one of the following best describes how you usually feel?

- ☐ Generally happy and free from worry
- ☐ Occasionally fretful, angry, irritable, anxious or depressed
- ☐ Often fretful, angry, irritable, anxious or depressed
- ☐ Almost always fretful, angry, irritable, anxious or depressed
- ☐ Extremely fretful, angry, irritable, anxious or depressed; to the point of needing professional help

15*. Which one of the following best describes your usual level of pain or discomfort?

- ☐ Free of pain and discomfort
- ☐ Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities
- ☐ Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities
- ☐ Frequent pain or discomfort; frequent disruption of norma activities. Discomfort requires prescription narcotics for relief
- ☐ Severe pain or discomfort. Pain not relieved by drugs and constantly disrupts normal activities

*Copyright Health Utilities Inc (HUInc) 2000

Part Two: Your general development

16*. For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of how things have been for you over the last six months.

	Not True	Somewhat True	Certainly True
I try to be nice to other people. I care about their feelings	☐	☐	☐
I am restless, I cannot stay still for long	☐	☐	☐
I get a lot of headaches, stomach-aches or sickness	☐	☐	☐
I usually share with others (food, games, pens etc.)	☐	☐	☐
I get very angry and often lose my temper	☐	☐	☐
I am usually on my own. I generally play alone or keep to myself	☐	☐	☐
I usually do as I am told	☐	☐	☐
I worry a lot	☐	☐	☐
I am helpful if someone is hurt, upset or feeling ill	☐	☐	☐
I am constantly fidgeting or squirming	☐	☐	☐
I have one good friend or more	☐	☐	☐
I fight a lot. I can make other people do what I want	☐	☐	☐
I am often unhappy, down-hearted or tearful	☐	☐	☐
Other people my age generally like me	☐	☐	☐
I am easily distracted, I find it difficult to concentrate	☐	☐	☐
I am nervous in new situations. I easily lose confidence	☐	☐	☐
I am kind to younger children	☐	☐	☐
I am often accused of lying or cheating	☐	☐	☐
Other children or young people pick on me or bully me	☐	☐	☐
I often volunteer to help others (parents, teachers, children)	☐	☐	☐
I think before I do things	☐	☐	☐
I take things that are not mine from home, school or elsewhere	☐	☐	☐
I get on better with adults than with people my own age	☐	☐	☐
I have many fears, I am easily scared	☐	☐	☐
I finish the work I'm doing. My attention is good	☐	☐	☐

17*. Do you have any other comments or concerns?

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

18*. Overall, do you think that you have difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

- ☐ No
- ☐ Yes minor difficulties
- ☐ Yes definite difficulties
- ☐ Yes severe difficulties

If you have answered "yes", please answer the following questions about these difficulties. If "no" then go to question 19.

a* How long have these difficulties been present?

- ☐ Less than one month
- ☐ 1-5 months
- ☐ 6-12 months
- ☐ Over a year

b* Do the difficulties upset or distress you?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

c* Do the difficulties interfere with your everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
Home life	☐	☐	☐	☐
Friendships	☐	☐	☐	☐
Classroom learning	☐	☐	☐	☐
Leisure activities	☐	☐	☐	☐

d*. Do the difficulties put a burden on you or the family as a whole?

- ☐ Not at all
- ☐ Only a little
- ☐ Quite a lot
- ☐ A great deal

*Goodman R 1997. Copyright material reproduced with kind permission of Dr R Goodman

Part Three: About your body

There are important changes to a boy's body that can start as early as 6 years of age for some boys but can start much later in others, up to 16 years of age. In this questionnaire we ask you to describe what changes you have noticed up to now. We would like you to complete the questionnaire yourself but you might want to ask your parents for help if you have difficulty answering any of the questions.

All the information you give will be treated in the strictest confidence. This means that we will not show it to anyone outside the study, and no one outside the study will know who this questionnaire belongs to.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

19. Firstly, could you tell us how active you are. In the last month, how often have you taken part in strong physical activity (such as running, football, swimming, athletics)?

- None ☐
- Less than once a week ☐
- 1-3 times a week ☐
- 4-6 times a week ☐
- Daily ☐

20. Has your voice changed at all?

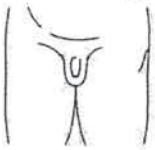
- No, it is the same ☐
- Yes, sometimes it is a lot lower ☐
- Yes, it has changed now totally ☐
- Not sure ☐

21. Have you started to have hair growing in your armpits?

- Yes ☐
- No ☐

We would now like to know about the changes that are happening to your body. The pictures on the next 2 pages show different stages of development that are often used by doctors to assess boy's growth and development. Please answer questions 22 and 23 by reading the instructions and looking at the pictures carefully.

22. Boys go through the different stages of physical development at different ages. We need your help in letting us know the stage of physical development you are going through at the moment. Look at each of the pictures below and read the descriptions carefully. Please put a tick in the box that is closest to your stage of development at the moment based on both the picture and the description.



☐ Stage 1. At this stage the size and shape of the testes, scrotum (the sac holding the testes) and penis are about the same as when you were younger.

☐ Stage 2. At this stage the penis is a little bit bigger. The scrotum has dropped and the skin of the scrotum has changed. The testes are also bigger.

☐ Stage 3. At this stage the penis has grown longer, and the testes have grown and dropped lower.

☐ Stage 4. At this stage the penis is longer and wider. The head of the penis is bigger, and the scrotum is a darker colour and bigger. The testes are also bigger.

☐ Stage 5. At this stage the penis, scrotum and testes are the size and shape of a man's.

☐ Please tick this box if you are not sure

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

23. As part of development pubic hair will start to grow just above your penis. The pictures below show different amounts of pubic hair. Please look at each of the pictures and read the descriptions carefully. Please put a tick in the box that is closest to the amount of pubic hair you have at the moment based on both the picture and the description. (Your stage of pubic hair growth might not be the same as your stage of physical development.)

☐ Stage 1. There is no hair at all.

☐ Stage 2. At this stage there is a little soft, long, lightly coloured hair at the base of the penis. It may be straight or a little curly.

☐ Stage 3. At this stage the hair is darker and more curled. It has spread out and thinly covers a bigger area.

☐ Stage 4. At this stage the hair is dark and curly as that of a man, but it hasn't spread out to the legs.

☐ Stage 5. At this stage the hair is like that of a man. It has spread out to the legs.

☐ Please tick this box if you are not sure

If there is anything else you would like to tell us about your health, please tell us here:

Thank you very much for completing the questionnaire.

Please can you check carefully that you have completed every section.

Please return it in the prepaid envelope provided to:

NIHR United Kingdom Oscillation Study (UKOS)

King's College London
King's College Hospital
Neonatal Intensive Care Unit 4th Floor
Golden Jubilee Wing
Denmark Hill
London SE5 9RS

© Queen's Printer and Controller of HMSO 2014. This work was produced by Greenough *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

This report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health

Published by the NIHR Journals Library