

A Randomised Control Trial Comparing Adjuvant Rituximab to Standard Anti-Thyroid Drug Treatment in Young Patients with Newly Diagnosed Graves' Hyperthyroidism.

Short title: Rituximab in Graves' Disease 2 (RiGD2)

PATIENT INFORMATION SHEET LEGAL REPRESENTATIVE

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INVITATION

The Individual who you are acting as Legal Representative for is invited to take part in a research trial. Please read the following information to help you decide if you would like The Individual to take part. We would like you to understand why we are doing this research trial and what it means for The Individual. You do not need to decide straight away, and you will have the chance to ask us more questions about the trial. We recommend you talk about it with The Individual as well as friends and family before deciding to take part.

Please remember that The Individual does not have to take part. If you choose for them not to take part their normal healthcare will not be affected in any way.

SUMMARY

The RiGD2 trial will include 124 young patients with Graves' hyperthyroidism (also called Graves' disease or GD) from hospitals around the UK. The aim is to see if adding a new treatment to the standard of care treatment for GD helps stop GD from coming back (known as 'relapse'). With the current treatment, more than two thirds of patients relapse once their anti-thyroid drugs are stopped. Everyone who takes part in the trial will be given the standard anti-thyroid drug treatment provided on the NHS for 2 years, as well as, either a single dose of rituximab (the new treatment- group 1) or a single dose of salt water (known as 'a placebo'- group 2). The individual will be randomly put into one of these treatment groups and there is an equal (50:50) chance of being in one group or the other. You and The Individual will not be told which treatment group they are in until the end of the trial. The trial will last for 3 years and will involve 19 trial visits in total. Where possible trial visits will line up with The Individual's usual hospital visits. During the trial The Individual will have bloods taken to check their thyroid function at 4 weeks, then every 8 weeks in the first year and every 3 months after this. The doctors that are looking after The Individual will use these results to decide whether their anti-thyroid drug dose needs to be changed to keep their thyroid hormone levels normal and them feeling well. The Individual will also be asked to complete some questionnaires about how they are feeling. All female participants, regardless of the group they get randomised to, will be asked to have a pregnancy test at the start and at the end of the first year, to make sure that it is safe to give them the new treatment.

This trial will give us more information on the best way to treat GD in young people, which will improve the care we give patients in the future. If you choose for The Individual to take part in this trial, we will use information that they give us, and which we get from their medical records and their GP.

In this trial we will use information from The Individual and their medical records. We will only use information that we need for the research trial. We will let very few people know The Individual's name or contact details, and only if they really need it for this trial. Everyone involved in this trial will keep The Individual's data safe and secure. We will also follow all privacy rules. At the end of the trial, we will save some of the data in case we need to check it and for future research. We will make sure no-one can work out who The Individual is from the reports we write. The information sheet tells you more about this.

The Newcastle upon Tyne Hospitals (NUTH) NHS Foundation Trust is the Sponsor of the RiGD2 trial. As Sponsor NUTH has overall responsibility for how the trial was designed, organised and managed. Throughout this Patient Information Sheet when it refers to 'we' it means 'Sponsor'.

**If you are interested in The Individual taking part in the RiGD2 trial, please
continue reading for further details.**

WHY ARE WE DOING THE RiGD2 TRIAL?

The trial aims to find out if giving one dose of rituximab (RTX), soon after diagnosis with GD, alongside the standard 2 years of anti-thyroid drug treatment (ATD), helps a patient's thyroid gland work normally even after they stop taking the ATD. The body protects itself from illness and infection by making special types of cells called 'B cells'. In GD the body mistakenly makes B cells that attack the thyroid gland and force it to make too much thyroid hormone. RTX helps kill these B cells. The good B-cells come back but we think that the bad ones will not come back, helping treat GD. In a recent research trial (RiGD1) we found that a single dose of RTX did help to treat GD and stop it from coming back (known as 'relapse') once the anti-thyroid drugs were stopped. However, the trial included only a small number of participants and did not have a second group of participants who received only the standard treatment (known as a 'control group') to compare the findings to. The next important step is to do a 'randomised control trial', where patients are randomly assigned to different groups receiving different treatments. Therefore, to get the most reliable results, in RiGD2, one group will be given a single dose of RTX by an intravenous infusion as well as the ATD treatment for 2 years and the other group will be given a single dose a placebo as well as the ATD treatment for 2 years. For this trial the placebo will be saline (salt water). Although the placebo will be given in the same way as the RTX, it does not have any active medicine in it. Salt water is already found naturally in the body, so it will not affect GD. Using a placebo helps us find out whether RTX increases remission rates in GD, or if the improvement might have happened by chance. By comparing the results between participants who receive RTX and those who receive the placebo, we can understand how well the RTX really works.

WHY IS THE INDIVIDUAL INVITED TO TAKE PART?

We are inviting The Individual to take part because they have just been diagnosed with GD, which means they have an overactive thyroid gland.

DOES THE INDIVIDUAL HAVE TO TAKE PART?

No, The Individual does not have to take part in this trial. If you choose for The Individual not to take part now or if you decide for them to take part but then later change your mind, The Individual will be able to leave the trial without giving a reason. Withdrawing from the trial at any point will not affect The Individual's treatment in any way and they will continue to receive the current NHS standard of care from their clinical team.

WHAT IS THE CURRENT NHS STANDARD OF CARE TREATMENT FOR GRAVES DISEASE?

The current NHS standard of care treatment for GD involves:

- ❖ Taking ATD for around 2 years and seeing the doctor for a check-up about 17 times over those 2 years. Out of every 4 patients 3 will find that their GD comes back once they have stopped taking anti-thyroid drug. At each of these visits patients would be asked to provide some blood so that their body's response to the ATD can be monitored. The amount of blood patients give at each of these visits would be about 8mls (less than 2 teaspoons). Sometimes patients would need to provide more blood than this if they are feeling unwell, or there are any complications related to their treatment.
- ❖ If ATD treatment does not work and the GD comes back, then the other treatment options (apart from returning to ATD treatment once again) are:
 - 1) Surgery (removing the thyroid gland)
 - 2) Radioiodine treatment (radioactive iodine is absorbed by the thyroid and destroys the cells in the thyroid gland).
- ❖ After surgery or radioiodine treatment, patients need to take thyroid hormone replacement medicine (levothyroxine) for the rest of their life. This medicine is needed to replace the hormones which are missing after removal of the thyroid gland by surgery or after destruction of the thyroid gland by radioiodine treatment. There are also important risks associated with both surgery and radioiodine options.

WHAT IS RITUXIMAB?

The body protects itself from illness and infection by making special types of cell, called 'B cells'. In GD the body mistakenly makes B cells that attack the thyroid gland and force it to make too much thyroid hormone. RTX helps kill these B cells. The good B-cells come back but we think that the bad ones will not come back, helping treat GD.

WHAT WOULD TAKING PART INVOLVE?

On page 7 of this Patient Information Sheet you will see a summary of all the trial visits. Below is a more in-depth outline of what will happen at each of those visits.

If you decide for The Individual to take part, we will need to see them 19 times in 3 years. Usual NHS care would involve patients seeing their thyroid doctor about 17 times over 2 years, so taking part in this study would mean around 2 extra visits compared to standard care. However, not all hospitals are the same. Sometimes clinicians might choose to see a patient with GD in clinic more or less than this, depending on their age and how well they are feeling. The trial research team at The Individual's hospital will do their best to line up their research visit appointments with their usual clinic appointments.

Talking about the trial

We will discuss the trial in full and you and The Individual can ask any questions you both might have about their diagnosis and the trial. This would usually happen during their clinic appointment. You and The Individual would then go away and think about it. You don't have to decide straight away, and you could talk to your friends and family or GP to help you decide.

Screening and Consent Visit- Visit 0 (1 Visit)- about 1 hour

If you are interested in The Individual taking part, we would ask them to come to the hospital for a screening and consent visit. You and The Individual will have a chance to ask questions, we will check that you both understand the trial and you and they are happy for them to take part. We will then ask you to read and sign a consent form. We will take a blood sample (less than 1 teaspoon) from The Individual to check for a current or previous viral infection of the liver (called 'hepatitis') or tuberculosis. It is important we know if they have ever had hepatitis or tuberculosis because RTX might worsen or reactivate these infections. We will also need to make sure that female patients are not pregnant so they will be asked to provide a urine or blood sample for testing. This is because RTX may pose a risk to the unborn baby. Every female who takes part in the trial, regardless of the group they get randomised to, must provide a urine or blood sample for this purpose, regardless of their age. If you refuse for The Individual to have the tuberculosis, hepatitis or pregnancy tests done or if any of the tests are positive, they would not be allowed to take part in the trial. They would then return to standard NHS care.

If The Individual receives a positive result on the Hep B/C and/ or the tuberculosis test their clinician will make sure they receive the appropriate follow up investigations and treatment. The Individual will not be able to take part in the trial, but they will still receive the standard NHS care for GD.

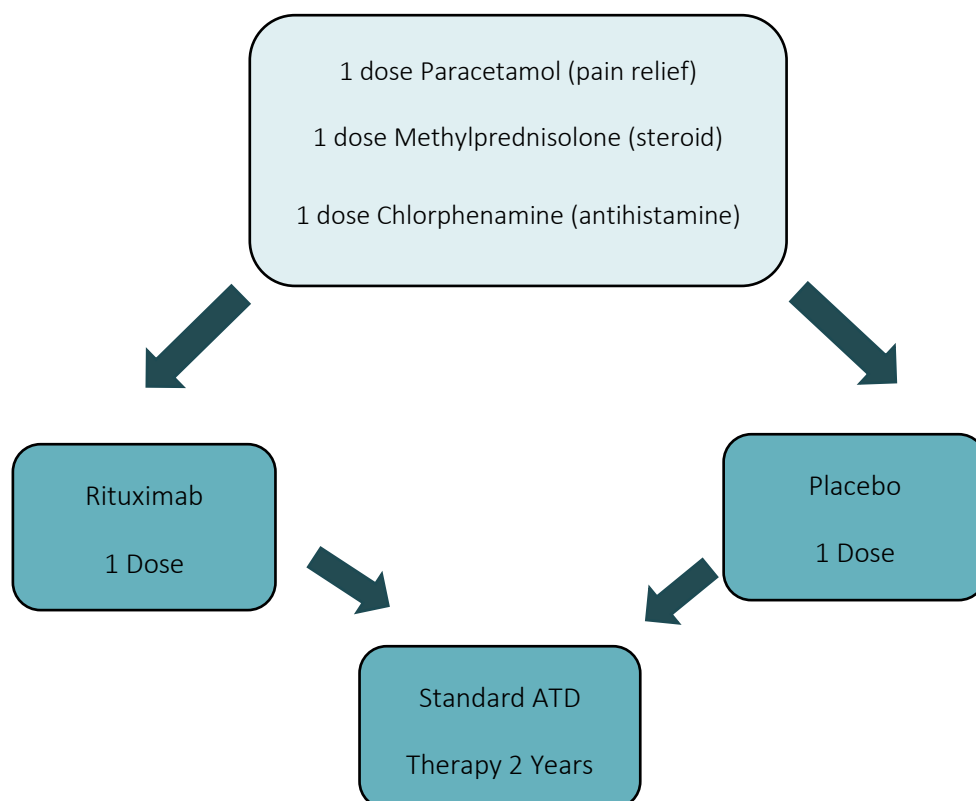
Treatment visit- Rituximab or Placebo Visit 1 (1 Visit)- about 4-6 hours

This visit will happen once it has been confirmed after the screening visit that The Individual does not have a hepatitis or tuberculosis infection and (for female participants) they are not pregnant. The Individual will be randomly allocated to have a single intravenous infusion of either rituximab or placebo (saline). An intravenous infusion is when a medicine or fluid is given slowly through a vein. You or The Individual will not be told which treatment they will be given. The Individual will then have a thin plastic cannula (tube) inserted into a vein, usually in the back of their hand or arm and around 18mls of blood (around 6 teaspoons) will be taken. Local

anaesthetic cream will be offered before the tube is put in place or before any blood tests. A member of the trial team will then set up the RTX or saline drip (or intravenous infusion). They will give the treatment using a pump, which will give The Individual the dose over approximately 3 hours. If the nurse needs to slow down the speed of the infusion this could mean it takes longer, maybe up to an hour longer. There is the possibility this might run over three hours depending on the person. The Individual will be monitored in hospital for a further 30 minutes following the treatment. The Individual will be asked to fill out 4 questionnaires to understand how the GD and treatment may be affecting The Individual's day-to-day life, which should take about 30 minutes in total to complete. The amount of time they spend at this visit will depend on set up time for the infusion, speed of the infusion, monitoring time and time to complete questionnaires. For this reason the visit could last from 4 to 6 hours in total. After this visit and at all follow up visits, a member of the team will call you once they have The Individual's thyroid hormone test results, to tell you what dose of anti-thyroid drugs The Individual needs to take.

WHAT IS IT LIKE TO RECEIVE RITUXIMAB?

RTX has been in use for more than 25years, with more than a million people treated world-wide – including many young people. It has been used successfully in people with other autoimmune conditions (GD is an autoimmune condition). If The Individual has been randomised to the RTX group, they will receive one dose. Around half of the people receiving an RTX infusion will feel some effects from having the drug. These can include, feeling hot or cold, shivering, feeling sick, or itchiness. We will give The Individual 3 medications immediately before the infusion (paracetamol, an antihistamine and a steroid) to prevent this but if it does happen then the treatment will be stopped for a few minutes, until they feel better, and then restarted at a slower rate. A nurse or doctor will be watching The Individual carefully during the treatment for any signs that they are feeling poorly.



WHAT IS IT LIKE TO RECEIVE SALINE (PLACEBO)?

Saline (salt water) is used regularly in medical care, often if a patient is unwell and dehydrated or if they have had an injury. It is very safe and puts fluid back into the body's tissues. Because it is safe to use, it is often given as a placebo in research trials. The amount of salt in the solution that we are using is the same amount of salt found in tears, blood and other body fluids in humans. It is very rare to have any side effects from a saline infusion. If The Individual has been randomised to the placebo group, they will receive one dose of saline. We will give The Individual 3 medications immediately before the saline infusion (paracetamol, an antihistamine and a steroid). Participants in the RTX group will need to be given these 3 medications to help with side effects of RTX. Because this is a 'blind' trial where participants are not aware which group they are in- it is important that both groups are given these 3 medications. The medications are safe and regularly used, so it is okay for The Individual to have them, even if they are in the placebo group.

For the first 2 years Visits 2 to 13 (12 visits)- about 30 minutes each

During the first 2 years of the trial, The Individual will be seen in hospital. We will check to see how they are feeling and record if they have felt unwell or needed to visit the doctor for any reason. We will also check if The Individual has started or stopped any other medications. We will then take up to 8mls of blood (less than 2 teaspoons) to make sure The Individual is OK and to check their thyroid hormone levels. At 3 of these visits, we will ask The Individual to complete some questionnaires to understand how the GD and treatment may be affecting their day-to-day life and take an extra 10mls of blood (less than 3 teaspoons) at 3 of the visits to compare how well their treatment may be working. After each of the 12 visits a member of the study team will contact you with The Individual's thyroid hormone blood results to tell you if they need to change the dose of their anti-thyroid drug. At the 1 year follow up visit all females will be asked to provide a urine sample for pregnancy testing.

2 years after the RTX or Placebo treatment Visit 14 (1 visit) - about 30 minutes

The Individual will be asked to stop taking their ATD at this visit. We will check to see how they are feeling and record if they have felt unwell or needed to visit the doctor for any reason. We will also check if they have started or stopped any other medications. We will need to take 8mls of blood to check The Individual's thyroid hormone levels and check they are well, and we will ask them to complete some questionnaires to understand how the treatment may be affecting their day-to-day life. We will also take an extra 10mls of blood to compare how well the new treatment or placebo may be working. We will ask The Individual to complete some questionnaires to understand how the GD and treatment may be affecting their day-to-day life.

The final year Visits 15 to 18 (4 visits) - about 30 minutes each

When The Individual comes for these visits, we will check to see what medications they are taking, ask how they are feeling and take blood tests to check their thyroid hormone levels. If the GD returns, then we may be able to detect this before The Individual develop symptoms. If The Individual starts to feel as though the GD is coming back between clinic visits, then you should let us know straight away so they don't become poorly. We will need to take 8mls of blood to check if the GD has returned. At the final visit, we will ask The Individual to complete some questionnaires to understand how the GD and its treatment may be affecting their day-

to-day life. We will also take an extra 10mls of blood to compare how well the new treatment or placebo may be working.

Once the 3 years are over The Individual will then return to normal NHS care.

HOW MANY BLOOD SAMPLES WILL THE INDIVIDUAL NEED TO GIVE IF THEY TAKE PART IN THIS TRIAL?

At every trial visit (Visit 1 to Visit 18) The Individual will be asked to give a sample of blood, which we have mentioned in the above section. If The Individual did not take part in the trial, they would still be asked to give a blood sample at each of their clinical visits.

At visits 1 and 10 we would like to take a small amount of extra blood (2.5mls or about a teaspoon) from all participants and an additional 2.0mls of blood from Newcastle participants only (that means Newcastle participants would give an extra 4.5mls of blood at these visits). These bloods will help us understand additional factors that influence remission in GD. If The Individual does not want to provide these extra bloods they do not have to. On the consent form you can tell us if you do not want The Individual to have these extra bloods taken.

SUMMARY OF TRIAL VISITS

Screening and consent

This is an opportunity to discuss the trial in more detail and ask any questions you have after reading this Patient Information Sheet. The Individual's doctor will discuss any reasons why they may not be able to take part in the trial. You will complete the consent form and The Individual will complete the assent form.

Visit 1 Baseline Assessments

(After confirmation that hepatitis, tuberculosis and pregnancy (if female) tests are negative)

- Medical history and medications
- Clinical examination and blood tests
- Questionnaires

Randomised to either:

Standard ATD daily for 2 years + 1 dose
rituximab (infusion of rituximab)

Standard ATD daily for 2 years + 1
dose placebo (infusion of saline)

Visits 2-14 Follow Up Visits (years 1 & 2)

- ATD compliance and other medications
- Well-being check
- Clinical examination and blood tests
- Questionnaires (at 4 of these visits)
- Contact from clinical care team to let you know of any changes to ATD dose
- Pregnancy test (if female) at Visit 10

Visit 14 (end of year 2)

- Stop taking ATD

Visits 15-18 Follow Up Visits (year 3)

- ATD re-dosing and other medications
- Well-being check
- Clinical examination and blood tests
- Questionnaires (at final visit)

Return to normal NHS care

WHAT QUESTIONNAIRES WILL THE INDIVIDUAL NEED TO COMPLETE?

The Individual will complete 4 types of questionnaires at some of their visits. These are standard questionnaires used very frequently in health research. The Individual will complete them on paper and electronically. If The Individual would prefer to, they can complete all of them on paper. We do not expect The Individual to become upset completing them. However, if they do feel upset and would like to speak with someone about how they are feeling please contact their clinical research team using the contact details at the end of this patient information sheet.

EQ-5D-Y-5L

This questionnaire measures The Individual's quality-of-life before and after treatment. It looks at 5 different areas of their life (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and asks them to score them from 1 (no problems) to 5 (extreme problems). This questionnaire takes a few minutes to complete.

ThyPro-39

This is a questionnaire that is specially made for people with thyroid disease to measure symptoms they may be having that are commonly related to GD (hyperthyroid symptoms, goitre symptoms, eye symptoms, tiredness, cognitive problems, anxiety, depression, emotional sensitivity, impact on social and daily life, feelings about how they look and quality of life). The questionnaire asks The Individual to score these symptoms on a scale of 1 (not at all) to 5 (very much). The questionnaire takes about 15 minutes to complete.

Health Resource Use

This questionnaire asks The Individual about their use of health and social care services and the medications that they currently take. This questionnaire aims to understand the costs of different treatments (like the one being used in this trial) to health and social care services.

Time to Travel

This questionnaire asks The Individual the length of time it takes them to travel to different health care appointments as well as how much money those trips cost them to make. This questionnaire aims to understand the costs to them and their family when using health care services.

WHAT HAPPENS AFTER THE TREATMENT?

Following their treatment, The Individual will go home with your ATD tablets. For the first 6 months after receiving the RTX or placebo treatment we advise patients not to have any live vaccinations such as the flu nasal spray. For the first 2 years The Individual will come into hospital for regular follow up visits to check they are well and to record the amount of ATD they are taking. In the third year of the trial, we will see The Individual every 3 months to check they are well and check their thyroid hormone levels to see if the GD has returned. If it has, The Individual may need to restart treatment.

WHAT WILL HAPPEN TO ANY SAMPLES THAT THE INDIVIDUAL GIVES?

For females who have given a urine sample for pregnancy testing, the urine sample will be destroyed soon after testing. Over the course of the trial, The Individual will have given us a blood sample at each visit. At every visit, some of the blood will be sent to the laboratory at The Individual's hospital to check their thyroid function and determine the dose of ATD that they need. These bloods would have been taken anyway as part of normal NHS care. At visits 1,2,7,10,14 and 18 we will also send blood (approximately 10mls) to a laboratory at the Newcastle Upon Tyne Hospitals. The team there will use the samples to look at the level of antibodies that cause GD and the levels of thyroid hormone and for an investigation into newly discovered markers of the way the body's immune system works. A small amount of the sample that are transported to Newcastle will be stored for about 5 years just in case we need to carry out further tests in future. At visits 1 and 10 we will collect an additional small blood sample of approximately 2.5mls (4.5mls if you are a Newcastle participant) for RNA analysis and DNA analysis (Newcastle participants only), to help us try to predict which patients are more likely to relapse after stopping treatment. Some of the findings from tests we do on these samples may be shared with other researchers doing similar research.

CAN THE INDIVIDUAL PART IF SHE IS (OR THEIR PARTNER IS) PLANNING ON BECOMING PREGNANT?

We cannot give RTX to any females who are pregnant or planning on becoming pregnant during the trial, because there may be risks to the unborn baby. We also cannot give RTX to any males who are planning a pregnancy with their partner during the trial. RTX might stay in the body for up to 12 months after the infusion. Because participants in the trial will not know which treatment they received (RTX or placebo) all males and females participating in the trial, who are sexually active, must agree to use highly effective forms of contraception for at least 12 months. The trial team will discuss highly effective forms of contraception with these participants. Please see Appendix 1 for further information on highly effective contraceptive methods.

If The Individual or The male Individual's partner becomes pregnant during the trial, you must tell the research team immediately.

WHAT ARE THE BENEFITS OF TAKING PART?

It is not possible to know if The Individual will directly benefit from taking part in this trial. Taking part could mean The Individual has access to a treatment not usually offered in their local hospital. The Individual may, however, receive the placebo and not the RTX and this trial may show that it is no more effective than just taking ATD. Hopefully, The Individual's participation in this trial will help us improve the treatment patients like The Individual receive in the future. Throughout the trial, you and The Individual will also have contact with members of the local research team, which patients sometimes find helpful.

WHAT ARE THE RISKS OF TAKING PART?

Because RTX works by reducing the activity of your immune system, there is a small risk that The Individual might develop a serious infection, such as pneumonia, after the infusion. If this happens to The Individual, then they may have to be hospitalised to receive antibiotic treatment. However, most people have RTX without any infection occurring as a result.

WHAT IF THERE IS A PROBLEM?

If you are worried about anything related to The Individual taking part in this trial, you can speak to the trial research team (see contact details at the end of this Patient Information Sheet) who will do their best to answer your questions. Or you can contact the doctor running this trial Dr Claire Wood (0191 2821813 or ask for Dr Wood via the Royal Victoria Infirmary Switchboard during office hours on 0191 233 6161) to discuss your concerns.

If you prefer to raise your concerns with someone not involved in The Individual's care, you can contact your hospital's Patient Advice and Liaison Service (PALS) in England and Wales or the Patient Advice and Support Service (PASS) in Scotland. This service is confidential and can be contacted through any of the details below:

Telephone **SITE TO LOCALISE**

Email **SITE TO LOCALISE**

Address **SITE TO LOCALISE**

Alternatively, if you wish to make a formal complaint you can contact the Patient Relations Department through any of the details below:

Telephone **SITE TO LOCALISE**

Email **SITE TO LOCALISE**

Address **SITE TO LOCALISE**

If you have a question about how your data is being handled, please contact **SITE TO ADD TRUST DPO CONTACT**

WHAT IF THE INDIVIDUAL BECOMES UNWELL?

If The Individual becomes unwell and they need medical attention please go directly to their nearest Emergency (A&E) department. Let the staff in A&E know The Individual is taking part in the RiGD2 trial. It will be helpful for them when treating The Individual to have the details of the trial so, if possible, please remember to bring along their RiGD2 trial Patient Safety Card.

WHAT IF SOMETHING GOES WRONG?

In the unlikely event that something goes wrong, and The Individual is harmed during this research due to someone's negligence, then you may have grounds for a legal action for compensation, but you may have to pay your legal costs. NHS Indemnity does not offer no-fault compensation (i.e., for harm that is not anyone's fault). Newcastle University also has insurance arrangements in place to cover Newcastle University staff involved in designing and managing the trial.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

If new information becomes available during this trial that is important to The Individual's care and treatment, you will be told about this by the research team at the earliest opportunity. This may be done via email, telephone, or letter in the post. You will then be able to decide to whether you wish for The Individual to continue or stop taking part in the trial.

WHAT WILL HAPPEN IF I WANT THE INDIVIDUAL TO STOP TAKING PART ('WITHDRAW')?

The Individual can stop taking part in the trial at any time and for any reason, without having to tell us why. However, by signing the consent form you agree to us keeping any information and samples that The Individual has given so far. We may continue to collect data from The Individual's medical records, but we will stop if you tell us to do so. If The Individual does withdraw from the trial, they will still need to be seen on a regular basis by their clinical care team at the hospital who are familiar with the normal management of GD.

WILL THE INDIVIDUAL'S GP BE TOLD THEY ARE TAKING PART?

Yes. If you decide for The Individual to take part in this trial, we will send a letter and this Patient Information Sheet to their GP. It will also be noted in The Individual's hospital medical records.

WILL THE INDIVIDUAL BE PAID FOR BEING IN THE TRIAL?

No, The Individual will not be paid for being in the trial. If The Individual needs to attend any trial visits, which are not undertaken as part of their normal clinical visit, we will reimburse them for reasonable travel expenses.

WHAT WILL HAPPEN TO THE RESULTS OF THE TRIAL?

The results of the trial will be published in scientific journals and presented in meetings to other doctors, nurses, researchers and patients and through the British Thyroid Foundation which is a patient organisation that supports people with thyroid disorders. The Individual will not be named in any publication or presentation. The Individual's identity will always be protected. A report will be written for the trial funder. The results will be available at the end of the trial through publications, in the wider press and directly to patient groups. The Individual will be provided with a copy of the summary of the results from their trial hospital.

We will also be publishing updates on the British Thyroid Foundation website.

WHO IS ORGANISING AND FUNDING THE TRIAL?

This study has been funded by the National Institute for Health and Care Research (NIHR) as part of an Efficacy and Mechanism Evaluation Programme Advanced Fellowship. This trial is sponsored and indemnified by the Newcastle Upon Tyne NHS Foundation Trust and Newcastle University. The Newcastle Clinical Trials Unit, part of Newcastle University, is organising and managing the trial.

WHO HAS REVIEWED THE TRIAL?

All research in the NHS is reviewed by an independent group of people called an NHS Research Ethics Committee (REC). This is to protect the interests of patients and the public taking part in research. This trial has been reviewed and given a favourable opinion London – Brighton & Sussex Research Ethics Committee ref:25/LO/0301. The trial has also been approved by the NHS Health Research Authority (HRA) and the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA are responsible for approving all studies involving medicines. The Newcastle upon Tyne Hospitals NHS Foundation Trust has reviewed all the trial documentation and assessed the risks of this trial as part of their responsibility as trial Sponsor. This is to ensure we are not doing anything harmful to The Individual during the trial and that their data is collected safely and stored securely.

HOW HAVE PATIENTS AND THE PUBLIC BEEN INVOLVED IN THIS TRIAL?

The RiGD2 PPI Steering Group based in Newcastle upon Tyne have reviewed this Patient Information Sheet and the consent form. This group contains patients with GD of different ages and locations around the UK. The CEO of the British Thyroid Foundation has also reviewed this Patient Information Leaflet and consent form.

WHERE WILL YOU KEEP THE INDIVIDUAL'S INFORMATION DURING THE TRIAL?

Database

The Individual's information will be collected and stored on a secure database called Ennov™ to ensure that it is kept safe. The information will be used for analysis to help us decide which treatment is better for patients.

This information will include The Individual's trial and personal information such as their:

- age
- sex at birth
- height
- weight
- ethnicity
- post code
- current medications
- blood results
- other information related to their GD treatment

Postcodes will be included in the trial analysis to get an idea of the diversity of the patients taking part in the trial and to see if patients from certain areas do better or worse on the treatment depending on where they live. However, only people working on the trial who need to see this information will be able to see it.

If you agree to have The Individual's complete the trial questionnaires electronically then your:

- email address
- mobile number

will be stored encrypted within Ennov™ to send you links and reminders for their questionnaires this will remain encrypted in Ennov™ during the archiving period.

The Individual's name and NHS number will not be stored on Ennov™.

NHS Server

The local trial team will store the Individual's:

- Name
- NHS number
- contact details

on their secure NHS server and will use these details to get in touch with them to suggest an appropriate ATD dose after trial visits 1-13. They may also need to contact The Individual regarding longer term thyroid status and well-being. Your/ their contact details (such as phone number, email address, home address or postcode) will only be available to authorised members of the research team at your hospital and will not be available to anyone from the sponsor in charge of the trial (The Newcastle upon Tyne Hospitals NHS Foundation Trust), the funder of the trial (National Institute of Health Care Research) or the trial management team (Newcastle Clinical Trials Unit, Newcastle University) or regulatory bodies (such as the Health Research Authority or the Medicine and Healthcare Products Regulatory Agency) who may need to view the trial information to check that the trial is being run correctly.

Newcastle University Server

Any trial data held by the trial management team at the Newcastle Clinical Trials Unit (NCTU), part of Newcastle University, will have a code number instead of The Individual's name. The NCTU will receive a copy of your consent form for safety purposes. This will be destroyed once it has been reviewed.

HOW WILL WE USE INFORMATION ABOUT THE INDIVIDUAL?

We will need to use information from The Individual and from their medical records for this trial.

This information will include their:

- name
- age
- ethnicity
- contact details (including postcode)
- NHS number
- diagnosis
- levels of thyroid hormones in their blood
- wellbeing

People will use this information to do the research or to check The Individual's records to make sure that the research is being done properly.

People who do not need to know who the Individual is will not be able to see their name or contact details. The Individual's data will have a code number instead.

The Newcastle upon Tyne Hospitals (NUTH) NHS Foundation Trust is the Sponsor of this research. NUTH is responsible for looking after The Individual's information. We will share their information related to this research trial with the following types of organisations:

- researchers at healthcare organisations who are providing a service for the trial (e.g., laboratories)
- Organisations undertaking the management of the trial
- Regulatory bodies

We will keep all information about The Individual safe and secure by:

- Making sure only people who need to see or know about The Individual's information have access to it
- Making sure access to The Individual's information is minimised so the people who need to access it only see the parts they need to see to undertake their role on the trial
- Storing the information we collect about The Individual securely on-site on NHS hospital computers and locked filing cabinets or off- site in a secure database called Ennov™
- Archiving (keeping) the information we collect about The Individual in special facilities designed to safely store patient information

We may share data about The Individual outside the UK for research related purposes to:

- aid other researchers in the future with their research

If this happens, we will only share the data that is needed. We will also make sure The Individual cannot be identified from the data that is shared where possible. This may not be possible under certain circumstances – for instance, if The Individual has a rare illness, it may still be possible to identify them. If The individual's data is shared outside the UK, it will be with the following sorts of organisations:

- researchers at other universities
- researchers at healthcare organisations who are also working to improve treatments for patients

We will make sure The Individual's data is protected. Anyone who accesses The Individual's data outside the UK must do what we tell them so that The Individual's data has a similar level of protection as it does under UK law. We will make sure The Individual's data is safe outside the UK by doing the following:

- (some of) the countries The Individual's data will be shared with have an adequacy decision in place. This means that we know their laws offer a similar level of protection to data protection laws in the UK
- we use specific contracts approved for use in the UK which give personal data the same level of protection it has in the UK. For further details [visit the Information Commissioner's Office \(ICO\) website](#)
- we do not allow those who access The Individual's data outside the UK to use it for anything other than what our written contract with them says
- we need other organisations to have appropriate security measures to protect The Individual's data which are consistent with the data security and confidentiality obligations we have. This includes having appropriate measures to protect The Individual's data against accidental loss and unauthorised access, use, changes or sharing
- we have procedures in place to deal with any suspected personal data breach. We will tell The Individual and applicable regulators when there has been a breach of The Individual's personal data when we legally have to. For further details about UK breach reporting rules [visit the Information Commissioner's Office \(ICO\) website](#)

HOW WILL WE USE INFORMATION ABOUT THE INDIVIDUAL AFTER THE TRIAL ENDS?

Once we have finished the trial, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that The Individual took part in the trial.

We will keep The Individual's trial data for a maximum of 25 years after the trial ends. The trial data will then be fully anonymised and securely archived or destroyed.

WHAT ARE MY CHOICES ABOUT HOW THE INDIVIDUAL'S INFORMATION IS USED?

- You can stop The Individual being part of the trial at any time, without giving a reason, but we will keep information about The Individual that we already have
- If you choose to stop The Individual taking part in the trial, we would like to continue collecting information about their health from their medical records. If you do not want this to happen, tell us and we will stop
- You have the right to ask us to access, remove, change or delete data we hold about The Individual for the purposes of the trial. We might not always be able to do this if it means we cannot use The Individual's data to do the research. If so, we will tell you why we cannot do this.
- If you agree for The Individual to take part in this trial, they will have the option to take part in future research using their data saved from this trial

WHERE CAN I FIND OUT MORE ABOUT HOW THE INDIVIDUAL'S INFORMATION IS USED?

You can find out more about how we use The Individual's information, including the specific mechanism used by us when transferring The Individual's personal data out of the UK.

- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to the Sponsor Data Protection Officer at nuth.dpo@nhs.net

WHAT SHOULD I DO IF I DECIDE FOR THE INDIVIDUAL TO TAKE PART?

If you would like The Individual to take part, have any further questions or would like any further information about the trial or the rights of participants, please feel free to contact the people below. You or The Individual's doctor should also contact them if The Individual goes on to take part in the trial and you or they have any questions during their participation.

Your contacts for the trial are:

Principal Investigator (the doctor in charge of the trial at your hospital):

Name:

Address:

Phone:

Email:

Research Nurse (the nurse working on the trial at your hospital):

Name:

Address:

Phone:

Email:

Thank you for taking time to read this Patient Information Sheet

APPENDIX 1 DESCRIPTION OF HIGHLY EFFECTIVE CONTRACEPTION

Highly effective forms of contraception that **are allowed**:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner (if partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)

The following forms of contraception are **not allowed**:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom* with or without spermicide
- Cap, diaphragm or sponge with spermicide

The following are **not acceptable** methods of contraception:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- withdrawal (coitus interruptus)

- spermicides only
- lactational amenorrhoea method (LAM). *Female condom and male condom should not be used together.