INFORMATION SHEET

Title	The Efficacy of Metformin as an Adjunctive Treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia or schizoaffective disorder newly commenced on clozapine (CADENCE CoMET)
Sponsor	The University of Queensland
Coordinating Principal Investigator	A/Professor Dan Siskind
Principal Investigator	A/Professor Dan Siskind
Location	
Protocol	CADENCE CoMET

This Participant Information and Consent Form is 13 pages long. Please make sure that you have all of the pages.

Introduction

You are invited to take part in a multisite clinical trial (CADENCE CoMET). This is because your treating psychiatrist has previously given you a diagnosis of schizophrenia or schizoaffective disorder. The clinical trial is testing a new add-on treatment for those with schizophrenia or schizoaffective disorder who have been newly commenced on clozapine. Before you decide if you wish to consent to your participation we would like you to understand why the study is being done, what it will involve and how your information will be used. Please take time to read the following information carefully and if appropriate discuss it with friends, family and your doctor. One of our team will go through the information sheet with you and answer any questions you have. Please ask questions about anything that you do not understand or want to know more about.

Participation in this research is voluntary. You are free to refuse to participate without it affecting your current or future care. It is desirable that your doctor be advised of your decision to participate in this study. If you have a doctor we strongly recommend that you inform them of your participation in this study. Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate

that you understand the information and that you give your consent to participate in the clinical trial. You will be given a copy of the Participant Information and Consent Form to keep as a record.

What is the purpose of this study?

As you will be aware, one of the side effects of clozapine is weight gain. At present there is no known treatment to help with minimising weight gain for people newly commenced on clozapine. This trial is looking at whether a drug called metformin can help in minimising weight gain in people who are newly commenced on clozapine. Metformin is usually given to people with Type 2 diabetes mellitus to help control blood sugar levels when diet and exercise alone is not enough. Some psychiatrists have offered metformin to people starting clozapine with the hope it will reduce weight gain, but this has not been systematically studied. We want to investigate if giving metformin to people newly commenced on clozapine results in less weight gain than people who are just being treated with clozapine. Your participation in this trial will help to increase our understanding of how metformin may help persons experiencing illnesses similar to yourself.

Medications, drugs and devices have to be approved for use by the Australian Federal Government. Metformin is currently approved for treating Type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in control of blood sugar levels. However, it is not approved to treat weight gain in schizophrenia or schizoaffective disorder. Therefore, it is an experimental treatment and it must be tested to see if it is an effective add-on treatment for schizophrenia or schizoaffective disorder.

This research has been initiated by the Coordinating Principal Investigator, Associate Professor Dan Siskind who is employed at Metro South Hospital and Health Service and The University of Queensland. The research has been funded by a National Health and Medical Research Council (NHMRC) and Royal Brisbane and Woman's Hospital Foundation.

Do I have to take part in the study?

No, you do not have to take part in this clinical trial. It is voluntary. If you decide to take part you will be given this Participant Information Sheet and asked to sign the attached Consent Form. You will be given a copy to keep for your records. If you decide to participate you can change your mind at any stage without this affecting your routine treatment or future health care.

What does participation in the study involve?

For this trial we need the help of male and female participants aged from 18 to 64 with a diagnosis of schizophrenia or schizoaffective disorder who has received clozapine for a period of no more

than two weeks. This clinical trial involves multiple steps; you need to be able to complete all steps in order to participate in this trial.

You will be participating in an add-on double-blind randomised placebo-controlled trial. The word add-on for this clinical trial indicates that you can remain on your usual treatments and will take the trial medication *in addition* to your usual treatment. A placebo is a medication with no active ingredients. It looks like the real thing but is not. The term randomised means that you will be allocated into either the metformin or placebo groups completely by chance (flip of a coin). This clinical trial will randomise participants in a 1:1 design, which means there is an equal chance of being in either the metformin or the placebo group. You will be participating in a double-blind study. This means that neither you nor the research staff will know which treatment group you are in. However in certain circumstances the trial Doctor can find out which treatment group you are in. Continual review and oversight will take place regarding the efficacy and safety of the experimental products and this will allow early detection of any problems research participants may experience. By keeping you and the research staff unaware of which treatment you are on, and then comparing symptoms in patients on metformin versus placebo, we will be able to learn if metformin works in reducing the amount of weight gain. This type of evidence can help all patients to receive better treatments in the future.

At the completion of all participants in the study, participants will be notified which arm of the study they took part in.

Step 1 Screening Process

At first contact with a member of the research team, you will be asked to take part in a diagnostic screening process which will take about 1 hour. You can have a friend or family member present if desired during this initial contact. If this screening process confirms that you can take part in the study, you will be provided with the opportunity to enter the next phase of the study.

Step 2 Medication regime

You will be asked to take up to 2 tablets (2000mg) per day of either metformin or placebo as per allocated group. The dose will start at half a tablet (500mg) and will be gradually increased over three weeks as tolerated for a total of 24 weeks. You will remain on the maximum dose tolerated for the duration of the 24 weeks. The medication should be taken once a day at night with meals.

	Week1	Week 2 increase	Week 3 increase
Dose	Half tablet (500mg)	1 tablet (100mg)	2 tablets (2000mg)

Step 3 Contact

Contact with a member of the clinical trial team will be once weekly for the first 4 weeks and then monthly for the duration of the study.

All visits will be face to face. You will initially be seen in hospital or Community Care Unit and then on discharge seen in your own home. At each face to face visit, a member of the clinical trial team will conduct a series of physical and clinical assessments which will take approximately 1.0 hour to complete. This will involve asking questions about your mental and physical health including diet and exercise, measuring your blood pressure, height, weight and waist circumference and questions about your thinking, memory and problem solving skills.

Step 4 Blood sample

You will be asked to provide three blood samples over the course of the trial. It is not possible to participate in this trial without providing blood samples. Each blood sample will consist of twenty-five millilitres (1.5 tablespoons) of blood being collected from your arm. Where possible these blood samples will be collected at the same time as your routine clozapine blood tests.

Participation in the clinical trial is voluntary and you are free to refuse to participate without it affecting your current or future care. With your permission we would like to collect DNA from one of the scheduled blood samples in this trial. This collection of DNA from your blood is voluntary. It is okay to say no, you do not have to have your DNA collected if you do not want to. You can still participate in this trial without your DNA being collected. By agreeing to have your DNA collected, you are providing unspecified consent which means you are consenting to your sample being used for future ethically approved mental health research.

Will participating in the study cost me anything?

There are no additional costs associated with participating in this clinical trial. All medication, tests and medical care required as part of the study will be provided to you free of charge. To compensate you for your time and any inconvenience you will receive a $20 gift card at baseline, week 4, 8, 12, 16, 20 and 24 (total of $140 worth of Coles/Myer gift vouchers).

What will happen to my DNA sample?

The DNA blood sample you donate will be sent to the Queensland Brain Institute (QBI). DNA will be extracted directly from one of the blood samples collected during the study. If you choose to consent for your DNA to be stored for future research you are providing what is termed "unspecified consent" whereby you are consenting for your DNA to be used for any future mental

health research for which ethical review will be obtained. With your consent, your DNA may be used indefinitely by scientists at the University of Queensland and/or Queensland Health conducting ethically approved research health related research topics.

Storage and disposal of your DNA sample

The DNA we retain will be stored in the laboratory at the Queensland Brain Institute and can only be accessed by authorised staff. Any results of the analyses (including the analysis of genes) will be published as combined data, and will not be individually identifiable. They will be stored with your initials and participant number so that they are not identifiable while being stored. The master list of your name and participant number will be stored in a secure separate location.

Future studies with the intention to use your stored blood samples will require approval from a Human Research Ethics Committee before they can be undertaken. If you consent to providing a blood sample for future research but decide at a later date you would like your sample destroyed you may contact a member of the clinical trial team listed and this will be carried out.

We plan to keep your blood indefinitely. Other data collected from you will be stored for up to 15 years or the maximum time frame as determined by local regulations, whichever is the longest. After this time it will be destroyed.

What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this clinical trial; however you will be helping the research community test if metformin is be an effective 'add-on' treatment to reduce clozapine weight gain. The benefit of metformin cannot be promised, nor can the chance of benefit be accurately predicted. Participants usually find the tasks interesting, and enjoy being able to help advance our knowledge of better treatments.

What are the possible risks and disadvantages of taking part?

There are some possible adverse effects or risks related to participation in this clinical trial which include:

(a) Very occasionally, talking about mental illness can be upsetting. If by chance the interview causes you discomfort, the interview will be stopped and support provided by a member of the clinical trial team to ensure your well-being. If you indicate a potential for self-harm or other serious risk, a member of the clinical trial team will report these responses immediately to the treating clinician.

(b) Clinical Assessments. The main inconvenience is the time spent completing these tasks. If you find the testing tiring, you can ask for a break, or complete this task over several sessions.

(c) Blood test. Complications associated with blood sampling are infrequent and minor, and may include local bruising and inflammation at the site of needle entry. Persons drawing blood have been trained in blood sampling techniques to minimize these complications.

(d) Medical side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. Some of the side effects are common so if you have any of these side effects, or are worried about them, talk with a member of the clinical trial team. A member of the clinical trial team will also be looking out for side effects and will discuss any problems with you at each face to face contact.

Side effects of metformin may include; nausea, vomiting, diarrhoea, abdominal pain and taste disturbance. There is also an uncommon potential for decreased vitamin B12, and a rare incidence of lactic acidosis (excessive acid in the body) and skin rashes. Lactic acidosis can also occur as a result of overdose of metformin and may in rare cases be life-threatening. Tell the member of the clinical trial team immediately about any new or unusual symptoms. The clinical trial team member will discuss the best way of managing any side effects with you and whether or not you should continue in the clinical trial.

The effects of the dose of metformin used in this study on the unborn child and on the newborn baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the study project. You must not participate in this clinical trial if you are pregnant, or trying to become pregnant, or breast-feeding. If you are female and becoming pregnant is a possibility, you will be required to undergo a pregnancy test prior to starting the clinical trial. If you are male, you should not father a child or donate sperm one month after last dose of clinical trial medication.

Both male and female participants are strongly advised to use birth control (chemical e.g. oral contraceptive pill or barrier e.g. condom) during the course of the clinical trial.

If you do become pregnant whilst participating in the clinical trial you should advise a member of the clinical trial team immediately. Your trial clinician will withdraw you from the clinical trial.

What if new information becomes available?

Sometimes during the course of a clinical trial, new information becomes available about the treatment that is being studied. This new information may mean that you can no longer participate in this research. If this occurs, the person supervising the research will stop your participation.

If new information does become available regarding metformin, you will be contacted to discuss whether you want to continue in the study. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information your trial clinician might consider it to be in your best interests to withdraw you from the trial. In all cases, you will be offered all available care to suit your needs and medical condition.

Can I have other treatments during this study?

You will be able to remain on all of your current treatments whilst participating in the trial. It is important to tell a member of the clinical trial team about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, or other alternative treatments. You should also tell a member of the clinical trial team about any changes to these during your participation in the clinical trial to ensure your well-being and suitability to participate. It is essential that you are completely truthful regarding your health history and any symptoms or reactions you may experience during the trial to ensure your wellbeing. Your medical assessment and treatment will in no way be altered by your decision whether or not to take part, or by your answers to the questions. No additional tests, investigations or treatment will be involved other than those already described.

What do I do if I wish to withdraw from the study?

Your participation in this clinical trial is voluntary. You may choose not to participate, or you may decide to withdraw your consent and discontinue your participation from this trial at any time without affecting current or future care. If you wish to withdraw from this study please advise the clinical trial team. You will be asked to complete and sign a "Revocation of Consent' form. This will be provided to you by the clinical trial team. If you wish to withdraw your consent, please notify a member of the clinical trial team immediately who will arrange a visit.

As part of consenting to this clinical trial, you agree that the data you provide will be used for the clinical trial if you decide to withdraw. If you consent to the collection of DNA and withdraw from the study, you may ask for your DNA to be destroyed.

Could this study be stopped unexpectedly?

This clinical trial may be stopped unexpectedly for a variety of reasons. These may include reasons such as: unacceptable side effects, the drug being shown not to be effective for reducing clozapine associated weight gain in schizophrenia or schizoaffective disorder, and the drug being

shown to work, and not needing further investigation. The trial clinician may end your participation in this clinical trial for any reason that they may feel is appropriate. These may include, but are not limited to, injury, pregnancy, a medical condition which may place you at risk of further complications if you continue to participate, failure to take the medication as instructed, or termination of the study by the investigators or for other administrative reasons.

What happens when the study ends?

Once the study is completed, the results will be grouped together and comparisons will be made between the metformin and placebo groups. These comparisons will be based on averages of each group and the results will not be able to identify any individual person. These results will be published in a scientific journal and presented at scientific and community forums. You will be provided a summary of these results including notification of which group of the study you took part in (metformin or placebo). It is important to note that notification of which group you took part in cannot be made until ALL of the participants have completed the study.

What will happen to information about me?

Any information obtained in connection with this clinical trial that can identify you will remain confidential and will only be used for the purpose of this clinical trial and it will only be disclosed with your permission, except as required by law.

The information collected is classified as re-identifiable. This means that details that identify you have been removed from the information (by replacing this information with a code), but that is possible to link the code back to you if necessary. The code will be stored separately from the data. The information collected from you in this clinical trial will be entered into a database, using the code rather than your personal identifiable details. However, the clinical trial team, regulatory authorities, and Metro South Human Research Ethics Committee (HREC) and site Governance, will be able to inspect and have access to confidential data that identifies you by name. Any analysis, interpretation and publication of the study results will not identify you.

The paper files from your interviews will be stored in locked filing cabinets in a dedicated research office. Computer files will be kept on a password-protected computer at each designated site (which has high level security). Only approved clinical trial staff, Metro South Human Research Ethics Committee, site Governance and the Therapeutic Goods Administration may access your data. Records relating to the results of the trial will be kept for 15 years. After the 15 year period your paper records will be shredded and destroyed and computer files deleted.

We may seek to review your health outcomes in future years via your medical records and Health Research Databases (e.g. Australian Institute of Health and Welfare). Should this occur, this will require approval from a Human Research Ethics Committee, and will not involve recontacting you personally. It will only involve your medical records or electronic health files.

How can I access my information?

In accordance with relevant Australian and/or Queensland privacy and other relevant laws, you have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named in the question section of this document if you would like access to your information.

What if something goes wrong?

In the event that you suffer an injury as a result of participating in this trial, hospital care and treatment will be provided at no extra cost if you elect to be treated as a public patient at a public health service.

Who is organising and funding the study?

This clinical trial is being sponsored by The University of Queensland and the conduct of the clinical trial is overseen by the Coordinating Principal Investigator Associate Professor Dan Siskind. The study has been funded by the National Health and Medical Research Council (NHMRC) and Royal Brisbane and Women's Foundation.

Who has reviewed the study?

All research in Australia involving humans is reviewed by an independent group of people, called a Human Research Ethics Committee (HREC). This clinical trial has been reviewed and given approval by Metro South Human Research Ethics Committee and site Governance.

How do I get more information?

You should ask for any information you want. If you would like more information about the study or if there is any matter about it that concerns you, either now or in the future, do not hesitate to ask one of the members of the clinical trial team or your doctor. Before deciding whether or not to

take part you may wish to discuss the matter with a relative or friend or with your doctor. You should feel free to do this.

If you have any questions about the study at any time, feel free to contact the researchers

A/Prof Dan Siskind	33171040
Andrea Baker	3271 8662
Toll free	1800 682 699
Fax	3271 8682
Email:	andrea_baker@qcmhr.uq.edu.au
	d.siskind@uq.edu.au

Postal Address QCMHR, The Park - Centre for Mental Health
Locked Bag 500 ARCHERFIELD BC QLD 4074

Ethical Guidelines and Independent Contact

This study has been approved by Metro South Human Research Ethics Committee and local site Governance, which is an appropriately constituted HREC under the National Health and Medical Research Council of Australia.

If you have any complaints about any aspect of the clinical trial, the way it is being conducted or any questions you can contact the HREC Coordinator, Metro South Human Research Ethics Committee on 3443 8047 (phone); or EthicsResearch.PAH@health.qld.gov.au (email). All complaints will be treated in confidence, investigated fully and you will be informed of the outcome.

Participant Consent Form

Study Title The Efficacy of Metformin as an Adjunctive Treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia or schizoaffective disorder newly commenced on clozapine (CADENCE CoMET)

- I have read (or had read to me), the Information Sheet and I understand the purpose of the clinical trial, what is involved, what data is being collected, any possible risks, inconveniences or discomforts involved, and what will be done with the data upon completion of the clinical trial.
- I have been given the time and opportunity to ask questions about the clinical trial and any questions I have asked have been answered clearly and to my satisfaction. I have also been given the opportunity to discuss this clinical trial with a person not connected to the clinical trial.
- I understand that all information provided by me is treated as strictly confidential and will only be shared with the clinical trial team and not be released by the clinical trial team unless required to do so by law.
- I agree that research data gathered for the clinical trial can be published as long as my name, or any identifying data, will not be used in any publication.
- I know that I may withdraw from the trial at any time without having to give any reason or affecting my current or future medical treatment.
- I understand I will receive a copy of the participant information and signed consent form to keep.
- I understand and consent to those regulatory authorities and other organisations referred to in the participant information having access to my confidential information.
- I agree to participate in this research and give my consent voluntarily.
- I understand that participating in this clinical trial requires three blood samples
- I understand a member of the clinical trial team will notify my primary physician (provided that such a physician can be identified for the participant) and treating Psychiatrist of my participation in the study.

In addition: (initial next to your response)

- I give permission for a member of the clinical trial team to recontact me within the next 5 years regarding possible participation in further mental health research. Yes No
- I give consent for my DNA to be collected at one of the three scheduled blood draws and stored indefinitely for the purpose of use in future unspecified mental health research for which ethical review will be obtained. Yes No

- I give consent for the research team to review my health outcomes via my medical records (paper and electronic) and Health Research Databases during the course of the current study. Yes No

_____	_____
Printed Name of Participant	Initial
_____	_____
Signature of Participant	Date (participant to date)

REVOCATION OF CONSENT FORM

Full Project Title: The Efficacy of Metformin as an Adjunctive Treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia or schizoaffective disorder newly commenced on clozapine (CADENCE CoMET)

I hereby wish to WITHDRAW my consent to participate in the clinical trial described above and understand that such withdrawal WILL NOT affect my current or future treatment.

As part of my original consent I agreed that my data would be used as part of the study, regardless of my decision to withdraw. However I have provided a blood sample and request that my sample be (initial all that apply):

- used for the purposes of this research project and/or;
- stored for future use as outlined in the participant information sheet
- destroyed after use for this research project
- destroyed immediately and not used for this research project or for future research projects

Participant's Name (printed) ……. Initial ……..

Signature…… Date……

Researcher's Name (printed)…….

Signature…… Date……