# Research Study
# Parent Information Sheet

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| **Study Title** | A Phase IIb, Single-Centre, Randomised, Double-Blind, Comparator-Controlled, Parallel-Group, Pilot Study of Ca-EDTA added to Inhaled Tobramycin vs Tobramycin Alone as Adjunctive therapy to a Course of Standard Treatment for Cystic Fibrosis Children Admitted to Hospital with a *Pseudomonas aeruginosa* Pulmonary Exacerbation. |
| **Study ID** | TEDIV-001 |
| **Protocol Version** | Protocol version 3.0 dated 31 October 2013 |
| **Principal Investigator** | Dr Barry Clements |
| **Institution** | Princess Margaret Hospital for Children |
| **Phone Number** | 9340 8830 or 9340 8222 (24-hr emergency) |

The following information applies to the participating child or adolescent and is for the child or adolescent's parent or legal guardian. Children and adolescents will be given a separate information sheet to read.

We are asking if your child would like to take part in this research study because they have cystic fibrosis (CF) and are growing a bug called *Pseudomonas aeruginosa* (*PsA*) in their lungs. This study is testing whether adding a small amount of a chemical called calcium edetate (Ca-EDTA) to their usual inhaled medicine will make the medicine work better.

Before you decide if you are willing to take part in this study, we want you to understand why it is being done, what your child will have to do and how their information will be used. Please take time to read the information carefully and, if you wish, discuss it with friends, family and your doctor. One or more of our team members will go through this information sheet with you and your child and answer any questions you have. Please ask questions about anything that you do not understand or want to know more about.

Your child does not have to do this study if they don't want to or if you are unhappy for them to participate. Even if they decide to take part, you and your child can still change your minds and stop doing the study. You do not have to give us a reason for stopping. Whatever you and your child decide, it will not affect their routine treatment or future health care.

If you and your child decide to take part in this study, you will be asked to sign the consent section of this form. By signing it you are telling us that you:

- understand what you have read
- give consent for your child to take part in this study
- give consent for your child to have the tests and treatments that are described in this information sheet
- consent for us to use your child's personal and health information as described in this information sheet

You will be given a copy of this information and consent form to keep.

**Why are we doing the study?**

Patients with CF often have lung infections which keep happening or get worse over time. These chronic lung infections may lead to worsening lung function. Lung infections are often caused by bacteria (germs). We treat this type of lung infection with antibiotics (a type of medicine that fights against bacteria). Antibiotics, such as tobramycin, either remove the bacteria, or stop or slow down their growth. This improves your child's cough and will help them to breathe. *Pseudomonas aeruginosa (PsA)* is a common bacteria that can cause lung infections in CF patients. Once it has become established in the airway, antibiotics alone will not be able to remove it. This is because the *PsA* protects itself by forming a slimy protective coat called biofilm. This biofilm stops the antibiotic from reaching and killing the *PsA*.

Calcium Edetate (Ca-EDTA) is a chemical that has been shown in the laboratory and in animal and human studies (but not in CF) to destroy the biofilm and to stop its production. If this happens, bacteria such as *PsA* are more likely to be killed by antibiotics. In this study, we want to see if adding Ca-EDTA to your child's inhaled tobramycin will remove the protective layer surrounding the bacteria in their lungs, and make it easier to kill.

Nebulised tobramycin by itself is approved to treat *PsA* lung infections in CF patients but adding Ca-EDTA to the tobramycin is an experimental treatment. This means that it has not been approved to treat CF lung infections, either in Australia or in other parts of the world. It must therefore be tested to see if it is safe and effective.

This study is designed to get information about how well the study treatment (tobramycin plus Ca-EDTA) works and how safe and well tolerated it is when given to CF patients to treat bacterial lung infections caused by *PsA.* If you participate in this study, no other aspect of your CF treatment will be altered. This includes your standard CF treatment and any other antibiotic or inhaled treatment your treating doctor may wish to prescribe.

**How is the study designed?**

To find out which is the best way of treating *PsA* lung infections we need to compare the study treatment (inhaled tobramycin with Ca-EDTA) to the normal treatment (inhaled tobramycin without Ca-EDTA). This type of study is called a comparator-controlled study.

There are two treatment groups. One group will receive the study treatment (inhaled tobramycin with Ca-EDTA) and the other group will receive the normal treatment (inhaled tobramycin without Ca-EDTA). Neither you, your child or the research staff will know which treatment group your child is in. This is called double-blinding. The study doctor will be able to find out which treatment group your child is in should it become necessary for medical reasons.

Patients are assigned to their treatment group by a computer. You have a 50:50 chance of being in either group. This is called randomisation.

Approximately 32 patients from Princess Margaret Hospital are expected to take part in this study. At the end of the study, if the 16 patients who received Ca-EDTA with their Tobramycin did better than the 16 who did not receive Ca-EDTA with their Tobramycin, then we know that treatment with Ca-EDTA works.

**Study Drug**

Ca-EDTA is a salt which can be dissolved in saline and injected into the veins or breathed into the lungs (inhaled). On this study the Ca-EDTA will be inhaled with your child's tobramycin. The Ca-EDTA will be added to the saline you and your child add to the tobramycin.

**Who is carrying out the study?**

This study is being done at Princess Margaret Hospital under the direction of Dr Barry Clements and with the support and approval of all the consultants in the Respiratory Department. No member of the research team will be awarded for carrying out this study, other than their ordinary wages.

The funding for this study is coming from Dr Clements' research fund. He may also apply for scientific research grants in order to fund this study.

**Does my child have to take part?**

You and your child do not have to take part in this study if either of you don't want to. Before you and your child decide if you want to take part, the study doctor or a member of his team will talk to you about all the options available to you. You and your child can feel free to ask any questions you like at this stage or at any stage throughout the study. If you and your child decide not to take part, they will continue to receive the standard clinic treatment which they have always had.

**What will my childhave to do if we decide to take part?**

The first visit is a screening visit where we will see if your child is eligible to be in the study. At this time (and at any time throughout the study) you and your child can ask the study team any questions you may have. We will seek permission from your child's regular consultant doctor before asking your child to participate in the trial.

The study runs for 71 days (10 weeks) with treatment for 6 weeks and one follow-up visit 4 weeks later to check how everything went and that everything is alright. The first two weeks of the study will take place while your child is in hospital. Members of the study team will see your child three or four times (approximately once a week) while they are on the ward. Once your child is discharged from hospital we will ask them to continue taking the study medication for four weeks at home. There is one telephone call during this time and then one visit to PMH at the end of the four weeks when your child will stop taking the treatment.. Finally, four weeks after your child has stopped taking the trial medication, we will ask your child to come in to PMH for a final follow-up visit.

Below is a table showing you what procedures will be done at each study visit.

**Schedule of assessments –** Outline of the visits and procedures for the TEDIV-001 study

| | Hospital | | | | At Home | | |
|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4 (TC)** | **Visit 5 (EoT)** | **Follow-up** |
| **Days ± visit window** | **Day 1 - 3** | **Day 1** | **Day 8 ± 3** | **Day 15 ± 3** | **Day 29 ± 3** | **Day 43 ± 3** | **Day 71 ± 7** |
| Informed consent | **X** | | | | | | |
| Eligibility criteria | **X** | | | | | | |
| Demographics | **X** | | | | | | |
| Medical history | **X** | **x** | | | | | |
| Respiratory symptoms check | **X** | **x** | **x** | **x** | **x** | **x** | **x** |
| Height and weight | **X** | | **x** | **x** | | **x** | **x** |
| Vital signs | **X** | | **x** | **x** | | **x** | **x** |
| Physical exam | **X** | | **x** | **x** | | **x** | **x** |
| Spirometry | **X** | **x x x**[1] | **x x** | **x x** | | **x** | **x** |
| Sputum collection | **X** | | | | | | |
| Blood collection | **X** | | | **x** | | **x** | **x** |
| Concomitant medications | **X** | **x** | **x** | **x** | **x** | **x** | **x** |
| CF Questionnaire | | | | **x** | | **x** | **x** |
| Dispense medication | | **x** | | **x** | | | |
| Adverse events | | **x** | **x** | **x** | **x** | **x** | **x** |
| First dose of study medication | | **x** | | | | | |
| Patient observation (1/2, 1 and 2 hours post-dose) | | **x** | | | | | |

**TC = Telephone Call; EoT = End of Treatment**

[1] At visit 1, spirometry will be performed pre-dose and at ½, 1 and 2 hours post-dose

[2] At visits 2 and 3, spirometry will be performed pre-dose and post-dose

Informed Consent and Eligibility Criteria

Before we do any study procedures we will ask you and your child to sign this form. We will then check that your child is eligible to take part.

Demography / Medical History

At the screening visit, the study doctor will ask you and your child questions about their medical history. Some of this information can be obtained from their medical notes.

Respiratory Symptoms Check

At all of the visits we will ask you and your child questions about their respiratory symptoms to see how they are going on the trial and to make sure there are no problems.

Height & weight, vital signs and physical examination

At each clinic visit the study doctor will perform a physical examination on your child, including chest sounds, height and weight. We will also record your child's vital signs (blood pressure, heart rate, respiratory rate and temperature). The study doctor will be happy to tell you and your child's doctor of any findings that may need further medical attention.

Spirometry

At each clinic visit your child will do a lung function test before and after a dose of their medication to see how they are progressing on the study and to make sure there are no problems caused by the medication.

Sputum collection

Your child will be asked to provide a sputum sample before they start the study, then at visits 2, 3, 5 and follow-up. To make sure that all the sputum samples on the study are the same, we will do sputum induction on all patients at all visits where we collect sputum. Sputum induction means that we will give your child 3% hypertonic saline to breathe in order to help them to cough up the sputum in their lungs.

Blood Collection

Your child will have a blood test before they start the study, then at visits 2, 3, 5 and follow-up. Your child will be offered numbing cream so that the tests don't hurt. Again, the blood test is to make sure that everything is going well on the trial.

Concomitant Medications and Adverse Events

At every visit we will ask about the medications that your child is taking and about any health events that your child has experienced while on the study.

First Dose of Study Medication and Patient Observation

Your child will take their first dose of study medication while they are at the hospital. We do not expect you or your child to notice any difference between the inhaled medication used in the study and the inhaled medication they normally take. It should taste and feel exactly the same. However, just to make sure that everything goes well, the research staff, including the doctor, will be there. In particular, the doctor will listen to your child's chest, check their breathing, and ask them to do blowing tests (spirometry) three times in the first couple of hours after their first dose. This again, is just to make sure the inhaled medication has no abnormal effect on their breathing.

Dispense Medication

During the rest of your child's hospital stay, the nurses will give your child their study medication each day in addition to all their usual medications. Nothing else will change. When your child is discharged from hospital, you will then be given your child's four weeks' supply of inhaled medication to take home with you. Please keep all unused study medication and used containers and bring them back at your child's next visit.

**Will this study benefit my child?**

If the medication is successful, it should improve the effect of treating the *PsA* infection, and this will help reduce the damage this bacteria causes to the lung.

**Will this study benefit other people?**

If this study shows that tobramycin plus EDTA helps treat *PsA* lung infections better than tobramycin alone, then other people with CF may benefit in the future.

**What are the possible risks?**

While it is always possible for any inhaled drug to cause a reaction in the lungs, we think it is extremely unlikely with this one. Previous studies in children inhaling this drug are limited although there was one study where children inhaled EDTA twice daily for three months with no adverse effects. At the most your child could experience some cough and possibly tight chest and wheeze. Ventolin should fix this very quickly. and we will explain how this should be used if it becomes necessary. Nevertheless, we have provided you with phone numbers (see below) to ring at any time if you think your child is experiencing any adverse effects or allergic reactions from this medicine.

Inhaled medications are far less likely to cause systemic (generalised body) adverse effects as most (or sometimes, all) of the medication stays in the lungs and only a small amount of Ca-EDTA is likely to be absorbed. In the past, Ca-EDTA has been given intravenously to children in much larger doses than will be used in this study, without causing any significant adverse effects.

We recommend that you report any untoward symptoms your child experiences on this study to a member of the study team.

**Risks Related to Study Procedures**

Sputum Sample Collection: Obtaining a good sputum specimen is very important in order to get accurate results. To help your child produce a good sputum specimen, we will be giving them a nebuliser containing hypertonic saline before trying to collect the specimen. Breathing this hypertonic saline will probably make them cough and this will help to bring up a good sputum specimen. Your child may also get a dry mouth, chest tightness, nausea (feeling like they want to throw up) or excess salivation (producing a lot of spit). Inhaled Ventolin can be given to help these symptoms if they are uncomfortable.

Blood Sample Collection: When blood samples are taken from a vein, your child may have discomfort or pain where the blood was taken. Sometimes a person may become dizzy or faint when blood is taken. There is also a risk of infection (rare), bleeding, redness or bruising

at the skin puncture. Bleeding and bruising can usually be reduced by putting pressure on the place where the blood was taken. The chance of infection is lowered by using standard skin cleaning and sterile needles. Your child will be offered numbing cream so that they can't feel the blood test

Spirometry (Lung Function Tests): Since your child must blow hard several times for this test, they could cough or feel short of breath during or after the test.

**Other risks**

The treatment and procedures involved in this research study may involve unexpected risks that are impossible to predict. These unforeseen risks may affect you while you are participating in the study or at some point in the future. If we find out any new information about the study treatment that may affect your willingness for your child to take part in this study, we will let you know what that information is. You can then decide whether you still want your child to do the study.

**What happens if my child is injured as a result of participating in this study?**

You will be compensated if your child suffers an injury as a result of their participation in this research project. Compensation will be provided in accordance with the Medicines Australia (formerly known as APMA) Guidelines for compensation for injury resulting from participation in a company-sponsored clinical trial subject to the scope of the conditions "No-Fault Compensation Insurance for Clinical Trials". A copy of the Medicines Australia Guidelines is available to you from the research staff on request.

**Can I withdraw my child from the study?**

You can withdraw your child from this study at any time. If you decide to withdraw your child from this study please inform a member of the study team. The study team may still want to use the information and samples they have already collected from your child. For safety reasons, they may also ask to see your child for a follow-up visit. There will be no penalty or loss of benefits in your child's routine medical care or any other benefit that you and your child are entitled to receive.

**Can someone else withdraw my child from the study?**

Your child may be taken off the study for various reasons. These reasons include, but are not limited to, the following:

- Dr Clements determines that it is in your child's best interest not to continue
- Your child is unable to complete required study treatments and examinations
- The study is stopped by Princess Margaret Hospital, the Sponsor, the Therapeutic Goods Administration (TGA) or other health authority in Australia
- The study is halted for safety reasons.

**Will my child be paid for taking part in the study?**

You or your child will not receive payment for taking part in this study. However you will be re-imbursed $75.00 for each visit where you and your child have to travel to the hospital, in order to cover travel expenses, parking, etc.

**Where is your child's information kept?**

During the study the study doctor and study staff will collect and record information about your child. This information will be transferred to a secure electronic database so that researchers can analyse it. Identifying information, such as your child's name or address, will not be stored in the database. Your child will be identified by a code that is assigned by the study staff. Information from this study will be kept by the Department of Respiratory Medicine at Princess Margaret Hospital for Children for a period of 25 years from the time when the last patient completes the study.

**What about my child's privacy?**

We hope to publish the results of this research study so that other CF clinics in Australia and New Zealand will be able to benefit. Information contained in your child's medical and research records will remain confidential to the extent permitted by law. Efforts will be made to keep your child's personal information confidential. However, we cannot guarantee complete confidentiality. Your child will be identified by a code, and personal information from your child's records will not be released without your written permission. Results may be discussed at conferences or may be published, but your child will not be identified.

The study will be conducted in accordance with recognised international quality standards, the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidelines. According to ICH-GCP guidelines the accuracy of information recorded for a study must be checked against source data (wherever information is recorded originally, for example your medical records, laboratory test results etc.) in order to ensure the results of the study are reliable and that study procedures were conducted correctly. By signing the informed consent form, you are giving your permission for authorised representatives of the study sponsor monitor(s), auditor(s), the ethics committee and domestic and foreign health authorities to be granted direct access to your child's original medical records and other source data to the extent permitted by the applicable laws and regulations.

**Who has approved the study?**

This study has been approved by the Princess Margaret Hospital Ethics Committee.

**Will my child and I be told about the results when the study is finished?**

We will send you a letter with the results of the study when it is finished, however, it may take some time before we are able to do this.

**Who can I contact for more information about this study?**

If you or your child would like any more information about this study, please do not hesitate to contact a member of the research team. They are very happy to answer your questions.

| Name | Contact Number | Position |
|---|---|---|
| Dr Barry Clements | (08) 9340 8830 | Principal Investigator |
| Dr Ramaa Puvvadi | (08) 9340 8830 | Respiratory Physician |
| Anneli Robbshaw | (08) 9489 7819 | Trial Coordinator |
| Annemarie Naylor | (08) 9489 7820 | Trial Coordinator |
| Lucy McCahon | (08) 9489 7820 | Trial Coordinator |
| Emergency (after hours) | (08) 9340 8222 | PMH switchboard – ask for Emergency Department |

**Who do I contact if I have concerns about the organisation or running of the study?**

If you or your child have any concerns or complaints regarding this study, you can contact the Director of Medical Services at PMH (Telephone No: (08) 9340 8222). Your concerns will be drawn to the attention of the Ethics Committee who is monitoring the study.

## Research Study - Consent Form

| | |
|---|---|
| **Study Title** | A Phase IIb, Single-Centre, Randomised, Double-Blind, Comparator-Controlled, Parallel-Group, Pilot Study of Ca-EDTA added to Inhaled Tobramycin vs Tobramycin Alone as Adjunctive therapy to a Course of Standard Treatment for Cystic Fibrosis Children Admitted to Hospital with a *Pseudomonas aeruginosa* Pulmonary Exacerbation. |

**Declaration by parent / guardian of participant**

I have read the information about this study.

I understand the purpose, procedures and risks of participating in this study.

I have had an opportunity to ask questions about this study and I am satisfied with the answers I have received.

I agree to give my consent for my child to participate in this study and understand that I am free to withdraw my child at any time without affecting my child's current or future health care.

I understand that I will be given a signed copy of this document to keep.

**Name:** _____

**Signature:** _____ **Date:** _____

**Child Assent**

I would like to take part in this study:

☐ Yes

☐ No

**OR**

Not Applicable:

☐ Child is not yet able to give assent

**Name:** _____

**Signature:** _____ **Date:** _____

**Declaration by person obtaining consent**

I explained this study, its procedures and risks and I believe that the parent / guardian of the participant has understood that explanation.

**Name:** _____

**Signature:** _____ **Date:** _____

**Research Study**

# Withdrawal of Consent

| | |
|---|---|
| **Study Title** | A Phase IIb, Single-Centre, Randomised, Double-Blind, Comparator-Controlled, Parallel-Group, Pilot Study of Ca-EDTA added to Inhaled Tobramycin vs Tobramycin Alone as Adjunctive therapy to a Course of Standard Treatment for Cystic Fibrosis Children Admitted to Hospital with a *Pseudomonas aeruginosa* Pulmonary Exacerbation. |

**Declaration by parent / guardian of participant**

I wish to withdraw my child from participation in the above study.

I understand that my withdrawal of consent for my child to participate in this study will not affect their routine treatment, my child and I's relationship with those treating them or my child and I's relationship with Princess Margaret Hospital.

I understand that the information and samples already collected on the study may still be used and shared as described in the study information sheet.

**Name:** _____

**Signature:** _____ **Date:** _____

**Declaration by person who received the withdrawal of consent**

I have explained the implications of withdrawing from the study and I believe that the parent / guardian of the participant has understood my explanation.

**Name:** _____

**Signature:** _____ **Date:** _____