AMIPROM: Amnioinfusion in preterm premature rupture of membranes

A randomised controlled trial of amnioinfusion versus expectant management in very early preterm premature rupture of membranes – a pilot study

Statistical Analysis Plan for Long-Term Outcome Data

Contents

1. Introduction

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the main, pre-planned analyses of the long-term outcome data for the study "Amnioinfusion in preterm premature rupture of membranes (AMIPROM) – A randomised controlled trial of amnioinfusion versus expectant management in very early preterm premature rupture of membranes – a pilot study".

The approach, as outlined in the introduction section of the short-term outcome data SAP, is to analyse the long-term outcomes after the short-term data results were presented to the DMC on 15th November 2011. The DMC have agreed to unblinding of the short-term data and this has been documented. It has been agreed that the publication will include results of both the short-term and long-term outcomes.

This statistical analysis plan details the intended analyses and should be clear and detailed enough to be followed by any statistician. This will prevent the introduction of bias or data dredging.

These planned analyses will be performed by the trial statistician under the supervision of the lead statistician. The results will be described in a statistical analysis report, to be used as the basis of the primary research publication.

All analyses are performed with Standard Statistical Software (SAS). The final analysis datasets, programs and outputs will be archived following good clinical practice guidelines (ICH E9). The testing and validation of the statistical analysis programs will be performed following the relevant Standard Operation Procedure.

2. Study Design and Objectives

2.1 Study design

This is a multi-centre, randomised controlled pilot trial involving 4 sites in the United Kingdom that planned to recruit 62 patients, 31 into each of the study arms. 58 participants had been recruited at the close of recruitment. Mothers randomised to receive the study treatment were treated with amnioinfusion and mothers randomised to the control treatment were treated with expectant management. Patients were randomised from a central randomisation list, held in the R&D office at Liverpool Women's Hospital, to one of the two treatment arms in a 1:1 ratio.

It was impossible to blind the treatments that the patients received due to the nature of the interventions so therefore AMIPROM was an open trial. However, due to the nature of the randomisation process allocation concealment prevented foreknowledge of the intervention they were due to receive and therefore preventing bias here. Analyses will be performed on unblinded data.

2.2 Study objectives

The aim of this analysis is to compare the long-term respiratory morbidity, orthopaedic and developmental outcomes in babies with very early PROM managed expectantly with those managed with serial amnioinfusions. As this is a pilot study all outcome measurements will be reported. These outcomes are:

1. Long-term respiratory morbidity:

- Respiratory questionnaire taken at 6 months, 12 months and 18 months corrected gestational age.
- Lung function tests taken after 1 year corrected gestational age.

2. Long-term developmental outcomes:
   - Developmental delay at 2 years corrected gestational age using Bayley's score.
   - Cerebral palsy.
   - Orthopaedic follow-up.

2.3 Inclusion/exclusion criteria

Eligibility criteria

a) All women with very early PROM who are booked at recruiting centre.
b) All women with very early PROM booked at other hospitals in the region but who are referred for assessment or delivery to the recruiting centre.

Entry criteria

a) Singleton pregnancy.
b) Rupture of membranes between 16 weeks gestation and 24 weeks gestation.
c) Rupture of membranes confirmed by presence of amniotic fluid in the posterior fornix on speculum examination and/or severe oligohydramnios on ultrasound examination.

Exclusion criteria

a) Obstetric indication for immediate delivery (i.e. fetal bradycardia, abruption, cord prolapse, advanced labour > 5cm).
b) Multiple pregnancy.
c) Fetal abnormality.

2.4 Sample size

An initial sample size was calculated for this study based on an audit performed at The Liverpool Women's Hospital. The audit revealed a composite adverse outcome of 75% in pregnancies with very early PROM: deaths 65% and 10% respiratory morbidity in the survivors (25% of survivors).

To reduce the composite outcome by half, the trial would need 31 cases and 31 controls. (80% power). A reduction in composite outcome by 50% has been chosen because the nature of the intervention is such (i.e. invasive and repeated) that only a large difference would justify its introduction into routine practice.

In the above-mentioned audit, 48 patients were studied over a 3.5-year period (~14 per annum). If we assume that 75% of women whose pregnancies are affected by very early PROM agree to take part in the study, it would take 6 years to recruit the necessary cases to complete the study. To reduce the time for recruitment, it is proposed that a multicentre trial be undertaken.

It is proposed that there will be five hospitals taking part in the study. If each hospital recruits five patients a year, recruitment will take less than three years.

2.5 Recruitment

The date first patient recruited was 03/09/2002. The last patient recruited before trial closure was 01/04/2009 with last follow-up on 26/07/2011.

3. Description of Study Population

3.1 Representativeness of study sample and patient throughput

Details of patients assessed for eligibility, those who meet the study inclusion criteria, those who are eligible and randomised, those who are eligible but not randomised, those who withdraw from the study after randomisation and those who are lost to follow-up will be summarised in a CONSORT flow diagram.

The number of ineligible patients randomised will be reported.

3.2 Baseline comparability of randomised groups

Baseline characteristics of all randomised patients were presented with the short-term outcome results. For the long-term outcomes the same baseline characteristics of the survivors will be presented split by treatment group and overall. Again, these will be the demographic details and history (parity, HVS, WCC, CRP, temperature, tender irritable uterus, foul smelling discharge, gestation at PPROM, gestation at randomisation, maternal age at randomisation, vaginal bleeding, thoracic circumference, abdominal circumference, lung length) at baseline. Details of measurements for the first amnioinfusion in amnioinfusion group at baseline will be summarised (fluid instilled, pocket before amnioinfusion, pocket after amnioinfusion, pocket difference (before-after)). Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted.

3.3 Definition of outcomes and losses to follow-up

The number (and percentage) of patients with scheduled follow-up for amnioinfusions and maternal investigations were presented with the short-term outcome results by treatment group (where applicable). The number lost to follow-up within each treatment group will be reported and reasons where known will be documented in the CONSORT flow diagram. Any deaths and their causes will be reported.

3.3.1 Long-term respiratory morbidity

1. Respiratory questionnaire taken at 6 months, 12 months and 18 months corrected gestational age. The questionnaire consists of two questions. The first of which asks if the child has ever had wheezing in the past (yes/no) and the second is split up into 9 separate domains. The first 8 domains (A-H) each contain 3-5 questions and ask about the child's wheeze, cough, rattly chest, shortness of breath and other symptoms in different situations and at different times of the day over the previous 3 months.

   A) During the day (when awake) – 4 questions.
   B) During the night (when asleep) – 5 questions.
   C) Number of colds and if the child had at least one there are questions that apply when the child has had a cold – 4 questions.
   D) When the child does not have a cold – 4 questions.
   E) When the child has been more active – 4 questions.
   F) Other problems the child may have had – 3 questions
   G) Child's chest symptoms affecting the child – 4 questions.
   H) Child's chest symptoms affecting the parent – 4 questions.

   The 9th domain 'I' consists of 6 questions asking about any treatment received during the previous 3 months. Domains A-H count towards the overall score and domain I is standalone. Details on how the questionnaire is scored are described in section 5.1.1.

2. Lung function tests taken after 1 year corrected gestational age. The three respiratory measurements that were specified in the protocol were lung volume FRC_P, resistance R_{eff} and airway function V_{maxFRC}. There is no standardised way of making resistance R_{eff} measurements equations to calculate predicted values so it was agreed that this data will not be collected.

   Only a small handful of babies were able to have lung function tests at around 1 year corrected gestational age. There are many reasons why such as difficulties getting the babies to Leicester to be tested, work pattern of the part-time research nurse, delay getting R&D approval, losing the lab when funding expired so having to arrange to take portable spirometer to Liverpool to do the remaining unseen patients.

   For infant testing they require sedation which is a big difficulty. Parents don't like it, it necessitates finding a doctor who is willing to write up a dose of chloral hydrate that exceeds what is usually used clinically, and provide the medical cover for several hours. The upper age limit at which these tests can be done is around 15-18 months. After that they are too big and stroppy to take the sedation and settle to sleep well enough to do the tests. Beyond 18 months there isn't anything much that can be done until they can start blowing down tubes in a reasonably consistent manner around the age of 3 (pre-school age).

   The measurements that were taken were:

   - FRC_P – predicted values are well-established in infants but there are none in place for pre-school children. Therefore, infants have the FRC_P results, predicted values and Z-scores were taken/calculated but the pre-school children only have the FRC_P results.
   - V_{maxFRC} –used to measure airway function in infants. V_{maxFRC} results, predicted values and Z-scores were taken/calculated.
   - FEV_1 – used to measure airway function in pre-school children. FEV_1 results, predicted values and Z-scores were taken/calculated.
   - FVC – used to measure forced vital capacity in pre-school children. FVC results, predicted values and Z-scores were taken/calculated.

3.3.2 Long-term developmental outcomes

1. Developmental delay at 2 years corrected gestational age using Bayley's score. The Bayley Scales of Infant Development (BSID-II) is a standard series of measurements originally developed by psychologist Nancy Bayley used primarily to assess the motor and cognitive development of infants and toddlers, ages 0-3. This measure consists of a series of developmental play tasks and takes between 45 - 60 minutes to administer. Raw scores of successfully completed items are converted to scale scores and to composite scores between 50-150. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The two scores reported in this trial are the Mental Developmental Index (MDI) score and the Psychomotor Developmental Index (PDI) score. Their classifications are as follows:
   - 50- 69 – Significantly delayed performance.
   - 70-84 – Mildly delayed performance.
   - 85-114 – Within normal limits.
   - 115-150 – Accelerated performance.

   The Bayley's assessments were carried out between the ages of 2 years and 3 months to 3 years and 3 months. The assessments were performed at the home of the child by a trained nurse. At the protocol stage a trained nurse was not identified so this explains why

some of the earlier children had their Bayley's assessment delayed. Other delays were due to the parents/trained nurse finding a convenient time to meet.

2. Orthopaedic follow-up. This is an opportunistic outcome. If any babies develop orthopaedic problems then they will be assessed accordingly.

3.4 Description of intervention received

Deviations from intended treatment (e.g. withdrawals from randomised treatment) were summarised for each treatment group and the distribution of the number of amnioinfusions received were described for women in the amnioinfusion group with the short-term outcome results.

4. Patients Groups for Analysis

4.1 Intention to treat (ITT) analysis

To provide a pragmatic comparison of the policies of the different drug treatments, the principle of invention to treat, as far as is practically possible, will be the main strategy of analysis adopted for the primary efficacy outcomes. These analyses will be conducted on all patients assigned to the two treatment groups Amnioinfusion or Expectant Management as randomised, regardless of the study treatment or non-study treatment received.

4.2 Per protocol analysis

Patients randomised to amnioinfusion that received at least one amnioinfusion and all patients randomised to expectant management that attended at least one visit will be included in the per protocol analysis set. Patients that withdrew from treatment or had a major protocol deviation will be excluded. This is a sensitivity analysis and will be used to demonstrate the robustness of the results. They will be performed for short term assessments of mortality and binary maternal and neonatal morbidty.

4.3 Safety analysis

Data for serious adverse events (SAEs) were only recorded for the short-term outcomes and were presented with the short-term outcome results.

5. Description for Analysis of Outcome Data

Analysis will focus on estimation of treatment effects including 95% confidence intervals and will follow the intention to treat (ITT) approach. No significance testing will be undertaken. The list of outcomes covers all aspects of safety and efficacy.

5.1 Long-term respiratory morbidity

5.1.1 Respiratory questionnaire

The data for the respiratory questionnaires taken at 6 months, 12 months and 18 months corrected gestational age will be summarised separately by treatment group.

The first question that asks if the child has ever had wheezing in the past (binary yes/no) will be presented as a relative risk with 95% confidence interval. Fetal deaths and neonatal deaths will be excluded from this analysis. A sensitivity analysis will be performed to include the neonatal deaths using the 'worst-case' approach by assigning them to be 'yes' to have wheezed.

Each question in sections A-H are answered on a 5-point scale starting at 'not at all' and increasing in descriptive frequency to 'every day/night/cold' depending on the question. They are scored from 0-4 with 'not at all' being 0 and 'every day/night/cold' being 4. For each patient, the total score for each section is the sum of the within-section question scores. The overall questionnaire score is calculated as the sum of all question scores for sections A-H. Higher scores indicate more severe respiratory symptoms.

A) During the day (when awake) – 4 questions, score between 0-16.
B) During the night (when asleep) – 5 questions, score between 0-20.
C) Number of colds and if the child had at least one there are questions that apply when the child has had a cold – 4 questions, score between 0-16.
D) When the child does not have a cold – 4 questions, score between 0-16.
E) When the child has been more active – 4 questions, score between 0-16.
F) Other problems the child may have had – 3 questions, score between 0-12.
G) Child's chest symptoms affecting the child – 4 questions, score between 0-16.
H) Child's chest symptoms affecting the parent – 4 questions, score between 0-16.
Overall score: between 0-128.

The questions from domain 'I' will be summarised descriptively by treatment group with n (%).

Sections A-H are grouped into four domains:

1. Daytime symptoms (sections A, C, D, E, F).
2. Night-time symptoms (section B).
3. Effect on the child (section G).
4. Effect on the family (section H).

Each domain score and overall score will be summarised and presented for each treatment group separately at 6 months, 12 months and 18 months. There are no validated methods available to handle missing data in this respiratory questionnaire so only those domain scores and overall scores that have no missing data (complete-case) will be summarised. The number of incomplete domains will be reported for each of the 3 time points.

If the data appear to be normal the summary measures of mean and standard deviation will be presented for each treatment group. The difference in means with 95% confidence intervals will be presented.

If the data appear to be skewed (i.e. non-normal) the summary measures of median and inter-quartile range (IQR) will be presented for each treatment The difference in medians with 95% confidence intervals will be presented. The difference in medians will be calculated using the Hodges-Lehman estimate with the corresponding Moses distribution-free 95% confidence intervals.

Fetal deaths and neonatal deaths will be excluded from these analyses. Any missing questionnaires due to loss to follow-up or parents not returning them will be excluded. Sensitivity analyses will be performed for each domain score and overall score by assigning the neonatal deaths the largest value observed in the trial for that particular domain/overall score. Further sensitivity analyses for each domain score and overall score will be conducted to include just the surviving patients that have questionnaires returned with missing answers to any of the questions:

(i) Best-case: assigning the missing question a score of 0.
(ii) Worst-case: assigning the missing question a score of 4.

In addition, the overall score will be analysed longitudinally using mixed models. Mean profile plots and individual plots by treatment groups will be presented. A table of summary measures at each time point will be also presented.

5.1.2 Infant lung function tests

Line listings of each patient's lung function test results will be presented in a table showing age at test, treatment group, test results, predicted values (where applicable) and Z-scores (where applicable).

For the infants, the Z-scores for FRC_P and V_{maxFRC} will be summarised and presented for each treatment group. For the pre-school children, the Z-scores for FEV_1 and FVC will be summarised and presented for each treatment group.

If the data appear to be normal the summary measures of mean and standard deviation will be presented for each treatment group. The difference in means with 95% confidence intervals will be presented.

If the data appear to be skewed (i.e. non-normal) the summary measures of median and inter-quartile range (IQR) will be presented for each treatment The difference in medians with 95% confidence intervals will be presented. The difference in medians will be calculated using the Hodges-Lehman estimate with the corresponding Moses distribution-free 95% confidence intervals.

Fetal deaths, neonatal deaths and patients that had no lung function tests performed will be excluded from this analysis. Sensitivity analyses will be performed:

(a) Firstly, assume that the neonatal deaths reached 1 year corrected gestational age to have FRC_P and V_{maxFRC} measured:
  (i) Assign the neonatal deaths the largest observed positive Z-score for each test.
  (ii) Assign the neonatal deaths the smallest observed negative Z-score for each test.

(b) Secondly, assume that the neonatal deaths reached pre-school age of around 3 years corrected gestational age to have FEV_1 and FVC measured:
  (i) Assign the neonatal deaths the largest observed positive Z-score for each test.
  (ii) Assign the neonatal deaths the smallest observed negative Z-score for each test.

If lung function tests are unable to be performed and assessed due to severe developmental delay they will be included in a sensitivity analysis. It will be assumed that they would have had their lung function tests at the correct time of 1 year corrected gestational age so they will be included in sensitivity analysis (a). These cases can be identified through supporting data and comments on the lung function test form and will be confirmed by the Chief Investigator and documented accordingly.

5.2 Long-term developmental outcomes

5.2.1 Developmental delay at 2 years corrected gestational age using Bayley's score

The MDI and PDI scores will be summarised and presented for each treatment group. If the data appear to be normal the summary measures of mean and standard deviation will be presented for each treatment group. The difference in means with 95% confidence intervals will be presented.

If the data appear to be skewed (i.e. non-normal) the summary measures of median and inter-quartile range (IQR) will be presented for each treatment The difference in medians with 95% confidence intervals will be presented. The difference in medians will be calculated using the Hodges-Lehman estimate with the corresponding Moses distribution-free 95% confidence intervals.

A summary table of classifications (shown below) by treatment group will also be presented.

- 50- 69 – Significantly delayed performance.
- 70-84 – Mildly delayed performance.
- 85-114 – Within normal limits.
- 115-150 – Accelerated performance.

Age is taken account for when assessing the child's developmental performance so this is not an issue for the analysis. Fetal deaths, neonatal deaths and patients that had no Bayley's assessment carried out will be excluded from this analysis. This will be a complete-case analysis so any missing data from the survivors will be ignored. Two sensitivity analyses will be performed for both the difference in means/medians and the classification summary:

(1) If a Bayley's assessment for either MDI, PDI or both was unable to be carried out due to the child having a significantly delayed performance then they will be included in a sensitivity analysis for the corresponding score analysis and classification summary. They will be assigned a score of 50 (i.e. the worst possible score) for the score analysis and classified as 'Significantly delayed performance' for the classification summary. These cases can be identified through supporting data and comments on the Bayley's form and will be confirmed by the Chief Investigator and documented accordingly.

(2) Those survivors with missing MDI/PDI data for reasons highlighted above will be handled as per sensitivity analysis (1) and the neonatal deaths will also be included by assigning them the lowest (i.e. worst scores) MDI and PDI scores and corresponding worst classification observed in the trial.

5.2.2 Orthopaedic follow-up

Any babies that have developed orthopaedic problems that required surgery for the two groups will be presented in terms of relative risks with 95% confidence intervals. However, if there are no babies that have developed orthopaedic problems then this will be reported. More specific details of these orthopaedic problems will be given if the Chief Investigator feels necessary.

5.3 Missing data

The amount and reasons for, missing data will be reported for all outcomes listed above.

Consideration will be given to a sensitivity analysis, in which assumptions regarding missing data are made, if the amount of missing data is large (>10%).

6. Reporting Protocol Deviations

Decisions to be made by an "Endpoint Adjudication Committee" (on masked data).
Protocol violations will be classified according to the following table and summarised for each treatment group.

Protocol specification	Potential deviation(s)	Impact	Justification
Entry criteria			
Singleton pregnancy	Any of the specified entry criteria violated	Major	Violations of these criteria would result in a different prognosis
Rupture of membranes between 16 weeks gestation and 24 weeks gestation			
Rupture of membranes confirmed by presence of amniotic fluid in the posterior fornix on speculum examination and/or severe oligohydramnios on ultrasound examination			
Exclusion criteria			
Obstetric indication for immediate delivery (i.e. fetal bradycardia, abruption, cord prolapse, advanced labour > 5cm)	Any of the specified exclusion criteria violated	Major	Patient may not have time to receive any treatment
Multiple pregnancy		Major	Violation of this criterion would result in a different prognosis
Fetal abnormality		Major	Violation of this criterion could result in a different prognosis
Treatment regime			
Allocated to amnioinfusion	Patient missing either 2 consecutive infusions or 3 infusions in total	Major	May influence effectiveness

Outcome data			
Respiratory questionnaire	Missing data in survivors	Major	May influence interpretation of results
	Timing of questionnaire: completed less than 3 month prior to or more than 3 months after completion due date	Major	May influence interpretation of results
Infant lung function tests	Missing data in survivors	Major	May influence interpretation of results
	Timing of lung function tests: completed less than 3 month prior to or more than 3 months after 1 year corrected gestational age	Major	May influence interpretation of results
Neurodevelopmental assessment	Missing data in survivors	Major	May influence interpretation of results
	Timing of neurodevelopmental assessment: completed less than 3 month prior to or more than 3 months after 2 years corrected gestational age	Major	May influence interpretation of results

8. Setting Results in Context of Previous Research

We will integrate the results of this trial within the context of up-to-date systematic review of relevant evidence from other trials (Clarke et al 2007).

References

Clarke M, Hopewell S, Chalmers I. Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report. *JRSM* 2007; 100: 187-190.

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Measurement conditions in *'Infant Respiratory Function Testing'* Eds Stocks J, Sly P, Tepper R & Morgan W. Wiley (New York) 1996 (Jan) 558 pages, hardback. ISBN 0-471-07682-1. Gaultier C, Fletcher ME, Beardsmore CS, et al. P29-44.

Powell CVE, McNamara P, Solis A, Shaw NJ. A parent completed questionnaire to describe the patterns of wheezing and other respiratory symptoms in infants and preschool children. *Arch Dis Child* 2002; 87: 376-379.

Appendix 1: Approval of AMIPROM Long-Term Outcome Data Protocol Deviations table

This AMIPROM Long-Term Outcome Data Protocol Deviations table (Version 1, 08/03/2012) has been completed and approved by the following personnel:

Trial statistician

Print Name: Mr. Andrew McKay **Date:** _____

Signature: _____

Supervising statistician

Print Name: Mrs. Gaynor Skotny **Date:** _____

Signature: _____

Chief Investigator

Print Name: Dr. Devender Roberts **Date:** _____

Signature: _____

Chair of Trial Steering Committee

Print Name: Prof. Jim Thornton **Date:** _____

Signature: _____

Chair of Independent Data Safety Monitoring Committee

Print Name: Prof. Andrew Shennan **Date:** _____

Signature: _____

Appendix 2: Approval of AMIPROM Long-Term Outcome Data Statistical Analysis Plan

This AMIPROM Long-Term Outcome Data Statistical Analysis Plan (Version 1, 08/03/2012) has been completed and approved by the following personnel:

Trial statistician

Print Name: Mr. Andrew McKay **Date:** _____

Signature: _____

Supervising statistician

Print Name: Mrs. Gaynor Skotny **Date:** _____

Signature: _____

Chief Investigator

Print Name: Dr. Devender Roberts **Date:** _____

Signature: _____

Chair of Trial Steering Committee

Print Name: Prof. Jim Thornton **Date:** _____

Signature: _____

Chair of Independent Data Safety Monitoring Committee

Print Name: Prof. Andrew Shennan **Date:** _____

Signature: _____

Appendix 3: Respiratory questionnaire

Study No : ……..

Date ……..

Name : ……..

Sex : male female (please circle)

Date of birth : ……

Place of birth : ……

Age (weeks) : ……

Address : ……

……

……

Telephone no : ……

The following questionnaire asks questions about your child and what has been happening to him/her over the last three months.

Please could you fill in the questionnaire by putting a circle around your response to each question.

It is important that every question is answered, even if your child has been perfectly well, with no problems at all.

Thank you.

Name of Child **Study Number**

1. This first question refers to at any time in your child's life:

Has your child ever had wheezing (whistling noise coming from the chest) at <u>any time in the past</u>?	*Yes*	*No*

2. The next questions are specifically aimed at the <u>last three months</u>:

A) During the day (when awake) in the <u>last three months</u>:

i) My child has had wheezing (whistling noise coming from the chest):

Every day *most days* *some days* *a few days* *not at all*

ii) My child has had a cough:

Every day *most days* *some days* *a few days* *not at all*

iii) My child has had a rattly chest:

Every day *most days* *some days* *a few days* *not at all*

iv) My child has been short of breath:

Every day *most days* *some days* *a few days* *not at all*

B) During the night (when asleep) in the <u>last three months</u> :

i) My child has had wheezing (whistling noise coming from the chest):

Every night *most nights* *some nights* *a few nights* *not at all*

ii) My child has had a cough:

Every night *most nights* *some nights* *a few nights* *not at all*

iii) My child has had a rattly chest:

Every night *most nights* *some nights* *a few nights* *not at all*

iv) My child has been short of breath:

Every night *most nights* *some nights* *a few nights* *not at all*

v) My child has snored :

Every night *most nights* *some nights* *a few nights* *not at all*

C) How many colds has your child had in the last three months:

None one two three more than three always has a cold

If the answer to the above question is *'none'* continue to questions in section D:

When my child has had a COLD in the last three months:

i) My child has had wheezing (whistling noise coming from the chest):

Every cold most colds some colds a few colds not at all with colds

ii) My child has had a cough:

Every cold most colds some colds a few colds not at all with colds

iii) My child has had a rattly chest:

Every cold most colds some colds a few colds not at all with colds

iv) My child has been short of breath:

Every cold most colds some colds a few colds not at all with colds

D) When my child does NOT have a COLD, in the last three months:

i) My child has had wheezing (whistling noise coming from the chest):

Every day most days some days a few days not at all

ii) My child has had a cough:

Every day most days some days a few days not at all

iii) My child has had a rattly chest:

Every day most days some days a few days not at all

iv) My child has been short of breath:

Every day most days some days a few days not at all

E) When my child has been MORE ACTIVE (e.g. crawling, walking or when excited) in the last three months:

i) My child has had wheezing (whistling noise coming from the chest):

Every day *most days* *some days* *a few days* *not at all*

ii) My child has coughed:

Every day *most days* *some days* *a few days* *not at all*

iii) My child has had a rattly chest:

Every day *most days* *some days* *a few days* *not at all*

iv) My child has been short of breath:

Every day *most days* *some days* *a few days* *not at all*

F) These next three questions are about other problems your child may have had. Over the last three months:

i) My child has had noisy breathing that does not seem to come from the chest :

Every day *most days* *some days* *a few days* *not at all*

ii) My child has had fast breathing:

Every day *most days* *some days* *a few days* *not at all*

iii) My child has had noisy breathing that appears to come from the throat or back of the throat:

Every day *most days* *some days* *a few days* *not at all*

G) The next four questions are on how your child's chest symptoms actually affect HIM or HER over the last three months:

i) My child's chest symptoms have affected my child's feeding or eating:

Every day *most days* *some days* *a few days* *not at all*

ii) My child's chest symptoms have woken up my child:

Every night *most nights* *some nights* *a few nights* *not at all*

iii) My child's chest symptoms have reduced my child's activity:

Every day *most days* *some days* *a few days* *not at all*

iv) My child's chest symptoms have made my child unusually tired:

Every day *most days* *some days* *a few days* *not at all*

H) The next four questions are on how your child's chest symptoms actually affect YOU and YOUR family's life the last three months:

i) My child's chest symptoms have limited my activities:

Every day *most days* *some days* *a few days* *not at all*

ii) My child's chest symptoms have resulted in adjustments being made to our family life:

Every day *most days* *some days* *a few days* *not at all*

iii) My child's chest symptoms have disturbed our sleep:

Every night *most nights* *some nights* *a few nights* *not at all*

iv) I have been worried about my child's chest symptoms:

Every day *most days* *some days* *a few days* *not at all*

Name of Child **Study Number**

I) This last section is asking about treatment. In the last three months:
(Please circle answers)

i) My child has taken treatment for chest symptoms (medicines, tablets or inhalers):

a. Inhaler **Yes** **No**

Name or describe ……

b. Medicine / tablets **Yes** **No**

Name or describe ……

For more than a week at any one time? **Yes** **No**

ii) My child has visited or has had a visit from the General Practitioner for chest problems: **Yes** **No**

Number of times ……

iii) In the last 3 months my child has attended hospital clinics for chest problems: **Yes** **No**

Number of times ……

iv) Has a doctor ever diagnosed asthma in your child? **Yes** **No**

v) My child has been admitted to hospital because of chest symptoms:

not at all once twice three times greater than three times

vi) If your child has problems with their chest or breathing, what diagnosis or label has been given or made?

Person completing the questionnaire :

mother father guardian other (specify)