PAEDIATRIC INFORMATION SHEET

Study title: A randomised, double-blind, placebo-controlled Phase 2B clinical trial of repeated application of gene therapy in patients with cystic fibrosis

Short title: Repeated application of gene therapy in CF patients

Invitation paragraph
We would like to tell you about a research study we are doing. A research study is a way to learn more about something.

Before you decide if you want to join in, it is important to understand why the research is being done and what it would involve for you. So please read this sheet carefully. Talk about it with your family, friends, doctor or nurse if you want to.

Why are we doing this research and what is the medicine being tested?
We are a group of scientists and doctors working together trying to develop a new type of treatment for patients with cystic fibrosis, called gene therapy. We are called the UK CF Gene Therapy Consortium. Cystic fibrosis is caused by a faulty gene. A gene is part of your cells that tells your body how to grow. Gene therapy replaces faulty CF genes with healthy copies within the nose and lungs. We have done research to find the best type of gene therapy, the best dose and the best nebuliser and we know that we can get the gene into the right place within the cells of the airways. This trial is to see whether the medicine can make people with CF better (higher lung function, feeling better, fewer infections etc). We don't know yet if the medicine works.

Why have I been invited to take part?
You have been invited to join this study because you have cystic fibrosis and we think you are likely to be in a group of patients with good (but not perfect) lung function. You may have been kindly helping with our Run-in study, in which case you will probably know quite a lot about gene therapy and the sorts of tests we're doing. If you're new to this research, you will have the opportunity to hear more about it and we will answer any questions you may have. In this study, around 130 people, which includes children (12 years and above), will help test this medicine in our clinical sites based in London and Edinburgh. If you are a patient from one of our collaborating participant identification centres you will attend the Royal Brompton Hospital or the Western General Hospital / Royal Hospital for Sick Children Edinburgh for all trial related visits but continue your clinical care at your own centre. Trial visits are not a substitute for your usual clinic visits and we will not make decisions about your treatment. We will be in close touch with your usual centre and will let them know the results of tests if we think they need to know.

We think you are likely to be in a group of patients with good (but not perfect) lung function. Because the trial itself is relatively long to talk through, we may ask you to perform lung function first to make sure that you will be in the right group to take part. If you fall below this range at the time of your visit we may be able to arrange for you to come again to test you again.

Do I have to be in this study?
No. It is up to you to decide (with your parents). If you do decide to take part, your research doctor will ask you to sign a form giving your agreement to take part. You will be given a copy of this information sheet and your signed form to keep.

You can decide to take part now but change your mind later and stop being in the study without needing to give a reason. If you decide to stop, this will not affect the care you will receive at your normal CF centre.

Talk with your Mum or Dad or guardian before you decide. We will also ask your Mum or Dad or guardian if it is okay for you to be in this study. Even if they say "yes", you have the final say and it is okay for you to say "no".

What will happen to me if I take part?
This is quite a complicated study so we have attached a flow chart to the end of this sheet, which might help explain what's going to happen

Firstly, we will see you at the hospital for one or two visits (2-3 hours each) to check you over, make sure you are fine to take part and do some tests; we call these 'baseline' tests and we will be looking at whether they change once you have had the treatment. If you are suitable and you agree to take part, the next stage is that a computer decides whether you get the gene therapy, or a 'dummy' medicine (half the people will be in each group). Neither you nor the study team will know which group the computer has placed you in. We know this is the best way to be certain whether a new medicine is actually working.

You will then have a visit every month for 12 months. At each visit you will receive a dose of the study medicine (gene therapy or dummy) and we will do some tests too. If you normally take DNase, we will ask you to miss this on the day of dosing and the next day (we will have checked this is okay with your clinic doctors). The tests are explained in detail further down this sheet. First we will give you a few puffs of a blue inhaler (salbutamol/ventolin) to open up your airways and reduce the chance that the medicine will make you wheezy. The gene therapy medicine (or dummy drug) will be in a nebuliser, which you will breathe in for around 40 minutes, with regular breaks. We will ask you to wear a noseclip while using the nebuliser, to make sure that all the medicine is getting into your lungs, but you will be able to take this off during the breaks. The nebuliser pot will be covered in tape so that none of us can see inside., We do all this inside a special cubicle to make sure that the nebulised medicine does not get everywhere; there is a window so you can see chat to the study nurse, and your parent or guardian will just be in the next room. You can come out if you need to, but we will ask you to wear a mask for the first half hour. After you have finished your dosing we will examine you and give you a dose of paracetamol (which should make side effects unlikely). You can then go home and we would like you to take another dose of paracetamol about 6 hours later. At the end of the 12 monthly visits, we will ask you to come back to the hospital for further tests 2 and 4 weeks later. That is the end of the study, but we will keep in touch with your regular clinic team to see how you are doing.

There are some patients in London who will be asked if they want to do also be part of a smaller study. Twenty four people will be asked to be in a 'nasal subgroup' – these patients will also be asked to spray some medicine up their nose during their nebuliser breaks. We will show them how to do them. There is more information about this test in Appendix 1 at the bottom of this test.

Another small study will also be the 'bronchoscopy subgroup', where 24 patients will also have a camera look into their lungs. There is more information about this test in Appendix 2 at the bottom of this sheet.

If you are asked to be in either of these groups, you can say no and still carry on with the rest of the study.

What are the tests I will have at the study visits?

You can see which tests are done at each visit on the sheet your parent/guardian has been given.

- *Full medical history:* we will ask about your general health, whether you've had operations and which medicines you take normally; this will be very like your clinic doctors do in out-patients.
- *Clinical examination*: we will listen to your lungs using a stethoscope and measure your height, weight, temperature, pulse, blood pressure and respiratory rate (you will have had all of this done in clinic too).
- *Pulse oximetry (finger probe):* we will measure the oxygen level in your blood using a finger clip.
- *Blood test:* There are quite a few blood tests needed in this trial, so we can be certain the medicine is safe. We will only let a very experienced person take your blood. If you like you may have anaesthetic cream or spray. If you have a portacath, and you would prefer that we used this to take blood samples, we may be able to use it instead.
- *Urine sample*: we will ask you to pee into a pot and give us a sample for testing. If you are a girl and you have started your periods, we will also do a pregnancy test, because we are not allowed to test this medicine on pregnant women.
- *Spirometry* (blowing tests, as usually done in clinic).
- *Lung clearance index (LCI)*: this test shows how evenly gas is distributed in the lungs and is a good marker of how healthy your lungs are. You will be asked to breathe a special gas mixture for a few minutes. You can't smell or taste this gas and it has no side effects. Once levels in your lungs are stable, we will switch you to breathing normal air and the time taken for the gas to leave the lungs is used to calculate the LCI. We will do the test 3 times, each one taking about 10 minutes.
- *Exercise bike test:* This test allows us to see how much exercise you can do and involves pedalling a bike which is fixed to the ground, whilst we monitor your heart rate and oxygen levels (finger clip). We will ask you to breathe through a mouth piece and wear a nose clip. You will be asked to pedal at a comfortable speed and to keep it up. The pedalling will get harder and harder and we will ask you to carry on until you either cannot keep up or you feel exhausted. We will ask you to stop if your oxygen level falls. Once the test is complete you will have a 2 minute cool down period, and we will continue to monitor your oxygen levels until they return to back to normal.

- *Sweat Test:* Although we are not in doubt about your diagnosis, if we can not find a document showing your blood test results, or your sweat test result we would like to perform one as part of the trial. An area of the skin on your arm will be cleaned and 2 electrodes will be attached with straps. One of these contains a gel which stimulates sweat and the medication is applied to the skin by a weak current; you will feel a little tingling but this is not painful. Following this a collection device will be attached to the skin surface and the sweat collected over a 30 minute period. This will then be analysed by the laboratory for the high levels of salt seen in CF.
- *Activity monitor:* this is a small band worn on your upper arm that collects step and movement data. You will be asked to wear this for 7 full days after 3 of the study visits.
- *Chest computed tomographic (CT) scan:* CT uses x-rays to create detailed images of the lungs. It is a good measure of how CF affects the shape of the airways. For each scan you will be asked to lie still on a table which will move slowly through the centre of a large x-ray machine, but at no time will you be in an enclosed space. You will be able to talk to the CT staff if you need to. You will be given breathing instructions at the time of the scan. No injections are involved and the test is completely painless.
- *Transfer factor (TLCO)*: this is a lung function test which measures how well gas travels across the lungs into the blood. You will probably have had this test before, as part of your annual assessment. You will be asked to wear a nose-clip and to breathe out as far as you can through a mouth-piece. You will then breathe in, as far as possible, a mixture of air and a low concentration of a 'tracer' gas and hold your breath for 10 seconds, before breathing out as far as possible. This will be repeated up to 3 times with rest periods in between tests.
- *Sputum sampling:* we will ask you to try and cough up around a teaspoon of sputum. At one of your first visits and one of your follow-up if you can't cough up sputum we will ask you to breathe in a salty solution which makes this easier. We will give you some ventolin beforehand to stop you becoming wheezy but if you feel tight, tell us. We will check your lung function through the test and stop if it falls. If we don't manage to get any sputum at the end of this, we will ask you to do a cough swab. For some visits, we will ask you to collect all your sputum for the 24 hours before you come and bring this with you.
- *CF specific quality of life questionnaire:* we will ask you to complete some questions about how you are feeling, which takes around 10 minutes.
- *Diary card:* we will ask you to write down at home when you are feeling unwell or when your treatments change. You may want to do this with a parent.
- *Home lung function:* we will show you how to use a small lung function machine at home which stores the results inside. We can then put the results onto a computer the next time you come to the hospital.
- *Bronchial blood flow measurement:* This test will just be for the people in London only. It is designed to look at blood flow to the airways, which is often increased in people with lung disease. It involves you breathing a small amount of a special gas combination (once again, you cannot smell this and it is harmless). You will be sitting down, wearing a nose clip and breathing in and out through a mouthpiece. After several normal breaths you will be asked to hold your breath for a fixed period (either 8 or 16 seconds) before breathing out again slowly. This will be repeated 10 times with a gap (3-4min) between each to allow us to save the data

and reset the equipment. Your heart rate and oxygen levels will be monitored during the test. The whole test takes about 45 minutes to complete

- *Nasal potential difference (Nasal PD) and nasal brushings: London subgroup only - see Appendix 1*
- *Bronchoscopy: London subgroup only - see Appendix 2*

What other medicines can I have instead?
You probably know a lot about your CF and the types of medicines you normally take. You will continue on these whether or not you decide not to take part in this trial. Any other decisions about changing your medicines will be made by your usual CF team.

What are the side effects of the medicines and might I get some if I take part in the research?
We have chosen a dose that we hope has the least chance of side effects, but at higher doses this medicine did make some people feel a little fluey- they had a temperature for a few hours and felt a bit shivery. This is why we ask all patients to take some paracetamol after receiving the medicine. Most people also have a slight drop in their lung function, but they felt fine in themselves at this dose. If you do get any side effects, please tell your Mum or Dad, who will report them to the study team. Do not worry about telling us about any side effects, it will not mean that we will automatically take you off the trial.

What are the possible benefits of taking part?
We don't know if being in this study will help you, but what we find out will help other people with cystic fibrosis. If we show that gene therapy can make people with CF better, we will work hard towards future trials which could lead to it becoming available as a treatment.

What happens if the research project stops?
When the study stops you will be looked after as usual by your hospital CF team and continue to take your usual treatments.

What happens if new information about the research medicine comes along?
Sometimes during research, new things are found out about the research medicine. Your doctor will tell you all about it if this happens. What is best for you might be:
• To carry on as before
• To stop taking part and go back to your usual treatment

What if there is a problem or something goes wrong?
If you have any concern about any aspect of this study you should speak to your study doctor who will do their best to answer your questions.

Will anyone else know I am doing this?
We will keep all your information confidential. This means that we will only tell those people who have a right or need to know. Wherever possible, we will only send out information that has your name and address removed. We will let your family doctor (GP) know that you are taking part in the study.

What will happen to any samples I give?
Samples such as blood, sputum, urine will be labelled with a special code, used for testing and stored for future tests. Some of the time we will be sending the samples out to other groups working with us; they will only have the code numbers and would not be able to tell that the sample was from you.

Who is organizing the research?
This study is being organized by the UK CF Gene Therapy Consortium.

Who has reviewed the study?
Before any research goes ahead it has to be checked by a Research Ethics Committee. They make sure the research is fair. This project has been checked by the Gene Therapy Advisory Committee, which specialises in trials such as this.

Can I ask questions?
You can ask questions about the study now. You can ask questions about the study whenever you want to. If you forget to ask a question and think of it later, you can call the doctor or ask your Mum, Dad or guardian to call the phone numbers below. You can ask the next time you see your doctor if you want to.

For further information please contact:

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Clare Saunders (Clinical Trial Co-ordinator) – Tel: [redacted]
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Appendix 1

Nasal dosing Subgroup

A group of at least 24 patients in the trial will be asked to have doses sprayed into their nose as well as the nebulisers. Because the nose is easy to measure from, we can get extra valuable information from this. *This is optional and you do not have to take part in this substudy if you do not wish to.*

Nasal Dosing: You will be taught how to use the nasal spray and will be asked to squirt one spray into each nostril every 5 minutes; the entire 2 mls will take around 1 hour to administer and will be given at the same time as your nebulised dose, during the 2 minute breaks.

Nasal potential difference (nPD)**:** These are measurements made in the nostril and help us to know how well the gene therapy is working. The test does not hurt; some children have this done if we are finding it difficult to decide whether they have CF and they don't usually mind. We will do this three times before your first dose (this is because we know the measurements can change quite a bit and we want to be as certain as possible that any changes we see are due to the gene therapy and not just these normal changes), and after the sixth and twelfth doses. We would also like to do tests after the third, sixth and ninth doses if you have time and don't mind. We rub a small area on your arm and then attach a wire with some cream and tape it on. A soft tube is then put into your nostril and taped in place. Whilst you lean forward over a bowl, some salty solutions pass through the tube and out of your nose; we watch the response of your nose to this on a portable computer. The whole test takes approximately 20 minutes. We may wish to perform this on both nostrils (one after the other) depending on the results. There are no serious side effects but you might get a slight salty taste from the solutions in your nose or feel like sneezing.

Nasal brushing**:** On two visits only, we will take some cells from the lining of your nose with a small brush. This is not particularly nice but only takes about 5 seconds. We can get a million cells by doing this, which really helps us to find out how well the gene therapy is working.

If you don't want to have the nasal test but would not mind taking part in the bronchoscopy subgroup we can still include you in the nasal dosing group and perform only a single nasal test and brushing, once before and once after dosing whilst you are under anaesthetic.

Appendix 2

Bronchoscopy Subgroup

A bronchoscope is a flexible telescope which allows the doctor to look down into your lungs, take samples and make measurements. It is done whilst you are asleep under a general anaesthetic. In this trial a group of at least 24 patients will be asked to have two of these tests, one before the first dose of gene therapy / placebo and the second at the end of the trial. The tests will allow us to learn how much gene we need to replace in order to achieve health benefits. *As with the nasal group, this is optional and you do not need to take part in this subgroup if you do not want to.*

We will take 2 small biopsies (pieces of the lining of the breathing tubes, about the size of a pinhead) and 10 airway wall brushings from one lung; we will also make measurements with a salty solution that will tell us how well the gene therapy is working. You will not feel any of this as you will be asleep and they are very safe procedures. You might notice you cough up tiny flecks of blood in your sputum afterwards for a day or two. This is nothing to worry about.

You will be asleep for around 45-60 minutes. Afterwards we will give you a dose of antibiotics through a cannula that you will have had put in whilst you're asleep. When you're fully awake, this can come out.

We will keep an eye on you for 4 hours afterwards. Most likely you will then feel fine and be able to go home. The side effects you might have are

- Drowsiness after the anaesthetic – this should wear off after a few hours
- A mild, sore throat for a day or so
- A temperature (this will be made less likely with the use of an IV antibiotic at the end of the procedure)
- A small amount of blood (specks) may come up when you cough for a day or so due to the biopsies

Many thanks for considering these additional tests; please feel free to ask any questions you may have.