Testosterone Intervention for the Prevention of Diabetes Mellitus in High Risk Men

PARTICIPANT INFORMATION & CONSENT FORM

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Study Title: A multi-centre double-blind, randomised, placebo-controlled trial to determine the efficacy of testosterone treatment together with a lifestyle program to prevent progression to type 2 diabetes mellitus in men with pre-diabetes and relatively low testosterone levels in comparison to a lifestyle program alone (T4DM).

You are invited to take part in a research study, called the T4DM trial. You have already provided a blood sample which has shown that you have lower testosterone and pre-diabetes and thus you may be eligible to enrol in this study, subject to further screening tests by the study doctor.
Please read the following information carefully and ask your study doctor if there is anything unclear or if you would like further information.

What is the purpose of this research?
The T4DM trial is a research study which aims to find out whether testosterone in combination with a lifestyle program is better in reducing the chance of developing Type 2 diabetes in men with lower testosterone levels and pre-diabetes, compared to men in a lifestyle program alone. The testosterone is given as an injection. While testosterone has been used for many years for patients who have conditions which prevent the body making sufficient of its own testosterone, this is an experimental study as testosterone has not been approved for the treatment of men with pre-diabetes. The current standard treatment for men with pre-diabetes is lifestyle change.

Why have I been asked to take part?
You have been asked to participate in this study because recent blood tests indicate that you have a raised fasting blood glucose level (classed as pre-diabetes) and a lower than normal testosterone level. This study will enrol approximately 1490 participants from 6 hospital clinics across Australia.

Why Testosterone?
Testosterone is a male hormone that is prescribed for the treatment of men who have conditions which prevent the body from producing sufficient of its own testosterone. Low levels of testosterone are associated with a higher risk of developing Type 2 diabetes. Men with pre-diabetes are also at higher risk of developing the disease. It is not known whether testosterone treatment will prevent Type 2 diabetes. In this study we are investigating whether pre-diabetic men with lower testosterone levels who have been given testosterone injections every 3 months for a minimum of 2 years, have a better chance of stopping the development of Type 2 diabetes compared to those given a placebo (a dummy treatment that looks like the genuine medicine but contains no active ingredient). All participants in the study will be asked to participate in a lifestyle program co-ordinated by Weight Watchers.

Who is running the study?
The study has been designed by doctors in Australia and is being conducted at their hospitals with the support of the University of Adelaide and the NHMRC Clinical Trials Centre. It is being funded by a research grant from the National Health and Medical Research Council (NHMRC). The study medication is provided free of charge by Bayer, a pharmaceutical company. The lifestyle component of the study is provided free of charge by Weight Watchers.

Do I have to take part?
Participation in this research trial is completely voluntary. It is your decision to participate or not. If you do not wish to participate, your medical care will not be affected in any way.
If you choose to participate, you will be asked to sign the consent form. You will be given a copy of this form to keep.
You will be free to stop taking the study treatment if you wish, or to withdraw completely from the trial at any time and without giving a reason. Withdrawal will not affect the ongoing medical care you will receive from your doctors. This study is not a substitute for your own primary medical care from your own doctor(s).

What will happen to me if I take part?
If you decide to participate you will undergo some additional procedures to check to see if you are eligible for the study. This will be done at your initial clinic visit and you will be required to fast from midnight and attend the clinic between 07:00 and 10:00 AM, the next morning.

Initial Visit: At the initial visit we will undertake a number of processes.

Firstly, we will conduct further screening to confirm that you are eligible for the study. The screening process will involve:

- Asking questions about your medical history and details of all medicines you are currently using (including prescription and over the counter medicines, including vitamins/dietary supplements).
- Physical examination, which includes a digital rectal examination. The digital rectal examination is a safety requirement of the study to confirm that you do not have an abnormal prostate as testosterone treatment cannot be used for men with prostate cancer.
- Height, weight and waist measurements.
- Your blood pressure and pulse rate will also be checked.

It is possible that, after all the screening tests and all your information has been reviewed, you will not be able to take part in this study. If this happens, the study team will make suggestions for you to obtain further medical care through your own doctor(s). We will provide the information regarding the outcome of the testing to you as well as your doctor/s if you permit.

If you are eligible for the study and consent to participate, your initial visit will also include the following assessments and procedures so that you can be enrolled onto the study and commence study treatment:

- You will be asked to complete quality of life and psychosocial questionnaires, as well as questionnaires about urinary and sexual function. You should complete these as accurately as possible and complete all required questions. It is estimated that it will take approximate 15-20 minutes to complete the questionnaires.
- A hand grip assessment will be conducted. This involves gripping a device called a dynamometer for 3-5 seconds. The test is done 3 times on each hand. It is not painful or invasive.
- You will be provided with information regarding the lifestyle program including directions on how to enrol. You will have the opportunity to either attend a weekly Weight Watchers group of your choice or enrol in the online program and we encourage both. Weight Watchers provides exercise and dietary advice to help you lose weight.
- Blood samples will be taken for insulin, glucose, and to measure markers of diabetes and blood fats, sex hormone and for DNA testing. For more information on this biomarker and

DNA testing please refer to pages 6 and 7 of this information sheet. (Approximately 50ml of blood will be collected in total).

- You will be booked in for a Dual Energy X-ray Absorptiometry (DEXA) Scan which measures bone density, and the amount of fat and muscle in the body. This can be done up to 14 days after you start treatment. You will need to attend a local scanning facility. It will involve lying on a padded table for approximately 20 minutes while the scan is performed. The scan is a type of X-ray and is not painful or invasive. The DEXA scan exposes you to radiation at a level that is less than you would be exposed to on a 1-hour aeroplane flight.

You will then be prescribed the study treatment which will be determined by chance (like tossing a coin) so you have an equal chance of receiving either:

- Testosterone injection in combination with a lifestyle program or
- placebo injection plus a lifestyle program

A placebo is a dummy treatment that looks like the genuine medicine but contains no active ingredient.

You, your study doctor, and the study staff will not know which treatment you are receiving. This is called a double blind study.

After your initial visit, you will need to come to the hospital 6 weeks later and then every 12 weeks for further injections of the study treatment which will be given by a qualified health professional and delivered by a very slow intramuscular injection into the muscle of your buttocks.

You will be asked to remain in the study for a minimum of 24 months unless you are unable to tolerate the study drug or your study doctor determines that you should begin another treatment or you decide to stop participating in the study.

Ongoing study visits (weeks 6, 18, 30.. etc): Each visit will last about 1 hour These visits will involve:

- Physical measurements being taken (including weight, blood pressure & pulse rate, waist measurements)
- Questions about the lifestyle program and any changes in your health, any side effects or changes to medications since your last visit
- Approximately 10 ml of blood taken for glucose testing.

At every second visit you will need to fast (not eat or drink anything except water) from midnight the night before the appointment and attend the clinic before 10.00 AM so that fasting bloods can be collected. These blood tests will be collected to check on the safety of your participation (haematology, biochemistry, insulin), as well as for exploratory & lipid biomarkers and sex hormone tests (approximately 50ml in total)

At the alternate (non-fasting visit) a hand grip assessment will be conducted and you will be asked to complete quality of life, psychosocial, urinary and sexual function questionnaires. This will take approximately 15-20 minutes. Approximately 5ml of non-fasting blood will also be collected to measure your blood sugar levels over the previous 3 months.

At 24 months you will have a repeat DEXA scan.

If at any time during the study your blood results indicate an increasing blood sugar level, then a repeat oral glucose tolerance test (OGTT), like the one during pre-screening, will be performed. You will be required to have a repeat OGTT at 24 months or prior if you withdraw from the study early. You will be asked to fast from midnight the night before the OGTT. At the OGTT you will be asked to drink a liquid containing a certain amount of glucose. A blood sample will be taken

before you do this and again at 60 and 120 minutes after you drink the solution. The OGTT takes up to 3 hours and 12mls of blood will be collected.

Unless you, or your doctor, decide to stop treatment early, you will receive 2-4 years of study treatment. We expect that participants will receive an average of 3 years treatment. The duration of your treatment will depend on when you are enrolled in the study. Your doctor will inform you when your treatment will cease.

After the visit where you receive your last injection of study drug you will need to attend two more visits at 3 months and 6 months after the last injection, to assess your health and well-being after treatment has been completed.

End of Study (3 months and 6 months after last injection of study drug): The following assessments will be performed:

- Blood pressure, pulse, weight, waist circumference
- Hand grip assessment (performed at the 3 month visit only if it was not performed at the previous visit, always performed at the 6 month visit)
- Blood will be collected for biochemistry and haematology and for Insulin, Exploratory Biomarkers, Sex Hormones and Lipid Biomarkers testing. Approximately 10ml of blood will be collected at the 3 month visit and 50ml will be collected at the 6 month visit.
- Review of lifestyle program and any change in health, any changes to your medications or side effects, since your last visit
- An OGTT will be performed3 months after you receive your last administration of study drug.
- You will also be asked to complete quality of life, psychosocial, urinary and sexual function questionnaires. This will take approximately 15 – 20 minutes.

Other medication: When you start the study medication, it is important to avoid some other medications which could interfere with testosterone. At study start your study doctor will instruct you about medications you should not take. Please contact your study doctor before taking any new medications.

What happens at the end of the study?
At the completion of the study your doctor will discuss your condition with you and recommend the appropriate treatment. Study treatment will not be available after the study finishes.
After the completion of the study we would like to continue to follow your health status. We will continue to contact you or your general practitioner periodically by telephone or through a questionnaire to check on your on-going health.
We may also periodically contact the Australian Institute of Health and Welfare (AIHW) to request updated information from them on your health status if we are unable to contact you directly.

What are the possible benefits of taking part?
All participants will have the opportunity to involve themselves in a lifestyle program co-ordinated by Weight Watchers. Whether you are assigned testosterone or placebo, you will have access to regular follow-up and care by the study medical team and nursing staff. The results of this trial will contribute to medical knowledge, and if positive, impact on the medical management of pre-diabetic male patients.

What are the possible disadvantages and risks of taking part?
All medical treatments involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions,

you might develop medical complication from participating in this study.
Although testosterone injection is a routinely prescribed medicine, side effects may occur in some people. The most frequently reported side effects are acne or pain at the injection site, and cough may occur for a short time following an injection.
Very common side effects (reported in more than 50% of patients treated with testosterone injection): Temporary reduction in sperm count. This effect is reversible but may take months to wear off completely. If you plan to father a child over the next year, we recommend that you do not take part in this study. Although your fertility may be temporarily reduced by participating in this study, this cannot be considered as a replacement for reliable contraception. The treatments in this study are not expected to have any detrimental effect on your sexual function.
Common side effects (reported in less than 10% of patients treated with testosterone injection) include: an increase in red blood cells, weight increase, an increase in prostate specific antigen value (prostate hyperplasia) and the occurrence of hot flushes.
Uncommon side effects (reported in less than 1% of patients treated with testosterone injection) include: difficulty in passing urine, unwanted increased sex drive, depression / nervousness / irritability, muscular pain, unwanted priapism (frequent or prolonged and painful erections), changes in liver function tests and jaundice (yellowing of the skin).
Rare side effects which have been reported with testosterone use include 'pins and needles', increased blood pressure, diarrhoea, increased lipids in the blood & painful, tender or enlarged breasts.

If you feel unwell or may have a side effect, please contact your own doctor or the doctor or nurse at your study site.

A study conducted in Boston and reported in 2010 was stopped early because of an increased number of heart attacks, strokes and worsening heart failure in the men being treated with testosterone. This has not been seen in any other study of testosterone. If anything, other studies have found that testosterone treatment decreases the risk of cardiovascular events like those listed above. The men in the aforementioned study were frail, and many already had heart problems. As part of the screening process we have checked to make sure that you do not have heart problems.

We do not expect you to experience an increased risk of heart problems as a result of taking part in this study. In fact we hope that the lifestyle program, combined with low dose testosterone or placebo and regular monitoring of your health may decrease your risk.

Other risks and discomforts
You may have some minor discomfort associated with the blood tests required, for example, you may have pain or bruising due to the needle. Fainting and local infection can also occur when blood is taken, although these are rare.

When having the OGTT some people may experience some nausea when drinking the glucose and occasionally as the blood glucose levels fall toward the end of the test some light headedness and or sweatiness.

You may feel slight, momentary discomfort during the digital rectal examination and some embarrassment.

This research study involves exposure to a very small amount of radiation due to the two scheduled DEXA scans. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) per year. The effective dose from this study is about 0.002 mSv. At this dose level no harmful effects of radiation have been demonstrated as any effect is too small to measure. The risk is believed to be minimal.

Disqualification from elite sports
If you participate in any elite competitive sports which require urine doping tests as required by the World Anti-Doping Agency (WADA), participation in this study could lead to your disqualification for up to a year after the end of the study.

Implications for men who undertake workplace drug testing for anabolic steroid use
If you are working in any job which requires urine drug testing (such as for anabolic steroids), the use of testosterone in this study may be detected for at least 6 months after this study.

Will taking part in this trial cost me anything and will I be paid?
Participation in this trial will not cost you anything and you will not be paid.

What if new information arises during this research trial?
During the research trial, you or your legally acceptable representative will be informed of any significant new finding that may develop during the course of the trial, which might affect your willingness to continue participation.

How will I be informed of the results of this research study?
Your doctor will inform you about your own results where relevant. Results of the study will be provided to you directly on request from the study team.

Data describing the outcome of the study will be available to participants on the Australian and New Zealand Clinical Trial Register website, in press releases and in research articles published in peer reviewed journals.

What will happen to the results of the research trial?
The results of the trial will be published in medical journals. This will be done anonymously using grouped data. Under no circumstances will your personal details be disclosed as part of this publication.

Could this research be stopped unexpectedly?
This research study may be stopped for a variety of reasons (e.g. if the treatment causes unacceptable side effects), a decision by local regulatory / health authorities, or study Steering Committee.

Your study doctor may end your participation in this study if a side effect or medical condition occurs which may place you at risk of further complications if you were to continue participating, or if you do not follow your study doctor's directions during the study.

Your rights
If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment. Treatment for the injury or complication will be provided free-of-charge at a public hospital.

Every reasonable precaution will be taken to ensure your safety during the course of the study. In the event that you suffer any injury as a result of participating in this research project, hospital care and treatment will be provided at no extra cost to you.

Will my taking part in the trial be kept confidential?
Nursing and medical staff involved in your care will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will not be disclosed without your permission, except as required by

law.

Your personal details will be held by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre. This information will be held securely and confidentially. Authorised representatives of the Clinical Trials Centre may contact you to obtain follow-up information if the site staff are unable to contact you.

Your health records and any information obtained during the study may be examined by authorised representatives of the hospital's Human Research Ethics Committee, the study sponsor, University of Adelaide, or by regulatory authorities such as the Australian Government's Therapeutic Goods Administration (TGA) or as required by law, for the purposes of verifying the study procedures or data. By signing the Consent Form, you authorise access to this confidential information to the relevant study personnel and regulatory authorities as noted above.

You will also be asked to sign a consent form allowing the Clinical Trials Centre to collect data from Medicare about your hospital admissions and use of other healthcare services during the study. This information will remain confidential and will not be disclosed without your permission, except as required by law. We may also request your updated contact details from the Health Insurance Commission (HIC) if we are unable to contact you directly.

What will happen if I don't want to carry on with the trial?
Participation in this study is voluntary. You can withdraw from the trial at any time without loss of benefits to which you would otherwise be entitled. If you do decide to withdraw from taking the study treatment and from your follow-up visits, we will keep the information we have already collected about you. If you decide to stop taking the study treatment we would still like to see you at the regular 6-monthly visits to check on your health. If you decide to withdraw from the study, please notify the research team.

Involvement of the General Practitioner/Family doctor (GP)
We ask that you notify your GP of your participation in this trial. In addition we are asking you to provide consent for your study doctor to inform your GP of your involvement in the study and of any concerns about your welfare and ongoing care that your study doctor may have, if required.

What are biomarkers?
Biomarkers are substances that may be found in blood and may be used to measure or indicate the effects or progress of a disease or condition. Identifying markers is important because they may be linked with disease or they may help to identify people most likely to be helped by the study treatment. As part of the study, we will collect and store samples of your blood for biomarker studies.

What is DNA testing?
Genes contain the instructions for making living organisms and are made up of DNA. Your genes contain information about characteristics of you as an individual. Most DNA sequences are identical among human beings, but the small variations we all have in our DNA sequences may explain why there are subtypes of disease and why individuals have different responses to the same drug. There is no genetic testing planned for the purposes of determining your personal susceptibility to disease or changing your diagnosis. A sample of your blood will be collected for DNA for future testing for research purposes.

What will my biomarker and DNA blood samples be used for?
Your blood samples will be used to study the known and yet to be identified genes and biomarkers involved in the regulation of blood sugar and fat, sex hormones and inflammation and how these genes interact with each other. They will also be used to investigate androgen action

on other important target tissues such as muscle, bone and reproductive organs. The research is experimental and not suitable for guiding decisions about your treatment. Your individual results from these studies will not be made available to you.

Your sample(s) will be stored securely at a central laboratory and identified by your unique study number. Researchers will not link your blood samples to your personal identifying information. You will retain the right to have your sample(s) destroyed at any time by contacting your study doctor. If you decide to have your samples destroyed, any data or analyses that were done before the request cannot be removed; however, no additional analysis will be done on your sample(s), and all of your remaining sample(s) will be destroyed. You will not benefit financially if this research leads to development of a new treatment or medical test.

Contact Details:
If you require further information or if you have any problems concerning this study (for example, any side effects), you can contact the principal investigator or study staff. To find out who to contact please call the T4DM coordinating centre on 1300 865 436.

Contact details if you have concerns about the conduct of the study:
This study has been approved by the Sydney Local Health District Human Research Ethics Committee - CRGH. If you have concerns or complaints about the conduct of this study, you should contact the Executive Officer who is the person nominated by the Human Research Ethics Committee to receive complaints from research participants. You should contact them on 02 9767 5622 and quote HREC/12/CRGH/79.

Thank you for considering taking part in this research study.
This information sheet is for you to keep.