Department of Medicine
Clinical Research Centre
Level LG, Building 507
Faculty of Medicine and Health Sciences
Private Bag 92019
Auckland 1142
New Zealand
Telephone 64 9 923 1482
Email: shirley.ward@auckland.ac.nz

PARTICIPANT INFORMATION SHEET

Combination T4/T3 trial for hypothyroidism

Principal Investigator: Dr Mark Bolland, Faculty of Medical and Health Sciences, University of Auckland.

Contact person: Shirley Ward. Ph 923 1482

Invitation

You are invited to take part in a study to determine whether combination treatment with two thyroid hormones liothyronine (T3) and thyroxine (T4) for hypothyroidism is better than the standard treatment which is thyroxine (T4) alone. 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 do want 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. We expect this will take about 15-30 minutes. You may also want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

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.

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

Voluntary participation and withdrawal from this study?

Your participation is entirely voluntary (your choice). You do not have to take part in this study and if you choose not to take part it will not affect any future care or treatment.

If you do agree to take part you may withdraw from the study at any time without having to give a reason, and this will in no way affect your future health care. Participation in this study will be stopped should any harmful effects appear or if the study doctors feel it is not in your best interests to continue.

Why are we doing the study?

Hypothyroidism (underactive thyroid) is a common condition that affects up to 10% of older people. The standard treatment is thyroxine (T4). However, about 10% of people who take thyroxine continue to have symptoms that might be due to hypothyroidism and are dissatisfied with their

treatment. There are a number of reasons to think that this might because levels of the most active thyroid hormone, T3, are too low, but simply increasing the T4 dose might actually make the situation worse.

Some clinical trials of adding T3 to T4 treatment have been done. Most trials have not shown a clear effect of combination treatment over T4 alone. However, many of the trials have not been done in people who are actually likely to benefit, using the best possible doses of T3, and assessed outcomes that matter to patients. Furthermore, all the trials so far have been analysed using groups rather than individuals. This means the trial can answer whether a group of people benefit or not, but they don't rule out the possibility that some members of the group might have had substantial benefits. So, the question as to whether T4/T3 might be better than T4 alone for some people currently still remains unresolved. Combination T4/T3 is used commonly in some countries, especially for people dissatisfied with T4 treatment, but T3 is not funded in New Zealand, and is used only occasionally by people who self-fund the T3 treatment. Some people take products called "whole thyroid extract" (or similar) in an attempt to use combination T4/T3, but such products do not have the optimum balance of T4 and T3.

It is possible that using combination T4/T3 might be better for some people with hypothyroidism, particularly if they have ongoing symptoms despite taking T4 regularly and having thyroid function tests that lie in the normal range.

What are the aims and design of the study?
We plan to study whether combination T4/T3 is better than T4 by itself for individuals who are dissatisfied with T4 alone, and analyse the results at an individual level (ie whether each person benefited or not, rather than whether the whole group benefited or not). If combination T4/T3 treatment improves symptoms of hypothyroidism better than standard T4 treatment, this would become the new standard treatment. On the other hand, if combination treatment is not better than standard treatment, we could conclude this definitively meaning that clinicians and patients would know that this treatment is ineffective, and that patients would not benefit from taking it.

<u>Study design</u>

- The study does involve periods of taking inactive (placebo) treatment.
- First, participants will be changed to a standard dose of a commonly prescribed brand of thyroxine (that will be used throughout the study) for four weeks. This is to make sure that participants have no issues with the study brand of thyroxine.
- Participants will then take either combination T4/T3 treatment or T4 treatment with an inactive (placebo) treatment for eight weeks. The decision as to which treatment will be made randomly (i.e. by chance) to
- Each of the eight week "treatment periods" will be followed by a "washout" period where the participant takes T4 alone for four weeks. This is to give time to allow the effects of the treatment to wear off.
- There will be four treatment periods of eight weeks in the study. By the end of the study, each participant will have received T4/T3 for two treatment periods and T4/placebo for two treatment periods.
- The treatment periods with placebo are important features of the study design because they allow a comparison for each individual of the periods where T4/T3 were received to the periods with T4/placebo. This comparison allows us to determine whether adding T3 is actually helpful for each individual.
- All participants and study staff do not know what treatment is administered (ie T4/T3 or T4/placebo) so that bias is not introduced.
- The total duration of the study for each person is one year.

Who designed and funded the study?
The study was designed by Associate Professor Mark Bolland and colleagues in the Department of Medicine and is funded from a HRC fellowship that he holds. No commercial companies are

involved with the design or funding of the study, and the sponsor of the study also is not involved with the design of the study.

How are participants selected?
We would like to enrol 25 people aged over 18 years with hypothyroidism confirmed on blood tests who have ongoing symptoms of hypothyroidism despite having thyroid function blood tests that lie within the normal range. Only individuals who meet these criteria will be eligible to take part. We will invite people to take part through advertisements and invitation letters given to relevant clinicians to pass on to patients who they think might be interested.

What would your participation involve?

- People who express an interest in the study will be sent a screening information sheet, consent form, and a questionnaire that collects information regarding their health in general, and a specific questionnaire related to hypothyroidism. You will also receive a detailed information sheet about the study.
- If interested, you will return the screening consent form and questionnaire, and your results will be discussed with you.
- At any time during this screening process, you can discuss the study with the study questions or ask them any questions you have about it.
- If eligible to take part, you will be sent a blood test form to check your thyroid tests, and your results will be discussed with you.
- If you meet criteria for study entry, you would be invited to come to the Clinical Research Centre, Faculty of Medical and Health Sciences, 22-30 Park Ave, Grafton, Auckland) to discuss and take part in the study. This visit will take approximately 30 minutes.
- The study takes 52 weeks.
- Each 2 weeks you would be asked to fill in the questionnaire about symptoms of hypothyroidism.
- For the first four weeks, you would be asked to change from your regular T4 medication to the brand we will be using during the study. This is called the “run-in” period.
- After the run-in is complete, you will have a treatment period of eight weeks followed by a wash-out period of four weeks.
- This cycle of treatment then washout period will occur four times in total, giving a total time of 52 weeks.
- During each treatment period, you will take T4 tablets and T3/placebo tablets, as directed. Generally, it will be one or two T4 tablets each morning, and one or two T3/placebo tablets twice daily.
- During each washout period, you will return to the previous T4 treatment.
- Blood tests to monitor your thyroid function and allow dose adjustments will be taken regularly. They will be taken prior to study entry, then at the beginning, after 2 weeks, after 4 weeks, and at the end of each treatment period, and at the end of the study. In total, there will be 18 blood tests during the study. No blood samples will be stored as part of the study.
- There will be a total of 13 visits during the 52 weeks of the study, 9 of these will be face-to-face visits, and 4 are optional phone call/face-to-face visit depending on participant preference. Each visit will take less than 30 minutes.
- We expect the study to commence in late 2021, and will be completed by late 2023.
- Your GP will be informed of your participation and results, if you agree to this.
- You will be issued a card to confirm your participation in the clinical trial. This card should be presented at the time of any medical treatment received during your participation in the trial.

What are the possible risks of taking part?
The only costs will be those incurred in travelling to the University of Auckland for the visits. Free parking is available on-site. Costs of public transport will be reimbursed.

T3 (liothyronine) is a medication that has been available for many years. There are no safety concerns relating to its use. There is a potential risk of side-effects of T3 if the dose is too high or

too low and causes your thyroid levels to be too high or too low. These side-effects would be similar to those if your thyroxine dose was too high or too low. In the study, your thyroid levels will be closely monitored so it would be unlikely that your thyroid levels would get too high or too low. If your thyroid levels are mildly high, most people have no symptoms but some people develop rapid heart beat, a feeling of shortness of breath, a tremor, lose weight or feel fatigued and generally unwell. If the thyroid levels are too low, most people have no symptoms but some people feel fatigued and generally unwell.

Blood tests involve the minor discomfort of the needle insertion and sometimes there is a small bruise.

What are the possible benefits?
There may be no benefit in you taking part in this study. People taking part might get benefits for their symptoms during periods which they are assigned to take T3 treatment. During the periods when you receive placebo (inactive) treatment, we would not expect there to be any benefits for your symptoms.

What are the alternatives to taking part?
You can continue taking your current thyroid medication. If you wished to take T3 without entering the trial, this can be obtained by prescription in New Zealand, but you would need to pay for the cost of the medication.

What would happen if you were injured in the study?
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 would happen to my information?
During this study the study doctors and staff will record information about you and your study participation. This includes the results of any study assessment. If needed, information from your hospital records and your GP may also be collected. You cannot take part in this study if you do not consent to the collection of this information.

<u>Identifiable Information</u>
Identifiable information is any data that could identify you (e.g. your name, date of birth, or address). The following groups may have access to your identifiable information:

- Study staff (to complete study assessments)
- Laboratory staff to process and report your blood tests
- The sponsor, ethics committees, or government agencies from New Zealand or overseas, if the study or site is audited. Audits are done to make sure that participants are protected, the study is run properly, and the data collected is correct.
- Your usual doctor, if a study test gives an unexpected result that could be important for your health. This allows appropriate follow-up to be arranged.

<u>De-identified (Coded) Information</u>
To make sure your personal information is kept confidential, information that identifies you will not be included in any report generated by the researchers. Instead, you will be identified by a code. The researchers will keep a list linking your code with your name, so that you can be identified by your coded data if needed.

The following groups may have access to your coded information:

- Regulatory or other governmental agencies worldwide.

The results of the study may be published or presented, but not in a form that would reasonably be expected to identify you.

Future Research Using Your Information.
Your coded information may be used for future research related to treatment of hypothyroidism with combination T4/T3 treatment. This future research may be conducted overseas. You will not be told when future research is undertaken using your information. Your information may be shared widely with other researchers or companies. Your information may also be added to information from other studies, to form much larger sets of data.

You will not get reports or other information about any / some research that is done using your information.

Your information may be used indefinitely for future research unless you withdraw your consent. However, it may be extremely difficult or impossible to access your information, or withdraw consent for its use, once your information has been shared for future research.

Security and Storage of Your Information.
Your identifiable information is held at the University of Auckland during the study. After the study it is transferred to a secure archiving site and stored for at least 10 years, then destroyed. Your coded information will be entered into electronic case report forms and kept by the University of Auckland in secure, cloud-based storage indefinitely. All storage will comply with local and/or international data security guidelines.

Risks.
Although efforts will be made to protect your privacy, absolute confidentiality of your information cannot be guaranteed. Even with coded and anonymised information, there is no guarantee that you cannot be identified. The risk of people accessing and misusing your information (e.g. making it harder for you to get or keep a job or health insurance) is currently very small, but may increase in the future as people find new ways of tracing information.

Rights to Access Your Information.
You have the right to request access to your information held by the research team. You also have the right to request that any information you disagree with is corrected.

Please ask if you would like to access the results of your screening and safety tests during the study. You may access other study-specific information before the study is over, but this could result in you being withdrawn from the study to protect the study's scientific integrity.

If you have any questions about the collection and use of information about you, you should ask the researchers (Dr Anne Horne or Dr Mark Bolland).

Rights to Withdraw Your Information.
You may withdraw your consent for the collection and use of your information at any time, by informing your Study Doctor. If you withdraw your consent, your study participation will end, and the study team will stop collecting information from you. Information collected up until your withdrawal from the study will continue to be used and included in the study. This is to protect the quality of the study.

What will happen after the study ends?
Individual results
At the end of the study we will review your results with you and whether you benefited from combination T4/T3 treatment or not. If you did benefit and you felt you wished to continue taking T3, it is available in New Zealand but not funded.

Overall study results
The results of the study will be presented to all study participants within a few months of the study finishing, and will also be published in medical journals. If the study showed evidence that combination T4/T3 was beneficial for patients, we would expect the results would be used to support approaches to regulatory authorities to fund this treatment in New Zealand.

What will happen if you change your mind?
If you wish to withdraw at any time, you should inform the study staff.

Who has approved the study?
This study has been approved by an independent group of people called a Health and Disability Ethics Committee (HDEC), who check that studies meet established ethical standards. The Southern Ethics Committee has approved this study.

The scientific aspects of this study have been approved by the Standing Committee on Therapeutic Trials (SCOTT), which is part of Medsafe.

Where can you go for more information about the study, or to raise concerns or complaints?
If you have any queries regarding this study, you are welcome to contact Anne Horne, Research Fellow, University of Auckland, phone 9239787, email a.horne@auckland.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@advocacy.org.nz
Website:	https://www.advocacy.org.nz/

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

Phone:	0800 4 ETHICS (438 442)
Email:	hdecs@moh.govt.nz

For Māori health and cultural support, consider speaking with your whānau in the first instance. Alternatively, you may wish contact the administrator for He Kamaka Waiora (Māori Health Team) on: 09 486 8324 ext 42324.

Please feel free to contact the researchers if you have any questions about this study

Shirley Ward, Dr Anne Horne, Dr Mark Bolland

Department of Medicine,
University of Auckland
Private Bag 92 019
Auckland
Phone 923 1482.
email: shirley.ward@auckland.ac.nz

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

Department of Medicine
Clinical Research Group
Private Bag 92019
Auckland Mail Centre
Auckland 1142
New Zealand
Telephone 64 9 923 9787
Facsimile: 64 9 3072865
Email: a.horne@auckland.ac.nz

CONSENT FORM: Combination T4/T3 trial for hypothyroidism

Please tick to indicate 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.		
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 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 consent to the research staff collecting and processing my information, including information about my health including contacting my family doctor, reviewing relevant medical records, and accessing my New Zealand Health Information Service/Ministry of Health records.		
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 that my coded information may be used for future research related to treatment of hypothyroidism with combination T4/T3 treatment	
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. These include filling in questionnaires, taking study tablets regularly, having blood tests, and coming to study visits.	
I wish to receive a summary of the results from 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: _____