Improving asthma treatments for children and young people

Application for ethics approval

1. Title of project

Asthma treatments for children with the MAS gene: a clinical trial assessing the efficacy of Exhalin vs Verabreath.

2. Details of researchers

The research project will be led by a Professor who is Chair of Paediatrics at the University of Hove and is also a consultant in paediatric asthma at North Brighton NHS Foundation Trust.

The Professor will be assisted by a medical doctor who is a Reader in Child Health at the General and Adolescent Unit at the University of Hove's Institute of Child Health.

Further support will be given by another doctor (a Senior House Officer) at North Brighton NHS Foundation Trust. This doctor is currently researching a PhD that focuses on how children with asthma and their parents manage living with the condition.

3. Type of project

- Clinical trial

4. Summary of experimental protocol

Background

Asthma is a very common illness in children and young people. On average, it affects two children in every classroom in the UK.

Asthma is usually controlled by a 'preventer' inhaler, usually brown in colour. Children with asthma also have a 'reliever' inhaler, usually blue in colour. The blue inhaler is taken on demand to relieve symptoms of breathlessness, while the brown inhaler is taken regularly to prevent symptoms occurring, or reduce their intensity. Where a child's asthma is inadequately controlled with these two forms of inhaler, a third 'line of defence' is needed. Thus the three 'lines of defence' are:

Stage 1 Defence: the use of a blue inhaler only, when necessary to relieve symptoms (e.g. for mild asthma)

Stage 2 Defence: the use of a brown inhaler on a regular basis to control asthma, plus a blue inhaler on demand in response to symptoms
Stage 3 Defence: an additional control (in conjunction with the use of the brown and blue inhalers), which includes two drug options:

- Exhalin or
- Verabreath

Aim

The protocol seeks to compare the efficacy of Exhalin and Verabreath, for a particular subgroup of children: children with asthma with a particular gene (MAS). Exhalin and Verabreath are both licensed and used at present as Stage 3 Defences.

Hypothesis

Randomised controlled trials suggest that Exhalin is better at controlling asthma in the child population as a whole. However, clinical practice suggests that some children nevertheless do better on Verabreath.

At present, we are unable to identify which children will do better on Verabreath, so physicians prescribe Exhalin first, and then try Verabreath later if Exhalin does not appear to work well. This means that children and young people may suffer with uncontrolled asthma for a longer period while their medication is modified, particularly since it may take some considerable time to identify longer-term patterns of asthma-related disability.

We have also observed that children who are have the MAS gene appear to be at *increased* risk of asthma attacks if they take Exhalin with their brown inhalers.

We suggest that it may be possible to find the children and young people who ought to have Verabreath by testing them for the MAS gene – i.e. that the presence of the MAS gene will be a reliable indicator that Verabreath will be better for this child. We will use ‘quality of life’ outcome measures such as how often a child misses school, and how often they need to use their blue inhaler, to measure the extent to which the Stage 3 Defence medication succeeds in controlling their asthma (see further detail of outcome measures below).

No other studies have yet been published that compare Exhalin with Verabreath for children with the MAS gene.

If our hypothesis is correct, the aggregated outcome measures for the children and young people in Group 1 should be better than the aggregated outcome measures for Group 2. This is because the children and young people in this group will have been allocated to the more appropriate measure straight away through the diagnostic tool of

genotyping. We therefore expect there to be fewer absences from school and less use of blue inhalers in Group 1 when compared to Group 2.

Method

Research subjects

We would like to take 200 children with persistent asthma, who require Stage 3 Defence and randomly assign them to two groups. Group 1 would be tested to find out whether they have the MAS gene. If they do, they will receive Verabreath, and if they do not they will receive Exhalin. We suggest that there will be a prevalence of approximately 25% of participants in Group 1 who have the MAS gene. Group 1 is therefore the trial group, as this is the group where genotyping will be used to allocate children to either Exhalin or Verabreath.

The children in Group 2 are our control group and will not be tested to see if they have the MAS gene. They will receive Exhalin, based on existing research. Both of these stipulations (no genetic testing and prescription of Exhalin) mirror existing normal practice. If participants in Group 2 are observed to react poorly to Exhalin, their medication will be changed in accordance with standard medical practice. If such changes are made, the participant will remain in the trial as the purpose of our research is to observe whether aggregated results in the genotype-directed prescribing model (Group 1) are better than those reached by the usual 'trial and error' model (Group 2).

The research subjects will be recruited from asthma clinics in hospitals in the Brighton area. Asthma doctors will be invited to identify children who meet the eligibility criteria (i.e. need a stage 3 line of defence as their asthma is not adequately controlled by blue and brown inhalers) and invite them to participate in the study.

Additional requirements for participation

Participants will need to discontinue their current Stage 3 Defence medication for a period of two weeks before the research begins. The purpose of this requirement is that the research participant must 'wash out' the effects of their previous medication to avoid any compounding factors in the research. For this period, participants must therefore only take their brown and blue inhalers to alleviate their symptoms. Ideally, this wash out period would be four weeks, but this was felt to be likely to be unacceptable to the children. Given the length of the follow up (a full year), two weeks is proposed as an acceptable minimum wash out period.

Outcome measures

There are two outcome measures which we propose to use.

Measure I

The first outcome measure we propose to use in comparing the approach taken to each group's asthma treatment will focus on each child's attendance at school.

Each participant will begin to take Exhalin or Verabreath at the start of the school year (September 2014). For a period of one school year (ending July 2015), we will record and compare the number of absence days recorded by each child's school register. We will seek permission from the child's parents and their schools to obtain these data.

Measure II

The second outcome measure will focus on whether each Group are able to use their blue inhaler less while taking Exhalin or Verabreath. To measure this, we propose to use an online questionnaire, which allows the data to be collected without the need for children to visit clinics, and potentially miss a day of school. These questionnaires will be completed at the start of the research (when the research subject stops taking their current Stage 3 Defence drug), two weeks later (i.e. at the point of randomisation), and then at three-monthly intervals for the remainder of the school year.

Collecting additional data on effectiveness of outcome measures

As part of this research project, we would also like to improve our understanding of the outcome measures used in children's asthma research. Participants will therefore be invited to contribute additional information as part of the study, in order to improve the accuracy of outcome measures in the future. Thus, in addition to the online data collection described above, participants will also be asked to visit their hospital four times during the year's research study, to undertake a number of tests (including lung function tests, and exercise tests). This additional data collection will not directly benefit the children participating in the research, but will contribute to a very valuable evidence base of the relationship between clinical data of this kind, and the quality of life data collected online, thus improving research methods in the longer term.

We would also like to retain and store the saliva sample that each participant provides. These samples would be used to answer further research questions that are not apparent at this stage.

5. Lay summary

We would like to carry out a research study which involves 200 children between the ages of 7 and 18 years of age. This study is based on the theory that children with a particular gene (MAS) may not react well to asthma medicine currently in use (Exhalin). Our theory is that, for these particular children, Verabreath may in fact work better than Exhalin.

These 200 children – all of whom will have asthma – will be split randomly into two groups. The first group (Group 1) will have their saliva tested to see if they have the MAS gene. If the child does have the MAS gene, they will be given Verabreath as an

extra treatment on top of their usual inhalers. If they do not have the MAS gene, they will be given Exhalin on top of their usual inhalers (which is what is likely to happen in hospitals at the moment).

Children in Group 2 will not be subject to a test to see if they have the MAS gene. Instead, they will *all* receive Exhalin. However, if – during the course of the research period – the child or young person in Group 2 does not do well on Exhalin, their medication will be changed. This mirrors how treatments are managed in standard medical practice.

The outcomes for children in Groups 1 and 2 will then be compared in order to find out if children in Group 1 have better outcomes overall than children in Group 2. We will measure this in two ways:

i. By analysing the school attendance records of each child who takes part.
ii. By analysing whether children in each Group use their blue inhaler less frequently while they take Exhalin or Verabreath. We will find this out by using an online survey.

In addition, we would also like each child who takes part in the study to visit the hospital on four occasions during the year that the research takes place. They will be asked to have a number of tests, including ones that test how well their lungs function, and also how they cope with exercise. The reason we would like to do these tests is to see how the results of these tests match up with the effect on the children's day-to-day lives, as described in the online surveys and school attendance records.

We would also like to retain and store the saliva (spit) sample that each participant provides. These samples would be used to for research that takes place in the future, but we are not able to state exactly what this research would be at this stage.

6. Duration of the study

The study will last for one academic (school) year.

7. Location(s) of the study

The study will be undertaken in three locations: the hospital clinic, the child's home, and the child's school.

8. Description and number of volunteers to be studies

200 children between the ages of 7 and 18.

9. Will written consent be obtained from all participants?

Written informed consent will be sought from participants' parents/guardians (see attached information sheets and consent forms). Potential participants will be given an information sheet and also asked for their written to participate in the study.

While the child's assent should be sought, if the child is unsure or says that they do not want to take part, it will still be acceptable to continue, as long as the parents consent.

10. Will any reward, recompense or reimbursement be offered to participants?

The researchers will pay the travel expenses of each child who takes part, and any parent or guardian who accompanies them.

At the end of the project, each participant will receive an Amazon voucher worth £20. They will not be made aware of this 'thank you' until the research project is completed.

11. Will the participants' general practitioners (GPs) be told about the study?

Yes. The research team will write to each GP to make them aware of the drugs that are involved in the research study, and to alert them to the need for the 'wash-out' period of two weeks.

12. Funding

The study is being funded by the UK Institute for Research in Medicine.

The research team will not receive any monetary benefit from taking part in the research.

The doctor who is a Senior House Officer will use the outputs of this research project to complete his PhD.

13. Drugs or other substances to be administered

Exhalin
Manufacturer: General Pharmaceuticals Ltd., Long Street, Brighton, UK.

Verabreath
Manufacturer: Normal Drugs Ltd., James Town East, Boston, Massachusetts, USA.

14. Will blood samples be required?

No. We will, however, take samples of each child's saliva.

15. How will the subjects be chosen?

Potential participants will be identified via medical records held at the Professor's hospital clinic.

16. Describe how possible participants will be approached

Where children fit the criteria for the research study, they (and their parents) will be contacted via letter initially. These letters will be signed or co-signed by a doctor that the child already knows. One week after letters are sent, members of the research team will follow up with a phone call.

Potential research participants will be given an opportunity to visit members of the research team to discuss how the study will be undertaken.

17. What sources of information will be included?

GP and hospital records, questionnaire, school attendance records, results of the lung function/exercise tests undertaken as part of the collection of data on appropriate outcome measures

18. Whose permission will be sought to access this information?

School headteachers, parents, children/young people, GPs and hospital consultants

19. What ethical problems do you foresee for this project?

Informed consent and assent

- Children and their parents may feel pressured to take part in the research because of their prior relationship with the project leader.

Risks to participants

- The 'washout' of the participants' current Stage 3 Defence medication for a period of two weeks before the research begins. This could cause discomfort or distress to the participants.
- Opportunity costs to the participants:
    - Playing sport: during the washout period, they may find taking part in sporting activities very difficult or impossible.
    - Missing school: we will make every effort to ensure that each of the four days of follow-up visits to the hospital will take place on either a weekend, in the school holidays, or after school hours.

Confidentiality and anonymity

All data will be secured in line with the Data Protection Act (1998).

- Confidentiality and data protection: we will ensure that the data obtained from each child/young person's school (i.e. attendance records) will be stored on an encrypted software programme on the University of Hove's server.

20. Declaration

I understand my obligations as to the rights, welfare and dignity of the subjects to be studies, particularly with regard to the giving of information and the obtaining of consent.

Signature of Lead Investigator:

Date:

Address for correspondence: Department of Paediatrics, Hospital Way, Brighton, B1 2NN.