PARTICIPANT INFORMATION SHEET

Short Title: Rescue Cumulative Dose Study

Study Title: Bronchodilation following repeated administration of budesonide/formoterol vs salbutamol in adult asthma: A randomised, open-label, cross-over study

Location: Medical Research Institute of New Zealand (MRINZ), Wellington Regional Hospital

Lead Investigator: Professor Richard Beasley **Contact phone number:** 04 805 0234

Ethics committee reference: 19/NTB/83

You are invited to take part in a clinical trial, a type of research study. It looks at two different inhalers used in asthma. Your decision to take part is entirely your choice. This Participant Information Sheet will help you decide. It explains why we are doing the study and what your participation would involve. It also describes the benefits and risks to you, and what would happen after the study ends. We will go through this information with you and answer any questions you may have.

If you agree to take part, you will be asked to sign an electronic version of the Consent Form when you visit us. There is a copy 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. This document is **11 pages** long. Please make sure you have read and understood all the pages. If you need an interpreter, we can arrange this for you.

What is the purpose of this study?

Asthma is a major health problem. New Zealand in particular has high rates of asthma. Currently, when someone goes to the Emergency Department with an asthma attack, they are given are medication called salbutamol (Ventolin).

Salbutamol is a rescue inhaler. It is called a rescue inhaler because it quickly works to open up the airways to make breathing easier. Due to this, salbutamol is used to treat asthma flare-ups in places like the Emergency Department. This study looks at what would happen if a different inhaler is used instead of salbutamol.

This other inhaler is named Symbicort. It contains budesonide (an inhaled steroid medication) and formoterol (a long-acting medicine that opens your airways). This inhaler is currently used by many people with asthma as a preventative inhaler. This means it is used daily to prevent asthma attacks. However, we do not know whether Symbicort could be used as a rescue inhaler to treat asthma flare-ups.

In this study, we are looking to see if Symbicort could be used as a rescue inhaler as well, like salbutamol. We want to see if Symbicort opens up the airways as quickly as salbutamol. We are first comparing the two inhalers in participants with stable, moderate to severe asthma, before comparing it in participants with asthma flare-ups. If Symbicort is shown to

be as effective as salbutamol, then Symbicort may be used to treat asthma flare-ups in the Emergency Department.

If you decide to take part in the study you will receive both salbutamol and Symbicort on two separate days. The amount of salbutamol used in this study is the same as what you would get if you were to go the Emergency Department for an asthma attack. This study has been approved by the Northern B Health and Disability Ethics Committee (ref: 19/NTB/83).

What will my participation involve?

In order to take part you must:

- Have a diagnosis of asthma
- Be 16-65 years old
- Not have had a chest infection or flare up of asthma in the past 4 weeks
- Not have required oral steroids (e.g. prednisone) in the past 6 weeks
- Not be a current smoker (ex-smokers can take part depending on their 'pack years'. We will let you know at the screening visit)
- Not be pregnant, breast-feeding or planning a pregnancy

We are looking for 44 volunteers. If you decide to take part, you will attend a screening visit at the MRINZ facility. At this visit, we will decide if you are eligible to take part. If you are found to be eligible, you will then be requested to attend TWO intervention visits. They will be up to 4 weeks apart. You will receive salbutamol during one visit and Symbicort during the other, in a random order. You may also be asked to withhold some of your asthma medication prior to the Intervention Visits. A study investigator will discuss this with you in detail at the screening visit. A computer will decide which medication you get first (randomisation). You have a 50% chance of being placed in either group. You may have to take time off work in order to attend these visits.

Screening Visit (Approx. 1.5 hours)

At this visit we will go over the study with you. We will answer any questions you may have. We will also obtain your electronically signed informed consent. As part of this study, the study doctor, and/or other MRINZ research staff will collect and record medical and personal information about you including your name, date of birth, your address and other contact details, information about your health and medication use.

You will also undergo some medical tests. Information about your health and medications along with your medical test results will help us to check if you are eligible to partake in the study.

We will also ask you to tell us which ethnic group or groups you belong to. If your ethnicity is not included in the list, then you may choose the option "other" and tell us what your ethnic group is. We ask this question because the NZ Ministry of Health encourages NZ researchers to collect ethnicity information from study participants in a standardised way. It

is your choice to answer this particular question. If you do not wish to, you may still participate in the study.

We will also measure your height and weight and do the tests described below.

1. Vital Signs

We will measure your blood pressure, heart rate, breathing rate and the levels of oxygen in your blood.

2. Spirometry

A spirometer tests your lungs by measuring how much and how fast air moves out of your lungs. This involves breathing deeply in and out, and blowing forcefully into a tube. Spirometry may make you cough or feel dizzy. This will go away shortly after the test is finished.

3. Reversibility Testing

This involves performing the spirometry test before and after taking salbutamol. It may briefly increase your heart rate and you may experience mild tremor after taking it. This should not last long.

4. Blood sampling

We will take your blood once during this visit. This lets us measure levels of potassium and eosinophils (allergic white blood cells) in your blood. If you are female, we may also do a pregnancy test using the blood sample.

5. ECG

An ECG is a tracing of your heart. ECGs are painless and involve placing stickers on your arms, legs and chest. We will then attach some wires to the stickers. We will do this once during the visit.

At the end of the screening visit, if you are found to be eligible we will arrange for you to come in for the two Intervention visits.

Intervention One (approx. 9 hours)

This visit will last about 9 hours. The order of your treatment will be random. If you get randomised to receive salbutamol on the day of Intervention One, then you will receive Symbicort on the day of Intervention Two and vice versa. Both you and the study doctor will know which group you have been allocated to. You may be asked to withhold some of your asthma medication prior to this visit.

Salbutamol Group:

If you are randomized to get salbutamol first, then you will receive 8 puffs of salbutamol over 90 minutes via an inhaler. This will be followed by four doses of salbutamol via a nebuliser. A nebuliser is a machine that helps you to breathe in salbutamol as a mist

through a mask. At the end of 8 hours, you will receive 12 puffs of budesonide. This is an inhaled steroid medication.

We will also do the following tests during the visit:

- Vital signs (13 times)
- Spirometry (13 times)
- Blood sampling (3 times)
- ECG (3 times)
- FeNO (13 times): FeNO stands for 'fractional exhaled nitric oxide'. This involves breathing deeply in and out into a device. The device measures the level of a gas called nitric oxide, in the air you breathe out.
- Breathing scores (13 times): We will ask how your breathing feels using a scoring system
- Urine pregnancy test (once): If you are female, then we may ask you to provide a urine sample for a pregnancy test.

Symbicort Group:

If you are randomized to get Symbicort first, then you will receive 12 puffs in total over the 8 hours. We will also do the following tests during your visit:

- Vital signs (13 times)
- Spirometry (13 times)
- Blood sampling (3 times)
- ECG (3 times)
- FeNO (13 times) Breathing scores (13 times)
- Urine pregnancy test (once)

Intervention Two (approx. 9 hours)

This visit will take place **up to 4 weeks** after Intervention One. This will also last about 9 hours. During the visit, you will receive the treatment that you did not receive during your first visit. Once again, you may be asked to withhold some of your asthma medication prior to this visit. We will repeat all the tests that were done in Intervention One.

What are the possible risks and benefits of this study?

Benefits

Taking part in this study will help us improve the current treatment of asthma. There will be no direct benefit to your health from this study.

Risk of medication side effects

We have listed the potential side effects from the medications given in this study. The list is of known symptoms associated with the inhalers. There could be other side effects we are

unaware of. However, this is unlikely as the inhalers have been commonly used in asthma for decades.

A study doctor will be present at all times during the visits. They will monitor you closely. Your study doctor will discuss the best way of managing any side effects with you. Your study doctor may need to stop your treatment if you get certain side effects.

If you feel unwell after your study visits, please get in touch with your GP or dial 111 for an emergency.

Salbutamol:

Common (1 in 10-100 people): Increased heart rate, tremor, headache

Uncommon (1 in 100-1000 people): Awareness of heart beating, mouth and throat discomfort, muscle cramps

Rare (1 in 1000-10,000 people): Low levels of potassium in the blood, peripheral vasodilatation

Very rare (less than 1 in 10,000 people): Severe allergic reaction, wheeze, changes in blood pressure, irregular heart beat.

Symbicort:

Common (1 in 10 - 100 people): Awareness of heart beating, headache, tremor, mild throat discomfort, cough, hoarseness.

Uncommon (1 in 100 - 1000 people): Increased heart rate, sickness, diarrhoea, muscle cramps, dizziness, bad taste, thirstiness, tiredness, restlessness, sleep disturbances, weight gain.

Rare (1 in 1,000 - 10,000 people): Severe allergic reaction, irregular heart beat, wheeze, bruising, low levels of potassium in the blood.

Very Rare (Less than 1 in 10,000 people): Severe chest pain/tightness, depression, hormone disturbances, high blood sugar, behavioural disturbances, changes in blood pressure.

Budesonide:

Common (1 in 10-100 people): Mil mouth and throat discomfort, hoarseness, thrush (fungal infection in mouth and throat)

Uncommon (1 in 100 - 1000 people): Dry mouth, bad taste, thirst, cough, headache, dizziness, diarrhoea, nausea, weight gain, tiredness

Rare (1 in 1,000 - 10,000 people): Skin bruising, rash, restlessness, low mood, behavioural changes (mainly in children), sleep disorders, wheeze

Risks associated with blood tests

You may feel some discomfort during blood sampling. There is also a low risk of bleeding, swelling and bruising at the site of the needle insertion. All samples will be taken by trained staff.

You may hold beliefs about a sacred and shared value of blood samples removed. There are a range of views held by Māori around these issues. Some iwi disagree with storage of blood samples and advise their people to consult prior to participation in research where this occurs. You have the right to choose how the blood samples will be dealt once analysed.

Risks associated with spirometry and FeNO testing

You may feel short of breath or dizzy during or after performing the breathing exercises. However this will be temporary. You will be monitored throughout the tests by study staff. You will be seated at all times for the tests.

Risks associated with pregnancy

If you are female and become pregnant during the study, please let a study investigator know as soon as possible. You will be withdrawn from the study. While salbutamol and Symbicort can be safely used in pregnancy in the current recommended doses, we will be using higher doses of Symbicort than usual. We do not know the effects of these in pregnancy and therefore exclude pregnant or breastfeeding women from the study.

Who pays for the study?

This study is funded by AstraZeneca, the company that produces Symbicort. This study is sponsored by the Medical Research Institute of New Zealand (MRINZ). The study investigators are part of the MRINZ. MRINZ is responsible for the design and running of this study.

It will not cost you anything to take part in this study. You will be reimbursed for your time and any incidental costs such as parking. This will be a total of $200 at the end of the screening visit and a total of $400 at the end of each Intervention visit. Tax will be deducted from this amount prior to payment. If you are receiving any benefits, you will need to discuss this with the appropriate authorities. If you do not earn a regular income, or if you are in a low income tax bracket, you may able to claim a tax refund at the end of the financial year.

What if something goes wrong?

If you were injured in this study, you would be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. 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 is entirely voluntary. Your decision will not affect your health care in any way. It will not affect your future relationship with your hospital or GP. If you do agree to take part in the study, you are free to withdraw at any time. You do not have to give a reason. Participation in this study may also be stopped if the study doctor decides it is not in your best interests to continue. It may also be stopped if the study as a whole is stopped for safety reasons.

In accordance with relevant New Zealand privacy and other relevant laws, you have the right to request access to your information collected and stored by the study team. You also have the right to request that any information with which you disagree be corrected.

We will also tell you if we find out new information during the study, which may affect your health or willingness to continue to take part.

You may have a friend, family or whānau to support and help you understand the risks and/or benefits of this study.

Privacy and Confidentiality

Information including medical and personal information will be collected from you. We may also need to access your GP records to check details. For example to check the date you last visited your GP and whether they prescribed you prednisone.

The information we collect from you in person as well as the results of the study tests are called "source data". The study staff will have access to this data. The study monitor (MRINZ) will have access to your health details. The monitor makes sure that the study is being run properly and that the data collected is accurate and is stored securely.

The ethics committee, regulatory authority and funder (AstraZeneca) may also access your personal records if the study is audited. This is to make sure that participants are protected and to make sure the study was run properly.

Access to your information by these people is allowed only for the purpose of these quality checks.

If you take part in the study and are happy for us to do so, we will write to your GP to let them know. If we find any abnormal results during the study (for example high blood pressure) we will write to your GP to inform them of this. We will also add an alert to your electronic hospital medical record to say that you are taking part in the study.

In order to analyse your data, we need to transfer some of the information from your Source Data individual record into the Study Database. The Study Database contains the records from all the study participants.

The information about you that we transfer into the Study Database is "coded" with a unique participant identification number. This means that your name and other uniquely identifying information are kept separate from the Study Database.

This way, when we need to send the data from the Study Database to the study statistician for analysis or if we need to provide the study data set to the funder of the study (Astra Zeneca), we can do so without breaching your confidentiality.

Your blood samples will also be de-identified and labelled with your unique participant identification number, date of birth and gender. After analysis, the samples will be destroyed according to lab protocols. Urine samples will be coded with you unique number and initials. They too will be disposed of as per protocol.

We will keep a log that can link your unique participant identification number to your name. We can match your Source Data record with your records in the full Study Database, if needed. The study staff, Sponsor and all other parties will keep your information secure and confidential, under restricted access as per the law. Your health information may be given if required by law.

It is also possible that in the future we may receive requests to share the study data set from other qualified researchers. We will never share identifiable information. Before any decision is made by the MRINZ about sharing de-identified information additional steps will be taken to safeguard your privacy. For instance, the researchers requesting the data will have to formally agree to use the data for research purposes only.

The MRINZ undertake to ensure that all information (data) collected about you by MRINZ study personnel and recorded in our electronic and paper hardcopy records will be stored securely under restricted access. Once the study finishes, due to international research guidelines this information will continue to be stored securely for at least another 15 years. During and after the study the electronic data will be stored on protected, secure servers including servers overseas (in Australia). Once the study information may be destroyed, we will use methods designed to protect the information including confidential shredding of all hardcopy paper records.

What happens after the study or if I change my mind?

Once you have completed the study, you will not be allowed to take any of the medications home with you. At the end of the study, we can give you a summary of the results. The results can be e-mailed or posted to you. There may be some delay between taking part in the study and receiving the results. This is because the whole study needs to be finished before the results can be analysed.

If you do agree to take part in the study initially and you change your mind, you can stop at any time. You do not have to give a reason. If you withdraw from the study, we will keep the data collected up to the time you withdraw. We are required under international research guidelines to continue to store the data we have already collected about you and your participation in the study.

We also have an obligation to analyse your information if it is relevant to the safety of others and if possible to collect any necessary safety follow-up information about you. We will stop collecting any further information about you unless you are willing for us to do so.

By signing the consent form you are agreeing to allow us to keep and use the information we have already collected about you up until the point of your withdrawal.

Once completed, the results of this study may also be published in scientific journals, social media, the MRINZ website and presented in conferences. No material which could personally identify you will be used in any of these publications.

Who can I contact for more information?

If you would like to **take part** please contact:

Name: Dr. Nethmi Kearns
Phone: 04 805 0261
E-mail: nethmi.kearns@mrinz.ac.nz

If have any **concerns or complaints** about the study, you can contact:

Name: Professor Richard Beasley
Phone: 04 805 0234
E-mail: richard.beasley@mrinz.ac.nz

If you want to talk to someone who isn't involved with the study, you can contact:

Independent Health and Disability Advocate
Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

Maori Health Support

Whanau Care Services, Wellington Hospital
Phone: (04) 806 0948
Email: wcs@ccdhb.org.nz

Health and Disability Ethics Committee (HDEC)
Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

Consent Form

MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

If you need an INTERPRETER, please tell us.

Please read the statements below, tick where there are boxes and sign at the end to indicate you consent to the following:

I have read, or have had read to me in a language I am fluent in, and I understand the Participant Information Sheet.	Yes ☐
I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐
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.	Yes ☐
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.	Yes ☐
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.	Yes ☐
I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐
I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, AstraZeneca 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.	Yes ☐
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.	Yes ☐
I understand the compensation provisions in case of injury during the study.	Yes ☐

I know who to contact if I have any questions about the study in general.	Yes ☐	
I understand my responsibilities as a study participant.	Yes ☐	
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw will continue to be stored and analysed.	Yes ☐	
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.	Yes ☐	No ☐
I wish to receive a summary of the results from the study.	Yes ☐	No ☐

The following statement will be added as applicable:

<<An electronic signature is equivalent to a wet ink signature>>

Declaration by participant:

I have read and agree to all of the above. I hereby consent to take part in this study.

Participant's name:

	Date:
Signature:	Time:

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:

	Date:
Signature:	Time: