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# Rituximab in Graves' disease 2

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| **Submission date**<br>28/03/2025 | **Recruitment status**<br>Recruiting | [X] Prospectively registered<br>[_] Protocol<br>[_] Statistical analysis plan<br>[_] Results<br>[_] Individual participant data<br>[X] Record updated in last year |
| **Registration date**<br>14/07/2025 | **Overall study status**<br>Ongoing | |
| **Last Edited**<br>11/08/2025 | **Condition category**<br>Other | |

## Plain English summary of protocol

Background and study aims
Graves' disease (GD) is one of the more common disorders of the thyroid, affecting 700 young people in the UK each year. In GD, the immune system mistakenly causes the thyroid gland to produce too much hormone, leading to 4 main symptoms: weight loss, shakiness, heart racing and feeling hot or sweaty. This leads to a profound impact on physical health, quality of life, attention span and education or work performance. Treating GD is more difficult in young people because standard antithyroid drug therapy (ATD) often causes side effects and is less likely to result in a cure when treatment is stopped. Only 1 in 4 patients is cured after 2 years of ATD. Other options if the GD recurs are thyroid surgery or radioactive iodine therapy. These are associated with additional risks and greater costs in the young, necessitate lifelong hormone replacement and reduced quality of life. Rituximab (RTX) medication is used to treat many immune disorders. It works by targeting blood cells that make the antibodies responsible for attacking the thyroid in GD. A recent exploratory study suggested that giving just one dose of RTX in addition to standard ATD is well tolerated and may increase the likelihood of remission, but needs to be explored in a bigger trial. This study aims to determine whether a single dose of RTX, given in addition to 2 years of ATD, increases the remission rate in young people with GD.

Who can participate?
Patients aged between 12 and 24 years old with GD in 26 UK centres.

What does the study involve?
Participants will be randomly allocated to receive either the usual 2-year course of ATD tablets or a single dose of RTX as well as 2 years of ATD. RTX is given by a 3-hour drip, and participants won't know whether they received RTX or a salt water infusion instead. The study will compare the numbers in each group with normal thyroid function and those who have had no further treatment 12 months after stopping ATD. If RTX works, it could be introduced as part of standard GD treatment.

What are the possible benefits and risks of participating?
It is not possible to know if you will directly benefit from taking part in this trial. Taking part could mean you have access to a treatment not usually offered in your local hospital. You 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, your participation in this trial will help us improve the treatment patients like you receive in the future. Throughout the trial, you will also have contact with members of the local research team, which patients sometimes find helpful.

1. There is an additional time burden relating to study participation, above that associated with the time to attend the hospital for the routine treatment of GD. There are an additional two visits required compared to the standard of care. The second of these visits involves a three-hour infusion of either the IMP or placebo. In addition, the research centre may be a greater distance from home than the participant's usual treatment centre. Whilst excess travel costs will be reimbursed, additional time burden can't be compensated for. It is possible that being in the study may make it easier for the participants to contact medical personnel about their condition /treatment, which could offset the time burden.
2. All participants must receive a cannula at visit 2 to receive either the IMP or placebo. Citing a cannula comes with associated risks and burdens – it can be a painful procedure (although this will be mitigated by offering either numbing cream or spray), and it is possible that the process may need to be repeated if the cannula can't be sighted in a vein at the first attempt. There is a possible risk of infection associated with sighting a cannula, although a non-touch, aseptic technique will be used to prevent this. The participant would require a blood test anyway at this stage of their disease management, but a cannula would not usually be needed. This will be explained to the participants in the patient information sheet and re-discussed at the time of consent. This issue was discussed at length with the focus groups prior to study design, and the young people involved felt it was very important that all participants should receive a cannula in order to be blinded to the treatment process, so that there is a reduced risk of bias introduced during the attainment of secondary outcomes.
3. Participants must commit to not becoming pregnant during the trial, or if male, using appropriate contraception, so that their partner does not become pregnant during the trial. This is because the potential risk of the IMP (rituximab) to the unborn fetus cannot be quantified. This is a theoretical risk, but the participants must be aware of this. A pregnancy test will be carried out within 7 days prior to the rituximab infusion and again at year 1 to reduce this risk.
4. There is a small risk associated with reduced immunity to infection for up to 6 months after receiving rituximab, the IMP. This is a very small risk, particularly as only one dose is being given at a relatively low dose. This risk will be reduced by the participants being aware of the effect of rituximab on immune response, as well as their GP and other medics involved in their care, so that this can be considered and appropriately investigated/managed if any symptoms arise that may be a result of reduced immunity. Studies have shown that the B-cell count returns to normal within six months, so this risk is short-lived.
4. During the infusion of the IMP (rituximab) itself, there is a very rare risk of an infusion reaction. This will be monitored carefully, and regular observations, including pulse and blood pressure, will be taken throughout the infusion. If the observations change or the participant reports any feelings of discomfort, the infusion will either be slowed or stopped temporarily before being restarted at a lower rate. There were no infusion reactions at all during the pilot study, so this risk is thought to be very low.
5. There is a very rare side of rituximab, known as progressive multifocal leukencephalopathy (or PML). This will be closely monitored at each trial visit. It is more likely to occur in participants who already have a weakened immune system, which is not the case in this trial cohort.
6. As with any study where participant data is collected and stored, there is a potential risk of a data breach, which could pose a threat to the participant's confidentiality. In order to minimise this risk, all data will be collected and stored confidentially according to GDPR regulations and participants' names will be replaced with a code. More information regarding data collection and storage can be made available to participants on request and will be discussed in further detail in the participant information sheet.

Where is the study run from?
Newcastle University, UK

When is the study starting and how long is it expected to run for?
March 2025 to July 2027

Who is funding the study?
The National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme.

Who is the main contact?
Dr Claire Wood, claire.wood@newcastle.ac.uk

# Contact information

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Scientific

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# Additional identifiers

### Clinical Trials Information System (CTIS)
Nil known

### Integrated Research Application System (IRAS)
1010765

### ClinicalTrials.gov (NCT)
Nil known

### Protocol serial number
10890, CPMS 58139

# Study information

### Scientific Title
Multi-centre randomised, placebo-controlled, single blind trial to investigate the efficacy of adjuvant Rituximab therapy compared to standard Anti-thyroid drug treatment of Graves' Disease in young people with newly diagnosed disease.

### Acronym
RIGD2

### Study objectives
To determine if a single dose of RTX, alongside 2 years of standard ATD therapy, results in a clinically significant increase in the proportion of young people with GD who are in disease remission at 36 months.

To determine relationship between cumulative ATD dosage and remission status.
To examine the relationship between longitudinal immunological markers and thyroid hormone status
To examine the safety of the intervention treatment regimen
To examine quality of life in patients in both treatment arms

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
Pending approval; ref: 25/LO/0301

### Study design
Randomized controlled single-blind parallel-group-assignment study

### Primary study design
Interventional

### Study type(s)
Safety, Efficacy

### Health condition(s) or problem(s) studied
Medical condition: Graves disease
Medical condition in lay language: Graves Disease (autoimmune hyperthyroidism).
Therapeutic areas: Diseases [C] - Immune System Diseases [C20]

### Interventions
Arm 1- Standard ATD therapy + Placebo: Participants will receive an intravenous (IV) infusion of saline (0.9% NaCl) over 3 hours together with antipyretic, antihistamine and steroid cover

administered just prior to the infusion as follows:
• Oral paracetamol (500mg 12-15 years of age or 1g ≥16 years)
• Methylprednisolone 125mg IV infusion over 30 minutes
• Chlorphenamine 10mg IV injection over 1 minute

Arm 2- Standard ATD therapy + RTX: Patients will be managed as per the standard therapy arm, except that instead of the placebo, they will receive a single dose of 500mg RTX. RTX will be administered by slow IV infusion over approximately 3 hours with antipyretic, antihistamine and steroid cover given just prior to infusion in identical doses to arm 1:
• Oral paracetamol (500mg 12-15 years of age or 1g ≥ 16 years)
• Methylprednisolone 125mg IV infusion over 30 minutes
• Chlorphenamine 10mg IV injection over 1 minute

Treatment allocation will be performed by permuted blocks (concealed block size) stratified for sex (at birth), age at diagnosis (>16 years) and initial free T4 (FT4) level (≥50pmol/l).
Visits 2-14 Follow Up Visits (years 1 & 2)
• Concomitant medications (including ATD compliance check)
• Clinical exam
• Pregnancy test (Visit 10)
• Research bloods (visits 2, 7, 10, 14, 18); Safety bloods (all visits); Additional bloods (visits 1 and 10)
• Questionnaires administered (visits baseline, 2, 7, 10, 14, 18)
• AEs and SAEs checked recorded/reported

Visit 14 (end of year 2)
• Stop ATD therapy

Visits 15-18 Follow Up Visits (year 3)
• Concomitant medications (including ATD extension)
• Clinical exam
• Bloods (Thyroid function); Research Bloods (visit 18 only)
• AEs and SAEs checked recorded/reported
• Questionnaires administered (visit 18)

## Intervention Type
Drug

## Phase
Phase III

## Drug/device/biological/vaccine name(s)
MabThera [Rituximab]

## Primary outcome(s)
The proportion of patients in remission from GD measured using thyroid function tests (TSH, free T4 and free T3) and the remission rate at 2 years post-ATD treatment

## Key secondary outcome(s))
1. The cumulative ATD dosage at the end of the treatment period, the time to stop ATD and the dosage of ATD measured using prescribed medication doses and patient reported compliance at the end of 24 months (V14)

2. The time to recovery (measured in days) of B cell numbers (CD 19+ cells) to 1% of total lymphocytes and concentrations of TRAb antibody levels at visits 1, 2, 7, 10, 14 and 18. Immunological markers will also be analysed by regimen, in relation to thyroid hormone status and as a predictor of relapse
3. The total number of serious adverse events measured using summative total from database from Day 0 (Baseline) to the participant's last visit (V18)
4. Quality of life (QoL) measured using the thyroid-specific QoL questionnaire (ThyPRO-39) and utility values measured using the EQ-5D-5L/EQ-5DY-5L questionnaires at visits 2, 7, 10, 14, and 18
5. Cumulative ATD dosage at the end of the treatment period, the time to stop ATD and the dosage of ATD using prescribed medication doses and patient reported compliance at the end of 24 months (V14)
6. Time to recovery (measured in days) of B cell numbers (CD 19+ cells) to 1% of total lymphocytes and concentrations of TRAb antibody levels at visits 2, 7, 10, 14, and 18
7. The total number of serious adverse events from Day 0 (Baseline) to the participant's last visit (V18) at 3 years.

### Completion date
31/07/2030

## Eligibility

### Key inclusion criteria
1. Excess thyroid hormone concentrations at diagnosis: elevated FT3 and/or FT4 (based on local assay)
2. Suppressed (un-recordable) TSH (based on local assay)
3. Patients between the ages of 12-24 years inclusive who are less than 12 weeks from the initiation of ATD treatment (CBZ or PTU) for the first time
4. Elevated thyroid binding inhibitory immunoglobulin or thyroid receptor antibodies (TRAb including TSH-Binding Inhibitor Immunoglobulins (TBII)) based on local assay. Patients may or may not have a raised TPO antibody titre
5. Confirmation of no current pregnancy. Participant must be willing to undergo pregnancy testing, as stipulated in protocol section 3.2.4.
6. Willingness to use effective forms of contraception for 12 months post-treatment with RTX /placebo (for sexually active patients, see protocol section 3.2.5)
7. Able and willing to adhere to a 3-year trial period
8. Able to provide informed consent (parent/legal guardian can if <16 years of age or is an adult lacking capacity)

### Participant type(s)
Patient

### Healthy volunteers allowed
No

### Age group
Mixed

### Lower age limit
12 years

### Upper age limit

24 years

### Sex
All

### Key exclusion criteria
1. Previous episodes of autoimmune thyroid disease
2. Patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections)
3. Severely immunocompromised patients
4. Patients with known allergy or contraindication to carbimazole and propylthiouracil
5. Participants with previous use of immunosuppressive or cytotoxic drugs (including RTX and methylprednisolone but excluding inhaled glucocorticoid and oral glucocorticoid for asthma or topical glucocorticoid for eczema)
6. Chromosomal disorders known to be associated with an increased risk of autoimmune thyroid disease including Downs' syndrome and Turners' syndrome
7. Currently pregnant or planning to become pregnant during the trial period
8. Currently breast-feeding
9. Participants with significant chronic cardiac, respiratory or renal disorder or non-autoimmune liver disease
10. Participants with known allergy or contraindication to RTX or methylprednisolone
11. Participants with evidence of Hepatitis B/C infection, assessed by determining hepatitis 'B' surface antigen (HBsAg) status, hepatitis 'B' Core antibody (HB Core antibody) status and hepatitis 'C' virus antibody (HCV antibody)
12. Participants with evidence of Tuberculosis infection, assessed by Quantiferon test
13. Participants in families who know they will be moving out of the United Kingdom during the 2 years following RTX treatment and thus unable to commit to attending follow-up visits
14. Participants currently involved in any other clinical trial of an IMP or who have taken an IMP within 30 days prior to trial entry
15. Absence of informed consent from parent/legal guardian for participants age <16 years

### Date of first enrolment
31/07/2025

### Date of final enrolment
31/10/2026

## Locations

### Countries of recruitment
United Kingdom

### Study participating centre
-
United Kingdom
-

## Sponsor information

**Organisation**
Newcastle upon Tyne Hospitals NHS Foundation Trust

**ROR**
https://ror.org/05p40t847

# Funder(s)

**Funder type**
Government

**Funder Name**
Efficacy and Mechanism Evaluation Programme

**Alternative Name(s)**
NIHR Efficacy and Mechanism Evaluation Programme, Efficacy and Mechanism Evaluation (EME), EME

**Funding Body Type**
Government organisation

**Funding Body Subtype**
National government

**Location**
United Kingdom

# Results and Publications

**Individual participant data (IPD) sharing plan**
The data-sharing plans for the current study are unknown and will be made available at a later date

**IPD sharing plan summary**
Data sharing statement to be made available at a later date