The Children's Hospital *of* Philadelphia®

Informed Consent Form and HIPAA Authorization

Study Title: Levothyroxine treatment and cardiometabolic outcomes in adolescents with Down syndrome

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Division of Endocrinology

You, or your child, may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of this research study, and the risks and possible benefits of participating.

If there is anything in this form you do not understand, please ask questions. Please take your time. You do not have to take part in this study if you do not want to. If you take part, you can leave the study at any time.

In the sections that follow, the word "we" means the study doctor and other research staff. If you are a parent or legal guardian who is giving permission for a child, please note that the word "you" refers to your child.

Why are you being asked to take part in this study?

You are being asked to take part in this research study because you are between the ages of 8 and 20 years old, have Down syndrome, your most recent TSH and T4 levels may indicate that you have subclinical hypothyroidism and you have either participated in the Down syndrome Metabolic Health Study or have completed the required screening procedures. "Subclinical hypothyroidism" means that your body's level of thyroid stimulating hormone (TSH) is above normal, but your thyroid hormone (T4) levels are normal.

What is the purpose of this research study?

The purpose of this research study is to learn about the effects of treating subclinical hypothyroidism with thyroid hormone replacement in children and adolescents with Down syndrome.

How many people will take part?

About 40 people will take part in this study.

What is involved in the study?

How long will you be in this study?

If you agree to take part, your participation will last for up to 18 months and will involve 1 study visit every 6 months (up to 4 study visits). The study also involves 3 blood draw

visits. Your participation will involve taking either an active medication called levothyroxine, or an inactive pill (a placebo). Your participation will also involve wearing a physical activity armband for 7 days after each study visit, and 3 telephone calls after each study visit.

How long you are eligible to participate will depend on your TSH level during the first 6 months of the study. The study team will let you know whether or not you are eligible to continue the study based on the results from study procedures either done as part of screening for this study or as part of participating in IRB# 9233.

If your TSH level is 5-10 mIU/L at the time of your first study visit: you will be eligible to continue with the study for at least 6 more months. If your TSH level is **not** between 5-10 mIU/L at the time of the first study visit, you will **not** be able to continue with the study.

If at the 6 month visit, your TSH level is still 5-10 mIU/L: you will be eligible to be randomized into the study. If at the 6 month visit, your TSH level is **not** between 5-10 mIU/L, you will **not** be randomized into the study.

"Randomized" means that you will be placed into one of two groups by chance, like flipping a coin. You will be assigned to receive either 12 months of treatment with levothyroxine, or 6 months of a placebo followed by 6 months of levothyroxine. You will not get to choose or find out which group you are in. Because the dose of your levothyroxine during the study may need to change (depending on your blood test results), the study team will know which group you are in.

If your TSH level is found to be greater than10 mIU/L at any point during the first 6 months of the study:

you will not be eligible to continue participating in the study, and you will be referred to an endocrinologist. A TSH level greater than10 mIU/L may mean that your hypothyroidism is not subclinical, and you may require treatment from an endocrinologist.

What are the study procedures?

The study involves the following tests and procedures:

Procedures involved in the study visits:

Interview: A team member will take your complete medical history, along with a listing of any medications you are taking. Throughout the study, you will be asked to report if you think that anything bad has happened as a result of the study.

Medical Record Review: Your medical record will be looked at by the study team. The purpose of this medical record review is to ensure that we do not miss any major medical events, and that we get accurate information about the duration of any illness or medication use. Relevant clinical lab results from this study will be in your medical record.

Physical Exam: Your blood pressure, height, weight, skin-fold thickness and waist will be measured. A study doctor will also examine your private areas (genitals) to check how you are developing there.

Overnight Fast and blood sample: A blood sample will be drawn to check thyroid hormones, lipids, and other factors. About 2½ teaspoons of blood will be drawn. You will not be able to eat or drink anything except plain unflavored water after 8:00 PM the night before your study visit in order to complete this procedure.

Urine Pregnancy Test: If you are eleven years old or older, or have already started having periods, you will be asked to take a pregnancy test before starting the study. The result will be shared with you and the authorized representative who accompanies you to the visit. If you are found to be pregnant, you will not be able to participate in this study.

DXA Scan: A special x-ray of the body called a DXA scan will be done to measure the amount of fat and lean (non-fat) tissue in your body. During the DXA scan, you will be asked to lie flat on your back on a table as the scanning machine moves above your body. The DXA scan is like an X-ray, and takes about 5-10 minutes. This test is painless and does not involve any needles.

Pulse wave velocity/Pulse wave analysis (Ultrasound): An ultrasound probe and cuff will track how fast your blood flows between your (neck) carotid artery and (thigh) femoral artery. You will lay on an examination table for the test, which should last for about 30 minutes. This test is painless and does not involve needles.

Echocardiography (Ultrasound): You will receive an ultrasound of your heart. You will remove your clothing from your upper body and will be covered by a gown or sheet to keep you comfortable and cover your private areas. You will lay on an examination table for the test. A colorless gel will be applied to your chest and a patch that will pick up signals electronically will be placed on your chest over the gel area. This test is painless and does not involve needles. This test should last about 45 minutes.

Questionnaires: During the study visit, a member of the study team will guide you through filling out 7 questionnaires. Our staff person will read each survey out loud to you and you will let that person know your answers.

Procedures involved in the blood draw visits:

Blood draw: Your blood will be drawn to check your TSH & T4 levels.

Procedures that take place at home:

Home Food Inventory: Before each study visit, we will send you a questionnaire called the "Home Food Inventory." We will ask you to complete this questionnaire in advance and bring it with you to the visit.

Study medication: If you are randomized into the study, you will take study medication by mouth once a day for 12 months. You will receive a 3-month supply of

study medication at a time. We will ask you to return your pill bottles and any un-used medication to us every 3 months, either in a postage-paid envelope or at your next study visit. Depending on the results of your blood tests, we may need to change the dose of your study medication. If this happens, we will contact you and provide the new dose of study medication. If your dose is changed, you have another blood draw visit, 6 weeks later, to check your thyroid hormone levels

Study medication calendar & diary: You will receive a calendar and a diary with your study medication. We will ask you to mark the calendar for each day that you take the study medication, and to keep track of how you are feeling.

Phone calls or e-mails: In the first 6 months of the study, we will contact you by phone or e-mail every month to ask if you have noticed any changes in your health. After you begin taking study medication, will contact you every week to ask if you have noticed any changes in your health.

Diet Assessment: After you complete each study visit, a nutritionist will be in contact with you by phone/email to record the type/amount of food/drinks you ate during the last 24 hours. This will be done 3 times (2 times to report on weekdays and 1 time for a weekend day).

Physical Activity Armbands: At the end of each study visit, you will be asked to take home and wear an armband. This armband is to be worn for 7 days straight, with the exception of bathing/showering or if participating in water activities, such as swimming. Wearing this armband measures your daily physical activity. After the 7th day, this armband will be returned to the study team.

Some of the procedures in this study will be repeated several times. Tests that are part of your regular, routine medical care should continue to be performed by your usual doctor. Additional tests may need to be performed by your usual doctor or by a specialist if any of your initial test results are not normal.

Visit Schedule

Visit	Purpose	Main Procedures	Duration
Study Visit #1, Month 0 *this visit is only done if you have **not** participated in the DS Metabolic Health Study	Baseline visit	Blood tests, echocardiography, pulse wave velocity, DXA, physical exam, interviews, questionnaires	4.5 hours
After Study Visit #1	At-home procedures	Physical activity arm band, 3 diet assessment phone calls	Arm band = 7 days, diet assessment = 30 minutes each
Blood draw visit A, Month 3	TSH & T4 check	Blood tests	15 minutes
Study Visit #2, Month 6	Routine visit	Blood tests, DXA, physical exam, interviews, questionnaires	4 hours
After Study Visit #2	At-home procedures	Physical activity arm band, 3 diet assessment phone calls	Arm band = 7 days, diet assessment = 30 minutes each
Randomization – no visit, phone call	Eligible participants continue with study	Begin study medication	5 minutes
Blood draw visit B, Month 7.5	TSH & T4 check	Blood tests	15 minutes
Study Visit #3, Month 12	Routine visit	Blood tests, DXA, physical exam, interviews, questionnaires	4 hours
After Study Visit #3	At-home procedures	Physical activity arm band, 3 diet assessment phone calls	Arm band = 7 days, diet assessment = 30 minutes each
Blood draw visit C, Month 13.5	TSH & T4 check	Blood tests	15 minutes
Study Visit #4, Month 18	Routine visit	Blood tests, DXA, physical exam, interviews, questionnaires	4 hours
After Study Visit #4	At-home procedures	Physical activity arm band, 3 diet assessment phone calls	Arm band = 7 days, diet assessment = 30 minutes each
Additional blood draw visits	TSH and T4 check	Additional blood draw visits may be required if we need to change the dose of your study medication.	15 minutes each

What are the risks of this study?

Taking part in a research study involves inconveniences and risks. If you have any questions about any of the possible risks listed below, you should talk to your study doctor or your regular doctor.

While in this study, you are at risk for the following side effects:

Risks associated with study medication (levothyroxine):

The most severe risks associated with levothyroxine are: restlessness, irritability, rapid heartbeats, palpitations, poor sleep and weight loss. The dose of levothyroxine that you receive will be low, and it is not likely that you will develop these symptoms. After you begin taking study medication, we will contact you to find out if you have any of these symptoms. If you have any of these symptoms, we may ask you to get your blood drawn and we may adjust the dose of your medication. Even if you are not having symptoms, we will ask you to get at least 6 TSH/T4 checks during the 18 month study to make sure that the dose that you are receiving is okay. These checks are done using blood collected from your vein.

Risks associated with placebo (lactase):

There are no commonly experienced risks of taking lactase. As with any ingested substance, there is the rare chance of an allergic reaction, such as hives, rash, or difficulty breathing.

Risks associated with overnight fast:

You will be participating in this study after an overnight fast of 8-12 hours. You will not be eating breakfast before your blood draw on the day of the study and this may cause you to have an upset stomach, a headache, or feel light-headed. These symptoms are occasional but not serious. We will provide you with a snack following the fasting blood draw.

Risks associated with blood draw:

There is a small and rare risk of infection and fainting. There may be some pain or bruising of the skin at the site where the blood is taken. The blood samples will be drawn by a health professional skilled in drawing blood in children and adolescents.

Risks associated with growth and maturity status and body composition:

Taking measurements of the body to determine growth and body compositions poses little risk. It is possible that you may experience some embarrassment when your pubertal status is determined. To minimize this possibility, the exam is done in private by a health professional skilled in determining pubertal status. In addition, you will be asked in advance if you prefer to have your parent/guardian present when the puberty exam is done.

Risks associated with DXA scan:

This study involves a very small exposure to radiation from the DXA scans. You will therefore receive a radiation dose. This dose is not needed for your medical care. You will get the radiation only because you are taking part in this study. At doses much higher than you would receive in this study, radiation is known to increase the risk of developing

cancer after many years. At the small dose of radiation you will receive, it is very likely that you will see no effects at all.

Risks associated with pulse wave velocity and analysis (ultrasound):

This non-invasive test uses sound waves and there is no radiation exposure. There are no known risks from the ultrasound. This procedure is associated with very little discomfort. Some people with sensitive skin develop rashes where the wires are taped to the skin. This procedure may be performed at the University of Pennsylvania. The doctors involved in performing this test may contact you to schedule the procedure.

Risk associated with echocardiography (ultrasound):

This procedure is associated with very little discomfort. The gel may feel cold when first placed on the body. Some people with sensitive skin develop rashes where the wires are taped to the skin.

Risk associated with questionnaires:

Sensitive issues may arise during the questionnaire assessment. A licensed clinical psychologist who is part of the study team will be available for support, if needed. You do not have to answer any questions that make you uncomfortable.

Risk associated with wearing the physical activity armbands:

There is little to no risk associated with wearing the physical activity armband. These armbands fit comfortably on the arm and can easily be removed should discomfort arise. There is a slight chance that the skin could be irritated from wearing the armband. If skin irritation occurs, you may use Aquaphor or Vaseline where the fabric of the band is to treat and prevent further irritation. If you are allergic to metal, you will not be required to complete this test.

Reproductive Risks:

For female subjects: There may be risks from some of the study procedures to an unborn child. If you are pregnant or nursing, you will not be allowed to participate in this study.

Risks associated with breach of confidentiality:

As with any study involving collection of data, there is the possibility of breach of confidentiality of data. Every precaution will be taken to secure participants' personal information to ensure confidentiality.
At the time of participation, each participant will be assigned a study identification number. This number will be used on data collection forms, blood samples, and in the database instead of names and other private information. A separate list will be maintained that will link each participant's name to the study identification number for future reference and communication.

Are there any benefits to taking part in this study?

Your health might directly benefit from levothyroxine treatment, as your thyroid hormone levels might become normal. However, we cannot guarantee or promise that you will receive any direct benefit by participating in this study. The knowledge gained

from this research may help doctors determine how to treat children with Down syndrome who have subclinical hypothyroidism.

You may indirectly benefit from your blood work by finding out if you have any abnormalities, such as abnormal cholesterol, blood sugar, or thyroid levels. If your TSH level is >10 at any point during the study, we will refer you to an endocrinologist.

Do you need to give your consent in order to participate?

If you decide to participate in this study, you must sign this form. A copy will be given to you to keep as a record. Please consider the study time commitments and responsibilities as a research subject when making your decision about participating in this study. You will need to follow the study doctor's instructions, keep all study appointments and take the study drug as directed.

What happens if you decide not to take part in this study?

Participation in this study is voluntary. You do not have to take part in order to receive care at CHOP.

If you decide not to take part or if you change your mind later there will be no penalties or loss of any benefits to which you are otherwise entitled.

Can you stop your participation in the study early?

You can stop being in the study at any time. You do not have to give a reason.

If you withdraw from the study after you have begun treatment, you will need to follow with your primary doctor for continued screening of thyroid studies after thyroid hormone medication is withdrawn.

Can the study doctor take you out of the study early?

The study doctor may take you off of the study if: Your condition worsens.

- The study is stopped.
- The study drug is no longer available.
- You cannot meet all the requirements of the study.
- New information suggests taking part in the study may not be in your best interests.

What choices do you have other than this study?

There are options for you other than this study including:

- Receiving care for your subclinical hypothyroidism outside this study. You may be able to receive levothyroxine treatment outside this study, but that will be up to you and your doctor.
- Not participating in this study.
- You may discuss other options available to you with your doctor.

What about privacy, authorization for use of Personal Health Information (PHI) and confidentiality?

As part of this research, health information about you will be collected. This will include information from medical records, procedures, interviews and questionnaires. Laboratory test results will appear in your medical record with the exception of: pregnancy test results, fasting glucose & insulin levels, lipid panel, other labs not performed in the CHOP Clinical Lab, and ultrasound results. We will do our best to keep your personal information private and confidential. However, we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The results of this study may be shown at meetings and published in journals to inform other doctors and health professionals. We will keep your identity private in any publication or presentation.

Several people and organizations may review or receive your identifiable information. They will need this information to conduct the research, to assure the quality of the data, or to analyze the data or samples. These groups include:

- Members of the research team and other authorized personnel at CHOP;
- People from agencies and organizations that perform independent accreditation and/or oversight of research; such as the Department of Health and Human Services, Office for Human Research Protections;
- People at the University of Pennsylvania, where some of the study procedures will be performed;
- The Data Safety Monitoring Board, who is monitoring the safety of this study;
- The National Institutes of Health, who is sponsoring this research;
- Public health authorities that are required by law to receive information for the prevention or control of disease, injury or disability.

By law, CHOP is required to protect your health information. The research staff will only allow access to your health information to the groups listed above. By signing this document, you are authorizing CHOP to use and/or release your health information for this research. Some of the organizations listed above may not be required to protect your information under Federal privacy laws. If permitted by law, they may be allowed to share it with others without your permission.

There is no set time for destroying the information that will be collected for this study. Your permission to use and share the information and data from this study will continue until the research study ends and will not expire. Researchers continue to analyze data for many years and it is not possible to know when they will be completely done.

Can you change your mind about the use of personal information?

You may change your mind and withdraw your permission to use and disclose your health information at any time. To take back your permission, you must tell the investigator in writing.

Dr. Andrea Kelly
The Children's Hospital of Philadelphia
34th Street and Civic Center Blvd.
Philadelphia, PA 19104

In the letter, state that you changed your mind and do not want any more of your health information collected. The personal information that has been collected already will be used if necessary for the research. No new information will be collected. If you withdraw your permission to use your personal health information, you will be withdrawn from the study.

Additional

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study.

You will be informed if changes to the study are needed to protect your health. You will be told about any new information that could affect your willingness to stay in the study, such as new risks, benefits or alternative treatments.

Financial Information

While you are in this study, the cost of your usual medical care – procedures, medications and doctor visits – will continue to be billed to you or your insurance. You may find out that some of your study results are abnormal, and we may refer you to your usual doctor or a specialist for treatment for additional tests. If additional tests need to be performed specialist, the study will not be able to pay for them. These will be billed to you or your insurance.

Will there be any additional costs?

The National Institute of Health (NIH) is providing financial support and material for this study. All procedures in this study will be covered. There are no costs to you or your health insurance.

Will you be paid for taking part in this study?

After the baseline study visit, parents/guardians will have be reimbursed with a total of $100 on a prepaid bankcard for travel, meals and parking. $50 will be loaded onto the bankcard immediately after the study visit, and an additional $50 will be loaded once all at-home procedures are complete. Participants will be compensated with a $50 gift card for their time and effort.

After the month 6, 12 and 18 study visits, parents/guardians will be reimbursed each time with a total of $75 on a prepaid bankcard for travel, meals and parking. $50 will be loaded onto the bankcard immediately after the study visit, and an additional $25 will be loaded once all at-home procedures are complete. Participants will be reimbursed each time with a $25 gift card and a small gift for their time and effort.

After the month 3, 7.5 and 13.5 blood draw visits, participants will be reimbursed each time with a $25 prepaid bankcard for their time and effort.

If additional blood draw visits are required, participants will be reimbursed each time with a $25 prepaid bankcard for their time and effort.

If you receive payment using a bankcard, the bank will have access to your name, address and phone number.

Who is funding this research study?

The National Institutes of Health is providing funding for this study.

What if you have questions about the study?

If you have questions about the study, call the study doctor, Dr. Kelly at 215-590-3174. You may also talk to your own doctor if you have questions or concerns.

The Institutional Review Board (IRB) at The Children's Hospital of Philadelphia has reviewed and approved this study. The IRB looks at research studies like these and makes sure research subjects' rights and welfare are protected. If you have questions about your rights or if you have a complaint, you can call the IRB Office at 215-590-2830.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Consent for Use of Data or Specimens for Future Research

As part of the study, we will collect blood, urine, and data on body composition. We may wish to use this information or any leftover samples in a future study about obesity, heart health, diabetes, or Down syndrome. The information and samples will be given a unique code and will not include information that can identify you. Information that can identify you or your blood or urine samples may be kept permanently in a password protected computer database at CHOP. Only the study doctors and those working with them on this study will be able to see information that can identify you.

If you leave the study, you can ask to have the data collected about you removed or your samples destroyed. You can also ask us to remove information that identifies you from the data or samples.

Please indicate whether you will allow your data or samples to be used for future research in thyroid disorders, obesity, heart health, diabetes, or Down syndrome by putting your initials next to one of the following choices:

_____ (initials) My data or specimens may be used for other future research studies. If the data or specimens are shared outside of CHOP, no identifiable information will be included.

_____ (initials) My data or specimens may be used for this study only.

OPTIONAL: Consent to be contacted for future studies

Please indicate if you will allow us to contact you for future studies.

_____ (initials) I give permission to be contacted for future studies.

_____ (initials) I do not wish to be contacted for future studies.

OPTIONAL: Consent to inform primary care physician of clinically relevant lab results

Please indicate if you will allow us to inform your primary care physician of any clinically relevant lab results. If you primary care physician is a CHOP doctor, some of your research specific information may be available in your medical record.

_____ (initials) I give permission for the study team to inform my primary care physician of any clinically relevant lab results.

_____ (initials) I do not give permission for the study team to inform my primary care physician of any clinically relevant lab results.

Consent to Take Part in this Research Study and Authorization to Use and Disclose Health Information for the Research

The research study and consent form have been explained to you by:

Person Obtaining Consent

Signature of Person Obtaining Consent | Date

By signing this form, you are indicating that you have had your questions answered, you agree to take part in this research study and you are legally authorized to consent to your or your child's participation. You are also agreeing to let CHOP use and share your or your child's health information as explained above. If you don't agree to the collection, use and sharing of your or your child's health information, you or your child cannot participate in this study. **NOTE:** *A foster parent is not legally authorized to consent for a foster child's participation.*

Name of Subject

Signature of Subject (18 years or older) | Date

Name of Authorized Representative (if different than subject) | Relation to subject: ☐ Parent ☐ Legal Guardian

Signature of Authorized Representative | Date

Assent to Take Part in this Research Study

For subjects capable of providing assent:

I have explained this study and the procedures involved to _____ in terms he/she could understand and that he/she freely assented to take part in this study.

_____
Person Obtaining Assent

_____ _____
Signature of Person Obtaining Assent Date

This study has been explained to me and I agree to take part.

_____ _____
Signature of Subject (optional) Date

For subjects unable to assent:

I certify that _____ was not capable of understanding the procedures involved in the study sufficiently to assent to study participation.

_____
Person Responsible for Obtaining Assent

_____ _____
Signature of Person Responsible Date