Waikato District Health Board

Participant Information Sheet

Study title: **Beta-blockers in Asthma**

Locality: **Waikato Hospital** Ethics committee ref.: **18/STH/113**

Lead investigator: **Drs R Hancox & C Chang** Contact phone number: **07 839 8899**

You are invited to take part in a study on *Beta-blockers for patients with Asthma*. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you decide to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep for your own records.

This document is 8 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

Beta-blockers are drugs that are very effective at treating heart disease. Beta-blockers are also used by some people to help with performance related anxiety. Beta-blockers are safely used by millions of people worldwide. With better treatments for asthma and health care in general people with asthma are living longer and therefore also developing other diseases such as heart disease. Beta-blockers have usually been avoided in asthmatic people because of concerns that they might cause airway narrowing and increased shortness of breath. Also they are effectively doing the opposite job of *beta-agonists* (salbutamol, blue inhaler) and it has been though that having both together may lead to decreased benefit from salbutamol treatment. Some beta-blockers are known to have very little effect on the lungs because they are *cardioselective,* which means that they are designed to work on the heart but not affect the lungs. Although these drugs appear to be safe in people with asthma, they have never been formally examined to see how they might affect the *beta-agonist* (salbutamol, blue inhaler) in practice.

We want to study whether giving beta-blockers in asthmatic patients affects the benefit you get from your beta-agonists (salbutamol, blue inhaler).

All patients will be screened to ensure there are no side effects from the medication by using a short acting cardio selective beta-blocker, Metoprolol, to test beta-blocker sensitivity. Each patient will then be randomised to take up to two weeks of a cardio selective beta-blocker (Bisoprolol) or up to two weeks of a placebo. After the first two weeks we will switch you over to receive the other medication. During this time we will invite all patients back for heart rate and blood pressure monitoring and undertake four phone calls so that we can reach an appropriate dose of the cardio selective beta-blocker (Bisoprolol). Each participant will finally be invited to complete a further two weeks of higher dose beta-blocker (Bisoprolol) after completing the first two study parts. The study will be stopped if participants experience side effects or cannot tolerate the Bisoprolol.

This is the first stage in a research programme that aims to improve treatment for patients with asthma. At the moment, asthma patients are missing out on potentially life-saving cardiac treatment because of concerns that they might have side effects. Most of the available evidence indicates that the side effects of cardioselective beta-blockers are no worse in patients with asthma than other patients, but the only way to know whether the benefits are greater than the risks is to do a study.

The study has been approved by the Southern Health and Disability Ethics Committee.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

We will check whether you are suitable for the study
You are being asked to participate because you have a diagnosis of asthma.

If you decide to take part in the study, we will ask you to attend our outpatient clinic, Reception F, Level 1 at Waikato Hospital at a time that suits you. We will check your pulse and blood pressure, and examine your heart, lungs, and circulation. We will do an ECG (heart tracing) and blood tests to check for kidney damage and undertake a pregnancy test to ensure you are not currently pregnant. Four times in the study we will ask you to do a questionnaire about your asthma symptoms. Four times in the study we will undertake lung function tests in our respiratory laboratory that is part of the outpatient clinic area. This involves a breathing test called fractional exhaled nitric oxide, FeNO, test (which involves breathing in and out into a mouth piece) and a mannitol challenge. The mannitol challenge is a controlled way in which we give small, increasing doses of an inhaled medication to replicate the airway hyper sensitivity seen in an asthma exacerbation. We measure your lung function throughout the test and then give salbutamol to return you lung function to baseline. We will also review your medical records. If any of these suggest that it would not be safe for you to take a beta-blocker, we will not enrol you in the study. Each visit will take between 30 to 90 minutes in total.

What will the study involve?

Day 0: Screening day 1 including checking medical history from notes, physical examination, ECG, blood tests including pregnancy test if female (we will not include pregnant participants) and baseline mannitol challenge. ACQ Asthma questionnaire to be completed
Day 1: Screening day 2 baseline fractional expired nitric oxide (FeNO) measurement, beta-blocker screening (5mg intravenous Metopolol) and monitoring of heart rate and blood pressure for 20 minutes followed by spirometry test (lung function test). Randomisation to Bisoprolol or placebo arm and supply of 32 capsules given to take one capsule each morning
Day 3-6: Phone call for tolerance of medication and possible instructions to increase to 2 capsules each morning
Day 5-10: Physical examination, ECG and spirometry (lung function test) and possible instructions to increase to 4 capsules each morning
Day 7-13: Mannitol challenge and repeat ACQ asthma questionnaire. Unused capsules returned and a new supply of 32 capsules supplied. Instructions to take one each morning
Day 10-16: Phone call for tolerance of medication and possible instructions to increase to 2 capsules each morning
Day 13-19: Physical examination, ECG and spirometry (lung function test) and possible instructions to increase to 4 capsules each morning
Day 16-22: Mannitol challenge, FeNO and repeat ACQ asthma questionnaire. Unused capsules returned. If tolerated previous arms to be given 42 Bisoprolol 2.5mg tablets and instructed to take one each morning. If not tolerated previous arms study to end here
Day 19-25: Phone call for tolerance of medication and possible instructions to increase to 2 tablets each morning
Day 22-28: Phone call for tolerance of medication and possible instructions to increase to 3 tablets each morning
Day 25-31: Physical examination, ECG and spirometry (lung function test) and possible instructions to increase to 4 tablets each morning
Day 28-34: Mannitol challenge, FeNO and repeat ACQ asthma questionnaire. Unused capsules returned.
End of study

In total, the study will last 5 weeks. You will be asked to take a certain number of capsules once a day throughout this time. The capsules will all look identical and will contain either placebo or 1.25mg of Bisoprolol. In the final arm we will ask you to take 2.5mg tablets of Bisoprolol. You will be given a symptoms diary to document any symptoms you had during this time. There will be 8 clinic visits, each lasting up to 90 minutes. At these clinic visits, you will be asked about any symptoms or possible side effects of the Bisoprolol, and to have physical examination, lung function test, blood pressure measurement, ECG and at four of them a mannitol challenge and a FeNO measurement. We will also call you 4 times to see if you have any symptoms from the medication. We will also consult your past medical records for background information on your health and to ensure that it is safe for you to participate in this study.

You will be given a card with contact details so that if you have any questions about your medication you can call us or if you are being prescribed any medication by another doctor they are aware that you are on the study.
Your data will be given a code so that your data can be de-identified. For safety a master code list will be held separately.

Your participation in the study will not affect any of your other treatments.

What if there are side effects?
You will be asked about any side effects that may be caused by the Bisoprolol. If these are judged to be serious, the Bisoprolol will be stopped. For minor side effects, we will discuss with you whether you want to continue or stop the Bisoprolol. We recommend that you do not stop the drug suddenly without talking to the study doctors or your own GP first. You will not be put under any pressure to keep taking the Bisoprolol if you wish to stop it.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

The main risk of participating in this study is that you experience a side effect from taking Bisoprolol. It is possible that Bisoprolol will cause airway narrowing making you more short of breath. This side effect is uncommon in patients with asthma, but it is why we will start with a very low dose of Bisoprolol.
Bisoprolol works by keeping the heart rate from getting too high. This means that if you exercise intensely while you are on Bisoprolol you may feel tired sooner than usual and your exercise capacity may be limited while taking Bisoprolol. This will stop when you are no longer are taking Bisoprolol.

Common side effects of Bisoprolol include:

- Dizziness and fainting (10-20%). Your heart rate and blood pressure will be monitored to try to prevent this.
- Tiredness and fatigue (1-10%). It is important we check how you react to this medication before operating any vehicles or heavy machinery. This will be done on your screening visit.
- Poor circulation (1%) and leg swelling (1%)
- Other uncommon side effects (<1%) include nausea, vomiting, and bowel disturbances, sleep disturbance, weight gain, depression, sexual dysfunction and impotence, skin rashes.
- If you are diabetic or at risk of low blood sugar this medication can mask some warning signs, especially a fast heart rate, that may alert you to your low blood sugar level.
- If you have coronary artery disease suddenly stopping Bisoprolol may give you symptoms of shortness of breath and leg swelling.
- Some other medications you are taking may interact with Bisoprolol and we will check for these before we start.

Bisoprolol may also be beneficial. It is known to improve survival in patients with heart failure and coronary artery disease. Patients with asthma have a higher risk of heart disease and may particularly benefit from Bisoprolol treatment.. The aim of the

study is to see if your usual inhaler medications are still effective while you are taking Bisoprolol.

The investigators will monitor you carefully during the study. We will provide you with contact details for the investigators and advice on how to proceed should you become unwell. If you have an asthma exacerbation we advise you to manage it exactly as you would normally manage your asthma, to document the exacerbation in your asthma diary and continue taking your Bisoprolol. If you develop any side effects from the Bisoprolol that need to be treated, the Bisoprolol will be stopped and we will ensure that you get the treatment and advice that you need. If you develop side effects in between clinic visits, we will provide advice by telephone, and arrange for an early clinic review, or a consultation with your usual doctor as appropriate.

WHO PAYS FOR THE STUDY?

The study is funded by the Health Research Council of New Zealand. The investigators are employees of the University of Otago, Counties Manukau, Waikato and Capital Coast District Health Boards, and the Medical Institute of New Zealand.

You will receive no payment for your participation in this study. However parking and travelling costs related to study visits will be reimbursed.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you may be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

Your participation in this study is entirely voluntary. You are free to decline to take part and if you decide to take part in the study, you are free to withdraw at any time. You will not experience any disadvantage if you decide not to take part or withdraw. Your usual healthcare will not be affected in any way.

We will collect health information about you during this study. This will be kept confidential between the investigators. No information that could identify you will be made public or published in any reports. You have a right to see this information.

If important new information about the adverse or beneficial effects of Bisoprolol becomes available during the study, we will inform you of this as soon as possible.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

If you wish to continue taking Bisoprolol treatment after the study, this decision can be made in consultation with you and your doctor. Bisoprolol is available in New Zealand and currently is fully subsidised by Pharmac.

The study data will be kept indefinitely or until it becomes clear that the data has no further use. When the study is completed, we will write to you to tell you what we have found.

If you decide to withdraw from the study, for any reason, we will keep the information about your participation on file.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:
Dr Miriam Bennett, Respiratory Research Fellow, Waikato DHB
078398899
Miriam.bennett@waikatodhb.health.nz

Dr Catherina Chang, Consultant Respiratory Physician, Waikato Hospital
07 839 8899
cat.chang@waikatodhb.health.nz

Associate Professor Bob Hancox, Consultant Respiratory Physician, Waikato Hospital & University of Otago
03 4798512
bob.hancox@otago.ac.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone:	0800 555 050
Fax:	0800 2 SUPPORT (0800 2787 7678)
Email:	advocacy@hdc.org.nz

For Maori health support please contact:

Name, position
Telephone number
Email

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone:	0800 4 ETHICS
Email:	hdecs@moh.govt.nz

Consent Form

If you need an INTERPRETER, please tell us.

Please indicate that you consent to the following:

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.

I have been given sufficient time to consider whether or not to participate in this study.

I have had the opportunity to use a legal representative, whanau/family support or a friend to help me ask questions and understand the study.

I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.

I consent to the research staff collecting and processing my information, including information about my health.

If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.

I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.

I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.

I understand the compensation provisions in case of injury during the study.

I know who to contact if I have any questions about the study in general.

I understand my responsibilities as a study participant.

I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.

I wish to receive a summary of the results of the study. Yes ☐ No ☐

Declaration by participant:
I hereby consent to take part in this study.

Participant's name:

Signature: Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature: Date: