

PARTICIPANT INFORMATION SHEET AND INFORMED CONSENT FORM

1. **Title of study:** “A multi-center, open label, randomized, parallel group study to compare the efficacy and safety of cholestyramine plus standard treatment versus prednisolone plus standard treatment versus standard treatment alone in the treatment of overt hyperthyroidism”

2. **Name of investigator and institution:**
 - a. Dr. Serena Khoo Sert Kim (Hospital Putrajaya)
 - b. Dr. Zanariah Hussein (Hospital Putrajaya)
 - c. Dr Fung Yin Khet (Hospital Queen Elizabeth II)
 - d. Dr. Vijiya Mala Valayatham (Hospital Ampang)

3. **Name of sponsor:** Ministry of Health, Malaysia

4. Introduction:

You are invited to participate in a research study because you have an overactive thyroid that requires the drug Carbimazole and Propanolol (Standard treatment) with or without Cholestyramine or Prednisolone as additional treatment.

It is important that you understand why the research is being done and what it will involve. Please take your time to read through and consider this information carefully before you decide if you are willing to participate. Ask the study staff if anything is unclear or if you'd like more information. After you are properly satisfied that you understand this study, and that you wish to participate, you must sign this informed consent form. To participate in this study, you may be required to provide your doctor with information on your health history and you may harm yourself if you are not truthful with the information provided.

Your participation in this study is voluntary. You do not have to be in this study if you do not want to. You may also refuse to answer any questions you do not want to answer. If you volunteer to be in this study, you may withdraw from it at any time. If you withdraw, any data collected from you up to your withdrawal will still be used for the study. Your refusal to participate or withdrawal will not affect any medical or health benefits to which you are otherwise entitled.

This study has been approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia.

5. What is the purpose of the study?

The purpose of this study is to establish the effectiveness of the treatment Cholestyramine or Prednisolone as additional treatment to current standard treatment (Carbimazole and Propanolol) for the treatment of overactive thyroid. If you have been diagnosed with an overactive thyroid, the first line treatment would be the standard treatment of Carbimazole and propanolol. It acts to reduce thyroid hormone production from the thyroid gland and it usually takes 6 to 8 weeks to achieve normal thyroid hormone levels. You would require a higher dose of

carbimazole or propylthiouracil if your overactive thyroid is severe. Standard treatment is effective but it takes a longer time to achieve normal thyroid hormone levels. We aim to study the effects and safety on thyroid hormone levels by adding Cholestyramine to standard treatment versus Prednisolone to standard treatment versus Standard Treatment alone in treating your overactive thyroid. We aim to achieve a more rapid control of thyroid hormones with additional treatment of Cholestyramine or Prednisolone and therefore may improve symptoms and complications better.

Cholestyramine powder helps to remove excess thyroid hormone through your gut. Prednisolone helps to prevent conversion of inactive thyroid hormone to the active hormone and also has effects on thyroid antibody levels.

A total of 135 subjects like you in Malaysia will be participating in this study. The whole study will last about one year and your participation will be about 7 weeks total.

6. What kind of study products will I receive?

If you agree to participate in the study, the doctor may need to perform some tests and examination to determine if you are suitable for the study. If you are deemed suitable, you will be randomly (by chance, like flipping a coin) assigned to one of the treatment groups below for 4 weeks:

Group	Treatment
Group 1	Cholestyramine and Standard Treatment
Group 2	Prednisolone and Standard Treatment
Group 3	Standard Treatment alone

You have equal chance of being assigned to each of the groups. Both you and your doctor will know which group you are assigned to and in case of emergencies this information is available to your doctor.

The study products do not contain porcine, bovine or animal components

If you are assigned to **Group 1 Cholestyramine and Standard treatment**, you will be given for **4 weeks**:

- a. Cholestyramine powder 4g (sachet) twice a day and**
- b. Tablet Carbimazole 30 mg daily (6 tablets) and**
- c. Tablet Propranolol 40 mg twice a day (1 tablet twice a day)**

Cholestyramine has been used in cases of thyroid crisis. It is approved for use in patients with hypercholesterolemia and itchiness due to high bile acids.

Cholestyramine 4g comes in a sachet, is mix with a cup of water or juice (60 to 180ml) to be taken before breakfast and dinner. Ensure that the powder is completely dissolved before drinking. You are advised to drink plenty of fluids to prevent constipation. Take other medicines at least 1hour before or 4 to 6 hours after you take cholestyramine powder. If you miss a dose of cholestyramine powder, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular schedule. Do not take 2 doses at once.

If you are assigned to **Group 2 Prednisolone group and Standard treatment**, you will be given for **4 weeks**:

- a. Tablet Prednisolone 30 mg (6 tablets) daily for week 1, 20 mg (4 tablets) daily for week 2, 10 mg (2 tablets) daily for week 3 and 5 mg (1 tablet) daily and**
- b. Tablet Carbimazole 30 mg daily (6 tablets) and**
- c. Tablet Propanolol 40 mg twice a day (1 tablet twice a day)**

Prednisolone or other steroid compounds has been used in cases of thyroid crisis. It is approved for use to treat inflammatory conditions, asthma and allergies

You are instructed to take the Prednisolone tablets in the morning after meals or with food to decrease gastrointestinal upset and do not stop taking the drug abruptly. Do not miss any doses. If you miss a dose take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once.

If you are assigned to **Group 3 Standard Treatment**, you will be given for **4 weeks**:

- a. Tablet Carbimazole 30 mg daily (6 tablets) and**
- b. Tablet Propanolol 40 mg twice a day (1 tablet twice a day)**

Carbimazole and propanolol is the standard recommendation nationwide in the treatment of hyperthyroidism.

7. What will happen if I decide to take part?

Study Procedures

If you agree to be in this study, you will undergo some activities, test and evaluations to determine if you are eligible for this study. Such tests and evaluations are completed during a screening period that takes place before participation in the main part of the study. Please refer to the study activities table below.

Study Activities Table

	Screening	Baseline Assessment and Randomisation	Treatment		Follow up
Visit	1	2	3	4	5
Timeline (wks)	-1	0	2	4	6
Procedures					
Informed consent	X				
Check eligibility	X				
Blood sample for screening ^a	X				
Randomisation		X			
Subject demographics	X				
Medical History	X				
Complete physical exam	X				
Height (cm), Weight (kg)	X	X	X	X	X
Vital signs (Blood Pressure, pulse rate, Weight, Temperature)	X	X	X	X	X
Free T ₄ & Free T ₃ & Thyroid stimulating hormone (Thyroid function test)	X	X	X	X	X
TSH Receptor Antibody levels		X			
Fasting blood glucose/ Random blood glucose	X		X	X	X
Renal function test	X		X	X	X
Urine pregnancy test ^b	X	X	X	X	
Ultrasound Thyroid		X			
Electrocardiogram		X		X	
Echocardiogram ^c		X			
Efficacy assessment			X	X	
Concomitant medication			X	X	
Report AE and SAE			X	X	X
Dispense study treatment			X	X	
Return of remaining study treatment			X	X	X
Assess compliance			X	X	

^a Hepatitis B surface antigen, Anti Hepatitis C ab, HIV1/2 antibody, Full blood count, Renal function test, Liver function test, Fasting plasma glucose, HbA1C (Glycosylated hemoglobin), Fasting lipid profile. Approximately 10 ml of blood will be collected.

^b For women of childbearing age

^c Only if clinically suggestive of heart muscle damage from overactive thyroid or atrial fibrillation

Screening visit (Visit 1)

Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. You will have 1 screening visit to determine if you qualify to take part in this study. You will be asked questions on your medical history and have a complete clinical examination. You will have some blood sampled, approximately 10 ml (2 teaspoon). Pre and post counselling would be given for HIV screening. The tests and procedures noted in the study activities table will be performed.

If based on the screening tests and procedures, you qualify to participate in this study, the study doctor will contact or schedule you to attend a baseline visit within 1 week from your screening visit.

Baseline visit and Randomisation (Visit 2)

If you pass Screening, you will have your vital signs taken and have some blood sampled, approximately 6 ml (1.5 teaspoon), and a urine pregnancy test if you are a woman of childbearing age, an electrocardiogram (ECG) (recording test to monitor your heart activity) and an ultrasound thyroid to scan your thyroid gland. Your study doctor will arrange for an echocardiography (ultrasound of your heart) if indicated. The tests and procedures are described in the study activities table.

Following that you will be randomly assigned by chance (like the flip of a coin) to receive either Cholestyramine plus standard treatment, Prednisolone plus standard treatment or Standard treatment alone. You will receive enough supplies of study drug to take at home and be given instructions on how to take it. You must remember to take the study drug as prescribed and careful not to miss any doses. You will be given 2 weeks supply of study drug. You will be instructed to record all treatment taken in a patient drug diary during your course of treatment and to bring it along for every study visit

Treatment Visit

Treatment Visit 3

The first treatment visit will be at week 2, which is 2 weeks after starting study drug. You will be assessed for any adverse reactions, side effects and be recorded for taking any concomitant medication. You will have your vital signs measured. You will have your blood sampled, approximately 6 ml (1.5 teaspoon). If you are a woman of childbearing age you will have a urine pregnancy test done on the same visit. You will have your patient drug diary assessed. You will return your unused study drug (including the empty bottles/ sachets/ packets) to your study doctor to check that you've taken the tablets as instructed. If you have missed any doses or if your last dose was delayed, it is important that you tell your study doctor. Following that you will be dispensed the study drug for the next 2 weeks. If there are any abnormalities detected in your blood investigation, your study doctor will contact you as soon as possible.

Treatment Visit 4

This is the second treatment visit at week 4, which is 4 weeks after starting study drug.

You will be assessed for any adverse reactions, side effects and be recorded for taking any concomitant medication. You will have your vital signs measured. You will have your blood sampled, approximately 6 ml (1.5 teaspoons) and an ECG performed. If you are a woman of childbearing age you will have a urine pregnancy test done on the same visit. You will have your patient drug diary assessed. You will return your unused study drug (including the empty bottles) to your study doctor to check that you've taken the tablets as instructed. If you have missed any doses or if your last dose was delayed, it is important that you tell your study doctor. If there are any abnormalities detected in your blood investigation, your study doctor will contact you as soon as possible.

This is the end of your treatment visit.

Follow up Visit 5

This is the final visit of the study, which is 2 weeks after the end of your treatment visit.

You will be assessed for any adverse reactions and side effects from your study drug. You will have your vital signs measured and your blood sampled, approximately 6 ml (1.5 teaspoon). You will be given a plan from your doctor for continuation of care after the end of this study. If there are any abnormalities detected in your blood investigation, your study doctor will contact you as soon as possible.

8. When will I receive the trial product and how should it be kept?

You will be given the study drug at each study visit throughout the treatment period of the study. You must not give the product to anyone else. The study staff will instruct you on how the product must be handled and stored. Please ensure that you keep your used and partly used study products after you have finished with them. For some visits you will need to bring back all study products (partly used, unused and empty packaging material) to your study site.

9. What are my responsibilities when taking part in this study?

It is important that you answer all of the questions asked by the study staff honestly and completely. If your condition or circumstances change during the study, you must tell the study doctor. There may be certain medications that you cannot take while participating in this study. The doctor will discuss those medications with you. You must not take any other medications without consulting your study doctor. You must inform your study doctor immediately if you make any changes to any of your current treatments, even those which you have been taking for a long time.

It is very important that your study doctor be informed very rapidly of any eventual changes to your health during your participation in the study. For your own security, it is important that you follow your study doctor's instructions throughout the entire duration of the study.

10. What kind of treatment will I receive after my participation in the trial?

You will continue on standard treatment for treating your overactive thyroid but the dose will be adjusted according to your clinical response and thyroid function tests. The other additional study drug such as cholestyramine or prednisolone will be discontinued. Whether you complete the study or withdraw early, your doctor will discuss the best alternatives for your future treatment with you.

11. What are the potential risks and side effects of being in this study?

Study Drug Risks

Your study doctor will be monitoring you for side effects from your study drug (Either Cholestyramine, Prednisolone or Standard treatment (Carbimazole and Propanolol). It is important that you report any side effects you have had to your study doctor right away. Your study doctor may give you other drugs to help with side effects. If you or your study doctor thinks that you cannot tolerate the side effects, the study drug may be stopped altogether.

While in the study, you are at risk for the following side effects. These side effects have been identified through past studies. These side effects will vary from person to person.

Cholestyramine

The most common adverse effect of cholestyramine is constipation. Other less common adverse gastrointestinal effects are abdominal pain and distension, bloating, flatulence, nausea, vomiting and diarrhea. Previous studies conducted using Cholestyramine as additional treatment to standard treatment is well tolerated with constipation as the commonest side effect.

Prednisolone

Prolonged treatment (usually more than 3 months) with prednisolone in high doses may cause clouding of the lens, skin thinning, weakened bones and raised pressure in the eye. Ulcer in the stomach may develop or worsen. You may have increased appetite, weight gain and increased susceptibility to infection. There is a 1.7 times risk of diabetes with long term steroid use. However, blood glucose will be monitored before, during and after study treatment period. It can cause muscle weakness during prolonged use and rarely may present with acute muscle paralysis with short term use.

Carbimazole

Carbimazole is the standard treatment. Adverse reactions may appear in the first few weeks of therapy and consist of skin rash, urticaria, joint pain, fever, sore throat and low white cell count. Standard treatment with carbimazole has reported 6% of patients developing skin rash.

Propanolol

Propanolol is also part of the standard treatment. It is usually well tolerated. The common adverse reactions are fatigue, slow heart rate, cold extremities, sleep disturbances and nightmares.

Allergic Reaction Risks

Sometimes people have allergic reactions to drugs and can be life threatening. Some things that happen during an allergic reaction that could be a sign or symptom of a life-threatening reaction (anaphylaxis) are:

- A rash
- Having a hard time breathing
- Wheezing
- A sudden drop in blood pressure (making you feel dizzy or lightheaded)
- Swelling around the mouth, throat or eyes
- A fast pulse
- Sweating

Inform the study doctor if you have had any allergic reaction to drugs in the past or if you know that you have an allergy or are sensitive to any other drugs.

You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during this study.

Side effects from blood sampling

Pain, bruising, bleeding or other discomfort at the blood drawing site have been seen.

Risk of hypothyroid (underactive thyroid)

You may have a risk of developing an underactive thyroid from treatment of your hyperactive thyroid. You will be monitored for symptoms and signs to suggest an underactive thyroid and confirm with a blood test. If you are confirmed to have an underactive thyroid, you will have to stop your study drug and have your blood tested again a week later and reviewed by the study doctor.

Reproduction

The effect of the study product on an unborn child is not known. You should not become pregnant or father a child while in this study. Women subjects should not breast feed a child while in the study as the study product may be present in the breast milk. Women who are able to become pregnant will be given a pregnancy test to confirm they are not pregnant. While in the study, if you are able to have a baby or father a child, it is important you use highly effective birth control methods consistently and correctly; the study doctor will discuss these methods with you. Notify your study doctor immediately if you think that you or your partner has become pregnant during the study. If you are pregnant, the study therapy will be discontinued immediately and you will be removed from the study. If you or your partner becomes pregnant while taking part in the study, the sponsor would like to follow the pregnancy until term to gather information regarding the pregnancy and the health of your infant.

Costs

You will not be charged for the study drug or procedures during the study. The costs of hospital visits during the study will be waived

Please ask your study doctor if you need more information on risks and side effects. The trial staff will inform you in a timely manner about any new findings or changes about the study drug which may affect your health or willingness to continue in this study. Where necessary, you may be asked to reconsent to participate.

12. What are the benefits of being in this study?

There may or may not be any benefits to you. You will not be reimbursed or paid for participation in this study. However, information obtained from this study will help improve the treatment or management of other patients with the same disease or condition. Your condition may get better, it may get worse or it may stay the same.

13. What if I am injured during this study?

If you are injured as a result of being in this study, you should contact your study doctor. In the event of a bodily injury or illness directly resulting from the study product or a medical procedure required for this study, the Ministry of Health will pay for reasonable and necessary treatment. The sponsor is not responsible for medical expenses due to pre-existing medical conditions, any underlying diseases, any ongoing treatment process, your negligence or willful misconduct, the negligence or willful misconduct of your study doctor or the study site or any third parties. You do not lose any of your legal rights to seek compensation by signing this form.

14. What are my alternatives if I do not participate in this study?

You do not have to participate in this study to get treatment for your disease or condition. Alternate treatments which are available are drugs already approved or being used for the treatment of this disease such as carbimazole or propylthiouracil. The study doctor will discuss in more details the benefits and risks of those treatments with you.

15. Who is funding the research?

This study is sponsored by Ministry of Health who will pay for all study drugs and procedures. All other drugs and procedures that are not required by the study but are part of your routine medical care will have to be paid by you or your insurance.

16. Can the research or my participation be terminated early?

The study doctor or the sponsor may due to concerns for your safety, stop the study or your participation at any time. If the study is stopped early for any reason you will be informed and arrangements made for your future care. You may be asked to attend a final follow-up visit.

17. Will my medical information be kept private?

All your information obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. When publishing or presenting the study results, your identity will not be revealed without your expressed consent. Individuals conducting this study and involved in your medical care, qualified monitors and auditors, the sponsor or its affiliates and governmental or regulatory authorities has access to your medical records and data and may inspect and copy your medical records, where appropriate and necessary.

Your biospecimens may be sent to laboratories for testing. If this is required, your biospecimens will be coded and information that can identify you will be removed. Only your study doctor and study staff will be able to link the code with you.

Data from the study will be archived.

With your permission your family doctor will be informed of your participation in the study.

You will be informed of the study findings.

18. Who should I call if I have questions?

If you have any questions about the study or if you think you have a study related injury and you want information about treatment, please contact the study doctor at site:

Hospital Putrajaya: Dr Serena Khoo Sert Kim (012 6833308)

Hospital Queen Elizabeth II: Dr Fung Yin Khet (019 8100072)

Hospital Ampang: Dr. Vijiya Mala Valayatham (017 375 7221)

If you have any questions about your rights as a participant in this study, please contact: The Secretary, Medical Research & Ethics Committee, Ministry of Health Malaysia, at telephone number 03-2287 4032.

INFORMED CONSENT FORM

Title of Study: “A multi-center, open label, randomised, parallel group study to compare the efficacy of cholestyramine plus standard treatment versus prednisolone plus standard treatment versus standard treatment alone in the treatment of overt hyperthyroidism”

By signing below I confirm the following:

- I have been given oral and written information for the above study and have read and understood the information given.
- I have had sufficient time to consider participation in the study and have had the opportunity to ask questions and all my questions have been answered satisfactorily.
- I understand that my participation is voluntary and I can at anytime free withdraw from the study without giving a reason and this will in no way affect my future treatment. I am not taking part in any other research study at this time. I understand the risks and benefits, and I freely give my informed consent to participate under the conditions stated. I understand that I must follow the study doctor’s (investigator’s) instructions related to my participation in the study.
- I understand that study staff, qualified monitors and auditors, the sponsor or its affiliates, and governmental or regulatory authorities, have direct access to my medical record in order to make sure that the study is conducted correctly and the data are recorded correctly. All personal details will be treated as STRICTLY CONFIDENTIAL
- I have received a copy of this subject information/informed consent form signed and dated to bring home.
- I agree/disagree* for my family doctor to be informed of my participation in this study. (**delete which is not applicable*)

Subject:

Signature:

I/C number:

Name:

Date:

Investigator conducting informed consent:

Signature:

I/C number:

Name:

Date:

Impartial witness: *(Required if subject is illiterate and contents of participant information sheet is orally communicated to subject)*

Signature:

I/C number:

Name:

Date:

