Barts and The London School of Medicine and Dentistry

CHILL
Children's Health in London & Luton

Protocol

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Short Title/Acronym:	Children's Health in London and Luton (CHILL)
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Version number	**Author**	**Effective date**	**Reason for change**
V1.1	**CG**	**13.07.18**	**Additions to analysis section in response to ISC comments**

1. Contents

2. Glossary of terms and abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
JRMO	Joint Research Management Office
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee
A&E	Accident and Emergency
AURN	Automatic Urban and Rural Network
ANOVA	ANalysis Of VAriance
AQ	Air Quality
ATS	American Thoracic Society
BMI	Body Mass Index
CAPTOR	Cost-effectiveness of Air PolluTiOn Reduction
CCG	Clinical Commissioning Group
CCZ	Congestion Charging Zone

CHS	Southern California Children's Health Study
CHU9D	Child Health Utility 9D
CRF	Case Report Form
CTISM	Clinical Trials Information System Manager
DEFRA	Department for Environment Food and Rural Affairs
DM	Data Manager
DMEC	Data Management and Ethics Committee
DM/P	Database Programmer
EU	European Union
eCRF	Electronic Case Report Form
ERS	European Respiratory Society
FEV1	Forced Expiratory Volume in one second
FVC	Full Vital Capacity
GLA	Greater London Authority
GP	General Practitioner
HDV	Heavy Duty Vehicle
ISAAC	International Study of Asthma and Allergies in Childhood
ISC	Independent Steering Committee
JRMO	Joint Research Management Office
KCL	King's College London
LAQN	London Qir Quality Network
LDV	Light Duty Vehicle
LEZ	Low Emission Zone
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OBE	Order of the British Empire
PEF	Peak Expiratory Flow
PI	Principal Investigator
PICO	Population Intervention Comparison Outcome
PPI	Patient and Public Involvement
QMUL	Queen Mary University of London
QOL	Quality of Life
REC	Research Ethics Committee
SE	South East
SMG	Study Management Group
TFL	Transport for London
ULEZ	Ultra Low Emission Zone

3. Signatures

Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 0.8, dated 05.01.18)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Chris GRIFFITHS

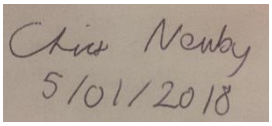
Chief Investigator Site: QMUL

Signature and Date: C Griffiths 05.01.18

Statistician Agreement Page (as applicable)

The clinical study as detailed within this research protocol (Version 0.8, dated 05.01.18), or any subsequent amendments, will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements.

Statistician Name: Chris NEWBY

Signature and Date: 

Principal Investigator Agreement *(if different from Chief investigator)*

The clinical study as detailed within this research protocol **(Version 0.8, dated 05.01.18)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal Investigator Name: Chris GRIFFITHS

Principal Investigator Site: QMUL

Signature and Date: N/A

4. Summary

Short Title	Children's Health in London and Luton (CHILL)
Methodology	Prospective two-arm parallel cohort study
Research Sites	Primary schools in London and Luton
Objectives/Aims	To answer the primary research question: • What is the impact of a large-scale public health intervention – the London Ultra Low Emission Zone (ULEZ) – on lung growth of primary school children. Secondary aims are to: • Determine impact on secondary outcomes, including air quality, respiratory and allergy symptoms, respiratory infections, physical activity, quality of life (QOL) and health care use. • Determine impact on health inequalities. • Assess value for money by undertaking cost-consequence and cost-utility analyses.
Number of Participants/Patients	3,120 (1,560 in each cohort)
Main Inclusion Criteria	Inclusion criteria: Children attending primary schools in the central ULEZ area of London, or Luton. Attending in school years 2, 3, 4. Exclusion criteria: Major respiratory illness.
Statistical Methodology and Analysis (if applicable)	Interaction analysis controlling for effect modifiers; Health economic cost-consequence analysis.
Proposed Start Date	1.1.18
Proposed End Date	31.12.23
Study Duration	6 years

5. Introduction: the problem to be addressed

5.1 Adverse effects of air pollution on children's lung growth

Primary studies and systematic reviews have linked air pollution with adverse respiratory effects across the life-course, for example increasing risk of pre-term birth,(1) pre-school wheeze,(2) incident childhood asthma,(3) and in adulthood, chronic obstructive pulmonary disease.(4)

Childhood and adolescence are periods of rapid growth when organ systems are susceptible to damage from traffic-derived air pollution. The ESCAPE meta-analysis of five European birth cohorts showed poor air quality was associated with reduced lung function in pre-adolescent children.(5) In the southern California Children's Health Study (CHS) adolescents showed clinically important restrictions of lung growth and function.(6-9) Even in a low pollution environment (Boston, USA) children's lung growth was related to lifetime pollutant exposure.(10) Deficits in lung growth in young adulthood evolve into cardiopulmonary diseases (11) and increased mortality.(12)

Data from the CHS suggests lung growth deficits are partially recoverable in adolescents subsequently exposed to improved air quality.(13) This evidence of improved lung development demonstrates that policies designed to reduce air pollution may provide a health dividend, but the extent this can be translated to a European context, where diesel vehicles are a dominant source is unknown.

5.2 Uncertain effectiveness of Low Emission Zones

Evaluations of LEZs on air quality to date are few and evidence for impact on health is poor.(14-21) In a systematic review which included studies to October 2015, Wang evaluated data of the impact of air quality strategies across Europe on health and health inequalities.(22) Of 15 studies identified, six addressed traffic LEZ-type emission control interventions (the remainder covered energy-related strategies and general regulations).(14, 16, 23, 24) (25) Of the six LEZ-type studies, only one(25) gathered health data directly from individuals, finding negligible effects on respiratory symptoms. The remainder relied on modeling effects of predicted (not necessarily achieved) emission reductions on health. In only two studies was health equity assessed, with opposing conclusions.(14, 24) Holman, in a narrative review, found limited evidence for impact of LEZs on air quality in five EU countries (Denmark, the Netherlands, Germany, Italy and the UK).(20) Health impact was not addressed. Holman noted that study conclusions were often limited by the challenges of quantifying the impact of such schemes on air quality, due to the influence of meteorological effects and concurrent air quality/traffic policies.

5.3 Limited effectiveness of London's original Low Emission Zone

We used a sequential cross-sectional study design to evaluate the impact of London's original LEZ (implemented 2008-2012) on the health of 2,297 east London primary school children aged 8-9 years.(21, 26) The London LEZ had limited impact on air quality(27) and we found no convincing health benefit. Furthermore, over the study period we found significant deficits in children's lung capacity of between 5-10%, attributable to exposures to traffic-related pollutants.

5.4 Summary and implications of research to date

- Traffic-related pollution is associated with clinically important damage to children's lung growth and development, with potential adverse impacts on health in adulthood.
- Whether this lung damage is reversible is unknown, but findings from the CHS demonstrate that improvements in air quality are associated with a reduction in risk of clinically significant deficits in lung function in children.
- The effects of public health interventions to improve air quality are unclear. LEZs are widespread, but evaluations are few and methodologically weak.
- There is an urgent need to determine the impact of emission reduction strategies, and LEZs in particular, on children's lung growth and health.

6. Study objectives

To answer the primary research question:

- What is the impact of the London Ultra Low Emission Zone (ULEZ) on lung growth of primary schoolchildren?

Secondary objectives are to:

- Determine impact on secondary outcomes, including air quality, respiratory and allergy symptoms, respiratory infections, physical activity, quality of life (QOL), health care use and health costs.
- Determine impact on health inequalities.
- Assess value for money by undertaking a cost-consequence analysis.

7. Methodology

7.1 Study design

A prospective two-arm parallel cohort study

7.2 PICO summary

Population: Children aged 6-9 yrs old, recruited in 26 London primary schools (years 2, 3, 4) within the Central London ULEZ area.

Intervention: Ultra Low Emission Zone.

Comparison: Children aged 6-9 yrs old, recruited in 26 Luton primary schools (years 2, 3 4).

Outcome: PRIMARY: Lung growth (post-bronchodilator forced expiratory volume in one second, FEV_1) SECONDARY: Air quality, forced vital capacity (FVC), respiratory symptoms, respiratory infections, physical activity, QOL, health care use, costs.

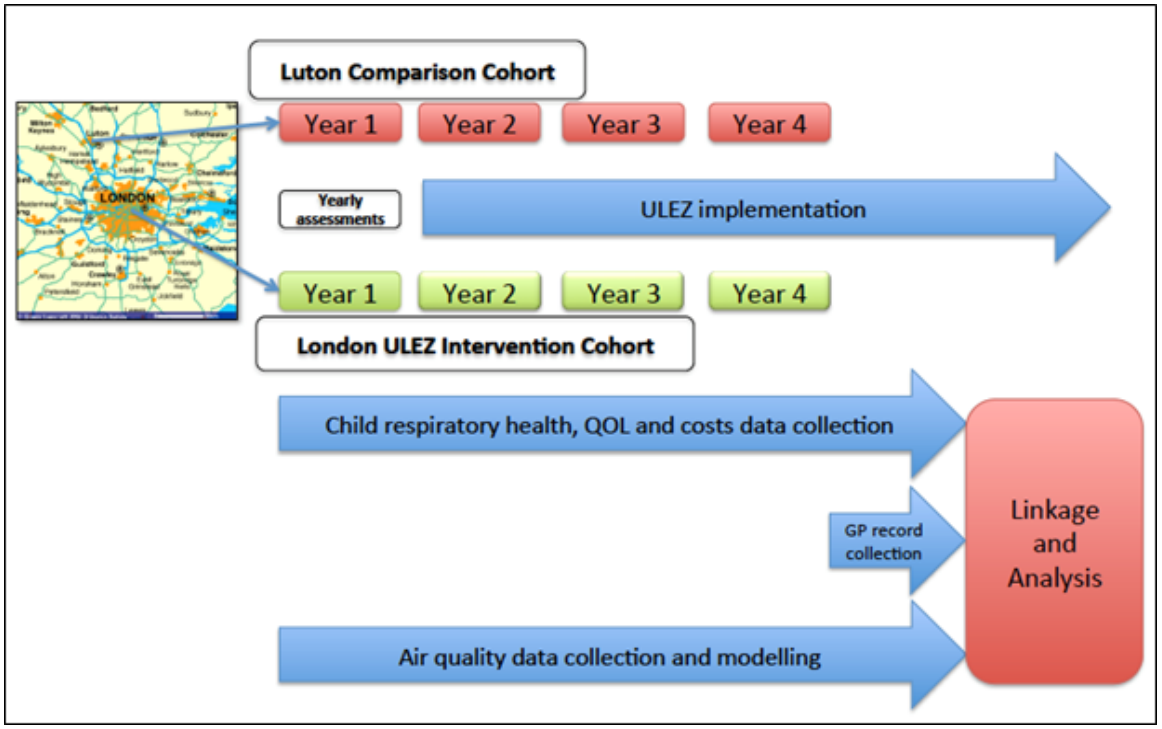
7.3 Methodology summary

We will establish two parallel cohorts of primary schoolchildren beginning in 2018 (Figure 1) - a Central London cohort where the ULEZ will be implemented from April 2019, and a comparison cohort in Luton, an area with broadly similar air quality, demography and social deprivation, but with less intense air quality improvement initiatives, and free from risk of contamination by effects of the ULEZ.

Starting in 2018, through to 2021, we will make annual school visits to gather physiological data from children. We will gather respiratory health status, child QOL, school and work absence and cost data from parents. The current KCLurban high resolution (20x20m) dispersion model for London will be extended outward to encompass Luton, to allow equivalent air pollution attributions for the 12 months prior to each assessment in both study areas. We will gather health care use and respiratory infection data from GP records and HES data.

Our primary analysis will explore relationships between exposures to a range of key pollutants including NOx, NO_2, $PM_{2.5}$, PM_{10}, with the primary outcome, lung function (FEV_1). Following completion of data collection and quality assurance measures, and linkage of air quality and participant data (see GANNT chart for detailed timings) we will complete statistical and health economic analyses describing relationships between air quality changes and lung growth, respiratory health, quality of life and healthcare use and health inequalities, and implement our dissemination programme to maximise influence on health policy.

Figure 1: Study Scheme Diagram



7.4 Inclusion and exclusion criteria

Inclusion criteria for schools:

- Primary schools within, or with catchment areas that include, the Central London ULEZ.
- Primary schools within the Borough of Luton.
- State or independent sectors.

Exclusion criteria for schools:

- Schools that are not primary schools within the above boundaries.

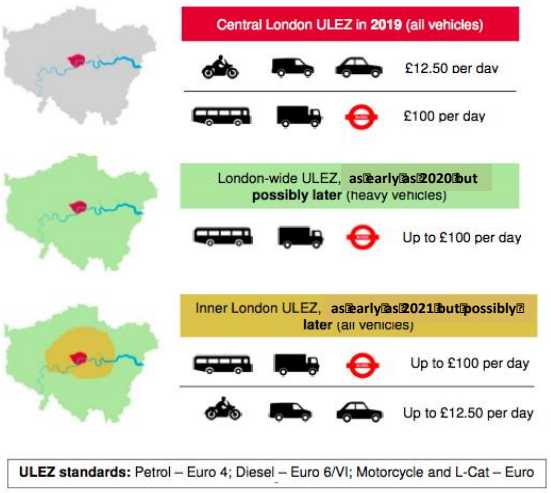
Inclusion criteria for children:

- Children attending a study school, in years 2, 3, or 4, at study inception.

Exclusion criteria for children:

- Children with learning or physical disabilities sufficient for them to be unable to give informed assent to the study, or to carry out study procedures.
- Children with major lung disease (not including asthma).

Figure 2: London Ultra Low Emission Zone: configuration and timing



7.5 Study interventions

London Ultra Low Emission Zone: configuration and timing

The ULEZ will initially comprise a Central London ULEZ covering the existing Congestion Charging Zone. TfL will implement the Central London ULEZ on 8th April 2019. Using number plate recognition technology, a daily penalty charge notice will be issued for vehicles entering this central zone not meeting the standard of Euro 4 for petrol, Euro 6/VI for diesel, and Euro for motorcycles.

Subject to consultation, the ULEZ will subsequently be extended to include:

1) In 2020, a London-wide ULEZ *for heavy duty vehicles (HDV)* within the LEZ boundary (green zone). HDVs not meeting Euro 6 standard will be charged daily.
2) In 2021, an Inner London ULEZ area *for all light duty vehicles* (LDV) within the boundary of the North and South Circular Roads (yellow zone). Vehicles not meeting the above criteria will be charged daily as for the Central London area.

Luton: comparison site

Luton's air quality is influenced by several factors: the presence of major industry (including a motor industry), the transecting M1 motorway and A505, and a rapidly expanding international airport, all bringing significant traffic flows into/through the town. Luton has no plans for a Clean Air Zone. It has three designated Air Quality Management Areas. Mean annual NO_2 values have remained largely unchanged over the last five years. Planned interventions for AQ improvement include a busway, car sharing, public information and advice systems, and provision of charging points for electric vehicles.

7.6 Outcome measures

Primary outcome

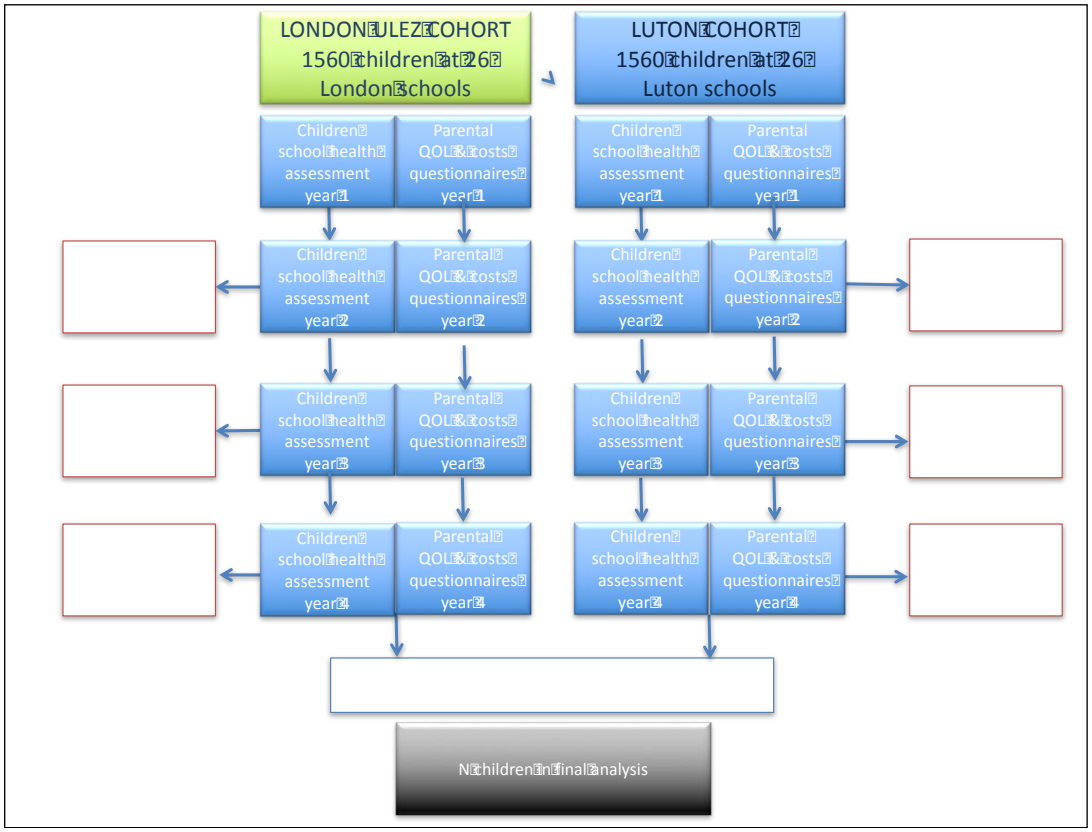
- Lung function growth as post-bronchodilator FEV_1 increase per year, measured by spirometry at sequential annual school visits over four years.

Secondary outcomes

- Air quality (monitoring stations / modelling)
- FVC increase per year (spirometry)

- Parent-reported respiratory and allergy symptoms (ISAAC questionnaire)
- Parent-reported paediatric QOL (CHU 9D questionnaire)
- Child physical activity (accelerometers)
- Respiratory infections (GP records)
- Health care use (GP records)
- NHS costs (GP records)
- Non-NHS costs (parental questionnaire)

Figure 3: School visits and data collection from parents



School sampling

We will invite all schools meeting the inclusion criteria. In London, we will initially invite schools within the central ULEZ, and subsequently, if needed, invite those situated outside the ULEZ, but with catchment areas that include the ULEZ.

School recruitment and retention

We will:

- publicise the study through local media and contact with local leaders.
- email invitation letters to schools, outlining the project, its time course and rationale, requirements and time commitment. To rapidly engage busy heads and teachers this invitation will contain a URL to a 90 second YouTube video summarising the study.
- meet teachers and parent groups as required.
- offer £1,000 to each school to aid retention.

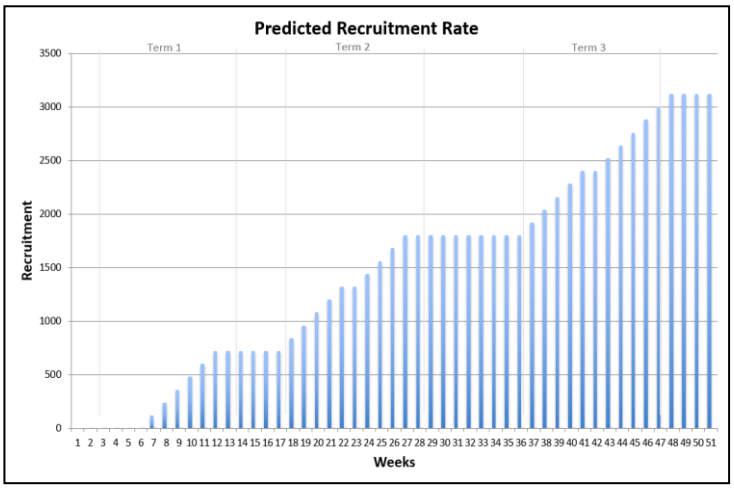
Child recruitment and consenting

Consent forms will be completed by parents and children at home, and will require opt-in to study components, including elements of the health assessments and access to GP health records and HES data. Forms will be completed via web-based questionnaire/s or returned to teachers in their

child's school bag. The study PI's phone number will be included should parents wish to discuss participation. The process is given in Figure 4.

Figure 4: Child recruitment process

Figure 5: Planned child recruitment rate across both cohorts in the first study year



Anticipated drop-out

Sample size is inflated to accommodate a maximum yearly attrition of 20%, reflecting children moving schools and deciding to withdraw. Measures to establish and maintain cohort identity and retention include certificates for children completing annual assessments, regular email and 6-12-monthly brief video updates of study progress to parents and children.

For children who move school during the study we will attempt to record to which school they have moved and to continue parental data, health record and HES data collection.

8. Study Procedures

8.1 Schedule of assessments

Type	Outcome	Method	Year 1	Year 2	Year 3	Year 4	Recording	Analysis
Primary	FEV_1	Annual health assessment: spirometry	school visit	school visit	school visit	school visit	Spirometer download	Interaction analysis
Secondary	Air quality: NO, NO_2, PM_{10}, $PM_{2.5}$	k-means clustering developed by Font et al.(27)	LAQN and AURN	LAQN and AURN	LAQN and AURN	LAQN and AURN	LAQN and AURN (Automatic Urban & Rural Network)	Interaction analysis
Secondary	FVC and other spirometric variables	Annual health assessment: spirometry	school visit	school visit	school visit	school visit	Spirometer download	Interaction analysis
Secondary	Physical activity and GPS tracking*	Annual health assessment: accelerometer and GPS tracker	school visit	school visit	school visit	school visit	Accelerometer and GPS download	Interaction analysis
Demography / potential confounding variables		Parent-completed questionnaire: (paper or web)	school bag prior to school visit	school bag prior to school visit	school bag prior to school visit	school bag prior to school visit	Clinical Record Form	Interaction analysis
Secondary	School absence; work absence	Parent-completed questionnaire: (paper or web)	school bag prior to school visit	school bag prior to school visit	school bag prior to school visit	school bag prior to school visit	Clinical Record Form	Interaction analysis
Secondary	Respiratory and allergy symptoms (ISAAC)	Parent-completed questionnaire: (paper or web)	school bag prior to school visit	school bag prior to school visit	school bag prior to school visit	school bag prior to school visit	Clinical Record Form	Interaction analysis
Secondary	QOL (CHU9D)	Parent-completed questionnaire: (paper or web)	school bag prior to school visit	school bag prior to school visit	school bag prior to school visit	school bag prior to school visit	Clinical Record From	Interaction analysis
Secondary	Non-NHS costs	Parent-completed questionnaire: (paper or web)	school bag prior to school visit	school bag prior to school visit	school bag prior to school visit	school bag prior to school visit	Clinical Record From	
Secondary	Respiratory infection Health care use NHS costs	Data extraction from GP health records	Gathered after year 4 school visits complete	Gathered after year 4 school visits complete	Gathered after year 4 school visits complete	Gathered after year 4 school visits complete	Clinical Record Form	Interaction analysis
Secondary	Health care use NHS costs	Data extraction from GP health records, HES data linkage	Gathered after year 4 school visits complete	Gathered after year 4 school visits complete	Gathered after year 4 school visits complete	Gathered after year 4 school visits complete	Clinical Record Form/HES data	Interaction analysis

* Subject to separate funding

Annual health assessments

Annual health assessments will take place at each school as far as possible during the same month of each year. During the first year each class will receive an outreach education session, delivered by QMUL's Centre of the Cell outreach team.

Children will be assessed in groups of four or five in an adjacent room identified by the class-teacher, or if none is available, at the back of the classroom, using standard protocols. The assessment will take about 35 minutes and will consist of the following elements:

1. Height (standing and sitting) and weight 5 minutes
2. Spirometry: pre-and post-bronchodilator 20 minutes
3. Physical activity: fitting accelerometer, questionnaire 5 minutes

Height (sitting and standing) and weight will be measured with SECA measures.

Spirometry
Lung function will be measured before and 15 minutes after bronchodilation, according to UK and European guidelines. Children will inhale four puffs (100mcg/puff) of salbutamol *via* a large volume Volumatic spacer. A new or sterilised spacer will be used for each child.

Physical activity
Each child will be fitted with an Actigraph accelerometer with instruction on how to use them (an instruction sheet and monitor wear diary will be sent home with the child). Children will be requested to wear the monitor during waking hours for 7 days, only removing it for water-based activities. After 1 week, we will revisit the school to collect monitors. Children will answer a question on their route to school and means of transport on the day of assessment. Children in some schools will have the option of wearing a GPS monitor for a week to track the routes they take to and from school.

Study questionnaires completed by parents at home
Parents will be asked to complete questionnaires in year 1 (when consenting to the study) and in study years 2, 3 and 4. We expect to provide on-line versions as an alternative to paper versions. These comprise:

- Demography and residential history
- ISAAC: prevalence of respiratory and allergy symptoms, such as cough and wheeze.
- CHU 9D: quality of life proxy questionnaire
- Non-NHS costs
- Child absence from school
- Parental absence from work due to child ill-health

NHS health records
With participants' consent we will approach the Caldicott Guardians of participants' general practices to request complete copies of health records. The format of records will depend on the method we will use for extraction. We expect by the fourth year of the study that electronic data extraction methods will be available.

8.2 End of study definition

The end of this study is defined as the date on which the last data is collected.

9. Statistical considerations

9.1 Sample size

We use 90% power and 0.05 significance level to test a clinically important 15 ml difference in FEV_1 growth per year between Central ULEZ and Luton comparison cohorts. For 24 schools/arm with 60 children from any of years 2, 3, or 4, the study is powered for 15ml per year difference in FEV_1 growth between the comparison zone and ULEZ. We further inflate the number of schools

by two per cohort to account for possible school drop-out. The total sample size is therefore N=3120 children, comprising 1560 in the ULEZ cohort and 1560 in the Luton cohort.

Assumptions:

- Adjustment for clustering of lung function outcomes within schools, by inflating sample size using an intra-class correlation for FEV_1 in schools calculated from our original ULEZ study (ICC=0.01)
- 70% success rate in children in classes Y2 and Y3 for a valid reading for FEV_1
- 20% attrition per year follow up
- 30% inflation for subgroup analysis
- 2 schools / cohort inflation for school drop out

9.2 Analysis

The primary outcome is the difference between FEV_1 growth per year as measured as an interaction of age in years and FEV_1, the difference in FEV_1 growth per year is between the London ULEZ and Luton comparison cohorts. FEV_1 and other spirometric secondary outcomes will be analysed longitudinally through a mixed effect model. This will allow for the effects of each centre and also the effects of each child by giving each a random intercept term. FEV_1 and FVC will be adjusted by adding in the subjects' level covariates gender, asthma diagnosis, ethnicity, deprivation (IMD) and zone time dependent covariates adjusted to include baseline age, height, and BMI. The interaction of the variables time in years and zone (comparison/ULEZ) will be calculated to determine the primary outcome difference in growth trajectory between ULEZ group and comparison group. An intercept school effect γ_k and a class effect μ_l will be tested to see if this makes a significant effect of the model fit, if not it will be removed. The parameter of interest is the β_2 which will indicate FEV_1 growth over time T_{ij} (in years) in zone Z,

$$Y_{ijk} \sim \alpha_o + \alpha_i + \gamma_k + \mu_l + \beta_0 T_{ij} + \beta_1 Z + \beta_2 Z T_{ij}$$

A mixed effect model will also be carried out with pollution level as an outcome to test whether pollution levels decrease over time allowing for ULEZ/comparison zones.

$$P_{ij} \sim \alpha_o + \alpha_i + \gamma_k + \beta_0 T_{ij} + \beta_1 Z + \beta_2 Z T_{ij}$$

Where P_{ij} is Pollution level of Subject i at time j, T is time from baseline of subject i at time j in years, Z is a binary variable, 1 for ULEZ, 0 for comparison group. The parameter of interest here is β_2 it would tell us if pollution changed over time in each zone, regardless of spirometry.
A mixed effect to test the interaction of both zone, time and pollution with FEV_1 will also be tested

$$Y_{ijk} \sim \alpha_o + \alpha_i + \gamma_k + \beta_0 T_{ij} + \beta_1 Z + \beta_2 P_{ij} + \beta_3 T_{ij} Z + \beta_4 P_{ij} T_{ij} + \beta_5 P_{ij} Z + \beta_6 P_{ij} T_{ij} Z$$

The parameter of interest here is β_6 which would determine if there are pollution, time effects on lung function between ULEZ and comparison zone.

To disentangle the health effects of regional (London vs. Luton) vs. temporal (ULEZ vs. non-ULEZ) differences in air quality, we will explore using individualised and sub-regionalised exposures to facilitate comparisons of children within London that have varying degrees of change in exposure over time. These temporal effects can be compared to the cross-community regional effects that we will be able to estimate naturally based on London-vs-Luton differences in pollution. We will also explore use of the data from the EXHALE study examining effects of air

quality exposures in similarly aged primary school children in east London between 2008 and 2013. We will explore effect modification by socioeconomic status, stress, and physical activity.

Subset analysis

Analyses will be carried out in the same way using a mixed effect model but adjusting for the presence/absence of current wheeze and asthma using the ISAAC questionnaire, and (separately) health care record diagnosis, as indicators of asthma. All spirometry-based analysis will be stratified by sex to determine if growth rates differ between girls and boys. We will also examine one-year growth for year 4 and year 5 for each class to identify temporal changes in growth rates within the zones. This would be in the form of a three-way ANOVA, one level for the year 4/5 (repeated measures) one for the class and one for the zone.

Sensitivity analyses

The possibility exists that children with compromised lung function early in development, such as children who have grown up in London, might experience improved (rebound growth) during follow up, even if pollution levels did not decline. We will explore individual or school-zone-specific exposure assessments over time in an effort to contrast children exposed to consistently higher levels (in both London and Luton) to those exposed to higher then lower levels during the study follow up, to those exposed to consistently lower levels to determine which parts of the growth trajectory depend on changing air quality versus possible rebound growth.

Missing values

The hierarchical modelling approach that we will use is designed to accommodate children with differing amounts of available data. Specifically, our model for FEV_1 growth will use all measurements that have been recorded, and will include random effects for children (and school site). In this way, every child will contribute to the estimation of the lung function trajectory as a function of age. The model naturally accommodates the amount of information contributed by each child, so children with more measurements will contribute a greater amount of information than those with fewer measurements.

We will carefully compare the distributions of multiple variables, including demographic factors, baseline and updated health status, pollution level, and lung function history for children with missing data to those with complete lung function data. While our primary analyses will utilize all subjects as described above, we will also conduct sensitivity analyses that are restricted to children with complete data over the study period. Similarity in pollutant effect estimates on lung function growth in the “all-children” *versus* “complete-history-children” will provide evidence that missingness did not occur in a manner that produced bias in the primary results. If a lack of similarity is observed, we will further investigate factors related to missingness and will consider whether a formal imputation analysis is warranted.

Outliers and assumptions

Z-scores will be calculated for each continuous variable and will be examined for values>4. Plots of residuals will be inspected for suspected outliers. Should any be found, data will be checked for accuracy. If the data are found to be correct, a model will be fitted excluding these as a sensitivity analysis. All data will be analysed as available. All data will be used in the mixed effect model and a linear trend of lung growth will be assumed over the four years. Model assumptions will be checked while modelling the data; these include normality of data, homoscedasticity, linearity and independence and normality of residuals. If linearity is not satisfied, we will explore linear and cubic splines to describe the lung growth.

Impact on health inequalities

We will express the effect of the intervention on participants by quintile of deprivation, by ethnic group, and by sex. Specifically, we will examine the following outcomes: change in air quality for each individual pollutant; lung growth; change in generic QOL; change in respiratory symptoms; change in respiratory infection rates; change in health care use. In addition, following the methods

of Tonne,(24) we will explore linkage of air pollution concentrations to small-area socioeconomic, population and mortality data. Using life table analysis and exposure-response coefficients from the literature we may then predict associated changes in life expectancy.

Assessment of cost-effectiveness

An economic evaluation from a societal perspective will relate costs associated with introducing the ULEZ to the impact of air pollution on children's lung growth, school attendance, parent work productivity and use/costs of healthcare services and quality of life. The main analysis will adopt a cost-consequences approach, as recommended in NICE public health guidance, to reflect both the 'wider remit than health and greater local element'.(28) This entails a detailed and disaggregated consideration of costs and benefits and (compared with composite approaches commonly adopted for health care interventions) provides greater transparency and resonance for stakeholders/commissioners.(29) The cost-consequences analysis will cover the full study period; pre-study data for a three-month period will also be collected to provide baseline covariates for the analyses. Copies of each child's complete primary care health record will provide data on primary (consultations, medications) and secondary (emergency visits, outpatient appointments and inpatient episodes) care. Unit costs from national sources(30, 31) will be applied to all resource use to estimate individual-level costs. Health-related absence from school will be obtained from parental questionnaire data. Impacts of school absence will be assessed in relation to meeting government attendance targets and consequent lost productivity/income due to work absence by parents, using appropriate assumptions, national wage rate data and a human capital approach to costing.(32) Quality of life and quality-adjusted life years will be assessed by administering the parent completed proxy Child Health Utility 9D (CHU9D) and its associated general population based preference weights.(33) A further economic analysis will estimate lifetime population-level cost-effectiveness associated with study data on air pollutant emissions. Quality-adjusted life year losses and health and social care costs per tonne of emission of $PM_{2.5}$ and NOx (or NO_2) emitted will be estimated using the 'Cost-effectiveness of Air PolluTiOn Reduction model (CAPTOR)' toolkit derived from the Leeds-Bradford LEZ feasibility study. This toolkit was developed to support local authorities in the UK to conduct economic evaluation of air quality measures and usefully enables us to examine the potential broader economic impacts of our study's findings.

Cost-consequence analysis

The cost-consequences analysis will report means and standard deviations for all costs and outcomes for both cohorts. Differences in means between the two cohorts will be tested using an interaction analysis. To avoid problems associated with multiple testing, statistical comparisons of costs will be restricted to major categories (GP consultations, total medication costs, total primary and secondary care costs, total health care costs, total lost productivity costs) rather than for all items separately. Sub-group analyses will be restricted to those adopted for other primary and secondary outcomes.

10. Ethics and Research Governance

The study will be sponsored by QMUL and will be managed by this institution in collaboration with King's College London, St George's Hospital Medical School, University of Edinburgh and the University of Southern California, according to MRC guidance: https://www.mrc.ac.uk/publications/browse/good-research-practice-principles-and-guidelines/

10.1 Ethical aspects of the study

We will seek University and NHS Research Ethics Committee approval and Local Authority and School Board approvals. The study will be carried out according to the principles of the Helsinki Agreement. Ethical concerns relate to consent, data protection and anonymity.

10.2 Consent

This research includes child participants who are unable to consent for themselves. We will seek informed written consent from parents or guardians, and verbal assent from children as described above. Parents/guardians and children will have at least 48 hours in which consider participation and consent. Children and/or their parents/guardians will be free to withdraw at any time from the study. To ensure parents and children can opt-in only to elements of the data capture with which they are comfortable, we will use a staged consent form for i) health assessments (anthropometry, spirometry, questionnaires, physical activity), ii) access to and copying of child's complete health record and HES data, ii) permission to approach the child/parent for longer term assessment/future studies. Parents and children will be free to decline any element of the assessment at any time. We will check all consent forms with teachers to confirm their validity. Paper based forms will be stored securely in locked filling cabinets in locked rooms in the pass-protected Centre for Primary Care and Public Health, E1 2AB.

In year three of the study we will give parents/guardians the option of withdrawing consent to access and copy the child's full health record.

10.3 Data protection

Participants will be allocated unique study ID numbers. Two researchers will access and extract data from NHS health records. We will manage data and its protection according to principles of good research practice and in line with our Clinical Trials Unit protocols.

11. Safety considerations and reporting

This is a low-risk study. Both study sites have policies in place to improve air quality; London policy (the ULEZ) is expected to have more impact on air quality than that of Luton.

Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the study subjects from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and Main Research Ethics Committee (*via* telephone) of this event immediately.

The CI has an obligation to inform both the Main REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office [JRMO]) must be sent a copy of the correspondence with regards to this matter.

Annual Safety Reporting

The CI will send an Annual Progress Report to the main REC using the NRES template and to the sponsor.

Overview of the Safety Reporting responsibilities

The CI has the overall oversight responsibility. The CI has a duty to ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

12. Data handling and record keeping

Data handling and record keeping will be overseen by the PCTU. The Data Manager (DM) and Database Programmer (DM/P) will be supported by the Clinical Trials Information System Manager (CTISM). The Data Manager will develop appropriate data management strategies for the study and advise on their implementation. They will advise on current regulatory framework regarding data protection and data management procedures in compliance with the Data Protection Act and trial regulations. The Data Manager will work with the chief investigator to draw up a study-specific Data Management Plan and advise on CRF design to ensure that all data entry requirements are taken into account. The DM/P will advise on suitable databases and develop database applications in liaison with CI, statisticians and health economists working on the study. All databases will have integrated data validation checks and audit trails. The DM/P will advise on electronic data security, and ensure when using electronic case report forms (eCRFs) that data transfer is encrypted. They will also advise on storage, back-up and archiving of data to ensure databases are regularly backed up and data safeguarded from accidental loss. All paper records, CRFs and consent forms will be held at QMUL. Recruitment logs will be held at QMUL. Schools will retain study information, aside from items here listed, in a site file.

13. Products and devices

The study will use:

- SECA height and weight measures
- Microlab spirometers
- Actigraph accelerometers

14. Monitoring and auditing

Monitoring and auditing of data will be carried out by the PCTU data manager (see (12) above). In addition, the CI will provide six-monthly study reports to the ISC (see (15) below), who act to monitor the study on behalf of the funder and sponsor.

15. Study committees

15.1 Independent Steering Committee (ISC)

The ISC will be chaired by Professor Bert Brunekreef and will meet at least annually. Its role is to monitor and advise on study conduct and progress on behalf of the Sponsor and the Funder. Meetings may be by teleconference at the discretion of the Chair. The ISC composition is designed to provide expertise in all relevant facets of the study design and conduct. ISC meetings will include at least two members of the PPI group.

15.2 Patient and Public Involvement group (PPI)

The PPI group will be led by Monica Fletcher OBE with the support of Ms Rachel Fernandes. Its role is to ensure that the perspectives and welfare of the participant children, parents and schools remain at the centre of the study throughout. The PPI group will provide comment and advice on study materials, support recruitment and retention in the study, and advise on dissemination of progress and findings.

15.3 Project Management Group (PMG)

The PMG will be led by the study CI and comprise the study applicants, the Project Manager, and relevant members of the PCTU. Its role is to oversee the study delivery and progress, ensuring it is conducted in an ethical and competent manner, that it keeps to time, and delivers its planned

outcomes. The PM will report to the PPI group to ensure the latter are appraised on study progress. PPI group members will be invited to join PMG meetings as required. The PMG will meet monthly.

16. Finance and funding

The overall study is funded by NIHR Public Health Research. The physical activity element is funded by NIHR CLAHRC North Thames.

17. Indemnity

The study sponsor is QMUL.

18. Dissemination of findings

Our strategy is to begin dissemination from the outset of the study, maximising public and professional awareness of the study and its relevance to public and child health. We have identified key stakeholder groups and linked these to our multi-channel approaches to influencing them.

Dissemination is a standing item on the PMG agenda, ensuring interim study findings are rapidly and effectively communicated. Our PPI group will co-write or review all study outputs for dissemination via traditional and social media throughout the study.

In the final year of the project we will convene a Stakeholder Meeting with our PPI members, our Asthma UK Centre for Applied Research (AUKCAR) Knowledge Exchange Group and our partner organisations (the GLA, London and Luton Councils, CCGs, the BLF, Asthma UK, CLAHRC North Thames) to generate key messages and jointly plan our study end dissemination strategy to maximise the impact of our findings.

Identified stakeholders – the targets of our dissemination strategy are: Study participants, their families, schools and local study communities; The general public - including voluntary organisations, charities, lay and pressure groups; Government - including parliament, national, regional, local councils, International governments; Academia – including HEIs, NIHR, Royal Colleges, NICE, WHO, leading international research groups and Industry – vehicle and transport-related manufacturers.

We will use multiple methods to target these groups to achieve impact including:

1) Social media, especially Twitter handles of our institutions to rapidly disseminate succinct information, particularly to the general public, study participants and lay groups.

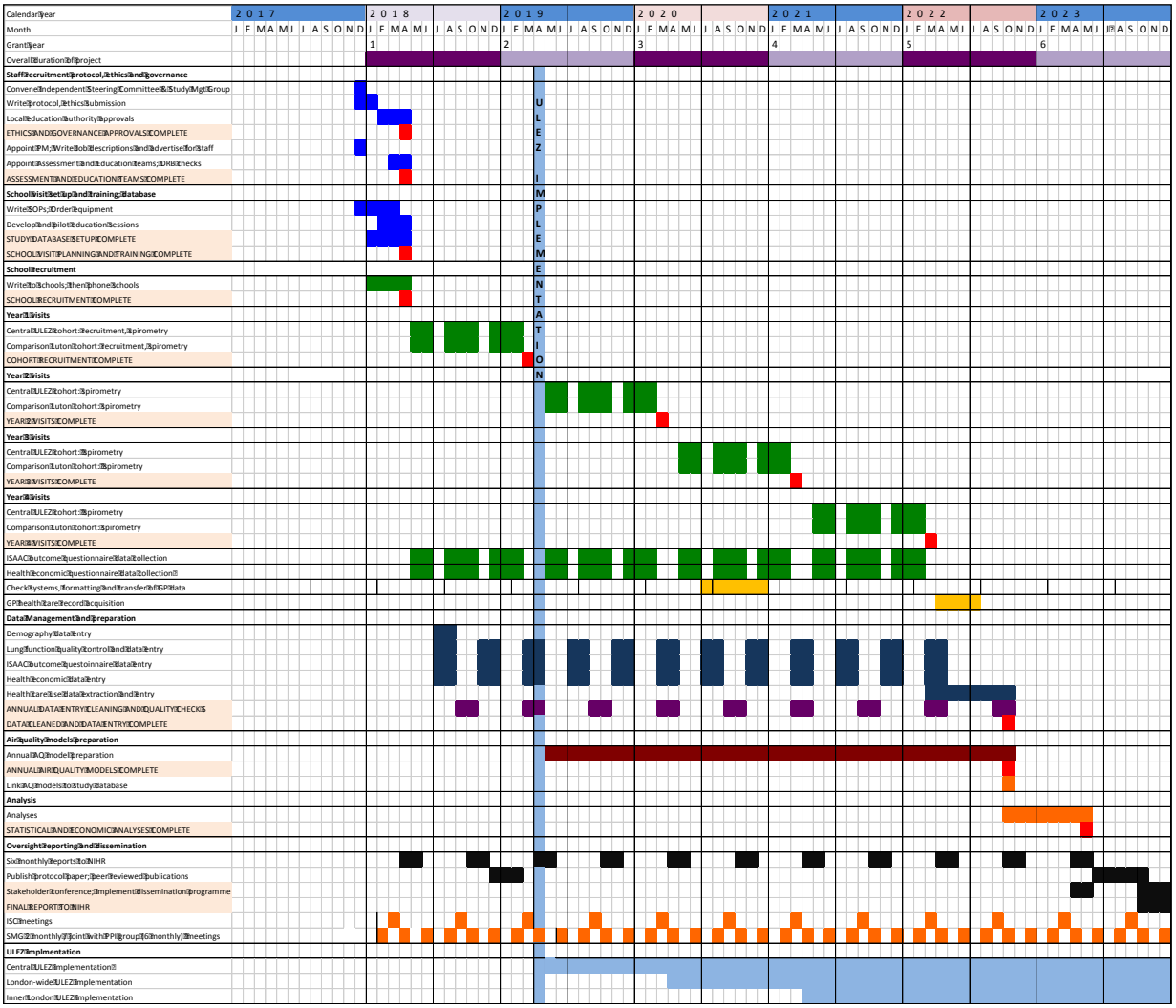
2) Webinars on websites of our institutions, to provide more detailed summaries of results, with downloads of key documents.

3) Presentations, especially to London and Luton partner organisations including the GLA, councils and Health and Wellbeing Boards. 4) Presentations at national and international conferences, including the European Respiratory Society and the American Thoracic Society.

5) Peer reviewed publications targeted at the world's leading medical journals.

19. Appendices

19.1 Study timeline and milestones



19.2 ISAAC questionnaire

1 Section 1. Questionnaire Text

Core questions for asthma (from ISAAC questionnaire for 6-7 year-olds)

1. Has your child ever had wheezing or whistling in the chest at any time in the past? Yes/No
   If you have answered "No" please skip to question 6

2. Has your child had wheezing or whistling in the chest in the past 12 months? Yes/No If you have answered "No" please skip to question 6

3. How many attacks of wheezing has your child had in the past 12 months? None/1-3/4-12/More than 12

4. In the past 12 months, how often, on average, has your child's sleep been disturbed due to wheezing? Never woken with wheezing/Less than one night per week/One or more nights per week

5. In the past 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths? Yes/No

6. Has your child ever had asthma? Yes/No

7. In the past 12 months, has your child's chest sounded wheezy during or after exercise? Yes/No

8. In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection? Yes/No

2 Core questions for rhinitis (from ISAAC questionnaire for 6-7 year-olds)

1. Has your child ever had had a problem with sneezing, or a runny nose, or blocked nose when he/she did not have a cold or the flu? Yes/No
   If you have answered "No" please skip to question 6

2. In the past 12 months, has your child had a problem with sneezing, or a runny nose, or blocked nose when he/she did not have a cold or the flu? Yes/No
   If you have answered "No" please skip to question 6

3. In the past 12 months, has this nose problem been accompanied by itchy-watery eyes? Yes/No

4. In which of the past 12 months did this nose problem occur? (Please tick any which apply)
   January/February/March/April/May/June/July/August/September/October/November/December

5. In the past 12 months, how much did this nose problem interfere with your child's

daily activities? Not at all/A little/A moderate amount/A lot

6. Has your child ever had hay fever? Yes/No

3 Core questions for eczema (from ISAAC questionnaire for 6-7 year-olds)

1. Has your child ever had had an itchy rash which was coming and going for at least six months? Yes/No
   If you have answered "No" please skip to question 7
2. Has your child had this itchy rash at any time in the past 12 months? Yes/No If you have answered "No" please skip to question 7
3. Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes? Yes/No
4. At what age did this itchy rash first occur? Under 2 years/Age 2-4 years/Age 5 or more
5. Has this rash cleared completely at any time during the past 12 months? Yes/No
6. In the past 12 months, how often, on average, has your child been kept awake at night by this itchy rash? Never in the past 12 months/Less than one night per week/One or more nights per week
7. Has your child ever had eczema? Yes/No

19.3 CHU 9D questionnaire

The University Of Sheffield.

Child Health Utility 9D

Instructions

These questions ask about how your child is **today.** For each question, read all the choices and decide which one is most like your child **today**.

Then put a tick in the box next to it like this ☑. Only tick **one** box for each question.

Example
Today my child feels quite upset so I will tick this box.

Upset
- ☐ My child doesn't feel upset today
- ☐ My child feels a little bit upset today
- ☐ My child feels a bit upset today
- ☑ My child feels quite upset today
- ☐ My child feels very upset today

Now think about and answer the rest of the questions below

1. Worried
- ☐ My child doesn't feel worried today
- ☐ My child feels a little bit worried today
- ☐ My child feels a bit worried today
- ☐ My child feels quite worried today
- ☐ My child feels very worried today

2. Sad
- ☐ My child doesn't feel sad today
- ☐ My child feels a little bit sad today
- ☐ My child feels a bit sad today
- ☐ My child feels quite sad today
- ☐ My child feels very sad today

3. Pain
- ☐ My child doesn't have any pain today
- ☐ My child has a little bit of pain today
- ☐ My child has a bit of pain today
- ☐ My child has quite a lot of pain today
- ☐ My child has a lot of pain today

4. Tired

- ☐ My child doesn't feel tired today
- ☐ My child feels a little bit tired today
- ☐ My child feels a bit tired today
- ☐ My child feels quite tired today
- ☐ My child feels very tired today

5. Annoyed

- ☐ My child doesn't feel annoyed today
- ☐ My child feels a little bit annoyed today
- ☐ My child feels a bit annoyed today
- ☐ My child feels quite annoyed today
- ☐ My child feels very annoyed today

6. School Work/Homework (such as reading, writing, doing lessons)

- ☐ My child has no problems with their schoolwork/homework today
- ☐ My child has a few problems with their schoolwork/homework today
- ☐ My child has some problems with their schoolwork/homework today
- ☐ My child has many problems with their schoolwork/homework today
- ☐ My child can't do their schoolwork/homework today

7. Sleep

- ☐ Last night my child had no problems sleeping
- ☐ Last night my child had a few problems sleeping
- ☐ Last night my child had some problems sleeping
- ☐ Last night my child had many problems sleeping
- ☐ Last night my child couldn't sleep at all

8. Daily routine (things like eating, having a bath/shower, getting dressed)

- ☐ My child has no problems with their daily routine today
- ☐ My child has a few problems with their daily routine today
- ☐ My child has some problems with their daily routine today
- ☐ My child has many problems with their daily routine today
- ☐ My child can't do their daily routine today

9. Able to join in activities (things like playing out with their friends, doing sports, joining in things)

- ☐ My child can join in with any activities today
- ☐ My child can join in with most activities today
- ☐ My child can join in with some activities today
- ☐ My child can join in with a few activities today
- ☐ My child can join in with no activities today

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