Newcastle University

NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

RiGD-2

Clinical Trial Protocol

Full 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

Short Title/Acronym: **R**ituximab **i**n **G**raves' **D**isease **2** (**RiGD-2**)

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This protocol has regard for the HRA guidance.

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RiGD2 LOGO

Logo was co-created with the RiGD-2 Young People Advisory Group and designed by Sophie Partridge

PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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Trial Website

[http://www.******.co.uk]

TRIAL SUMMARY

Trial Title	A randomised controlled trial of adjuvant rituximab in young people with Graves' disease	
Acronym	RiGD2	
Clinical Phase	Phase III	
Summary of Trial Design	Multi-centre randomised, placebo-controlled, single-blinded (to participants)	
Summary of Participant Population	Patients between 12 and 24 years (inclusive) with new-onset Graves' hyperthyroidism who are within 12 weeks of commencing antithyroid drug (Carbimazole or Propylthiouracil) for the first time	
Planned Sample Size	124 (62 RTX; 62 Placebo)	
Planned Number of Sites	13 Paediatric and 13 Adult tertiary care units across 26 sites	
Intervention Duration	24 months	
Follow Up Duration	36 months after baseline visit	
Planned Trial Period	72 months in total (36 months trial running at site)	
Investigational Medicinal Product(s)	Rituximab (RTX)	
Dose & Route of Administration	One dose of RTX (500mg) given by intravenous infusion.	
Placebo	Saline (0.9% NaCl)	
Dose & Route of Administration	One dose of saline (250ml) given by intravenous infusion	
Non-Investigational Medicinal Products	Thionamide oral anti-thyroid drugs (ATD): • Carbimazole (CBZ) Or • Propylthiouracil (PTU)	
	Objectives	Outcome Measures
Primary	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 (12 months after discontinuing ATD)	Comparison of the proportion of patients in remission from GD at 3 years (36 months) between randomised groups.
Secondary	To determine the relationship between ATD	Comparison of the cumulative ATD dosage at the end of the treatment

	therapy and remission status.	period, the time to stopping ATD and the dosage of ATD at the end of 24 months between the two treatment arms.
	To examine the relationship between longitudinal immunological markers (time to recovery of B-cell function and concentrations of TRAb antibody levels) and thyroid hormone status	Comparing time to recovery of B cell numbers (CD 19+ cells) to 1% of total lymphocytes and concentrations of TRAb antibody levels between both treatment arms at various time points throughout the trial. Immunological markers will also be analysed by regimen, in relation to thyroid hormone status and as predictor of relapse.
	To examine the safety of the intervention treatment regimen	Comparing the total number of serious adverse events fromthe point of consent to participants last visit between both treatment arms.
	To examine quality of life in patients in both treatment arms	Comparing mean per patient scores on the ThyPRO-39 and utility values on the EQ-5D-5L/EQ-5D-Y-5L questionnaires between both treatment arms at various time points throughout the trial.
Exploratory Objectives	To conduct cost-effectiveness analysis comparing the intervention treatment regimen to the current ATD regimen standard of care offered in the NHS from the perspective of the NHS.	Comparing mean per patient costs and outcomes (QALYs or ThyPRO-39 scores or the primary outcome measure) between both treatment arms using the incremental cost-effectiveness ratio.
	To investigate potential relationships between immunological markers and remission or relapse rate.	A longitudinal study of immunological markers in response to ATD +/-RTX and between remission and relapse groups. Expression of specific immunological markers will be quantified.
Intervention	Arm 1) Standard ATD therapy (usually CBZ but occasionally PTU) daily for 2 years + 1 dose of placebo (250 ml infusion of 0.9% NaCl) Arm 2) Standard ATD therapy (usually CBZ but occasionally PTU) daily for 2 years + 1 dose of 500mg RTX	

CONTENTS

GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
ALT	Alanine Aminotransferase
APRIL	A Proliferation Inducing Ligand
AR	Adverse Reaction
ATD	Anti-Thyroid Drug
BAFF	B-Cell Activating Factor
BCMA	B Cell Maturation Antigen
βHCG	BetaHuman Chorionic Gonadotropin
BR	Block and Replace
BTF	British Thyroid Foundation
^{o}C	Degrees Celsius
CAPA	Corrective and Preventative Actions
CBZ	Carbimazole
CD	Cluster (of) Differentiation
CDMS	Clinical Database Management System
CEA	Cost effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation

CTIMP	Clinical Trial of an Investigational Medicinal Product
CUA	Cost Utility Analysis
CV	Curriculum Vitae
DNA	Deoxyribonucleic Acid
DT	Dose Titration
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EDTA	Ethylenediamine Tetra-acetic Acid
EME	Efficacy and Mechanism Evaluation
Ennov™	Ennov Clinical V8.2.400 database
EQ-5D-5L	EuroQol questionnaire (5 dimensions, 5 levels), administered to adults
EQ-5D-Y-5L	EuroQol questionnaire (5 dimensions, 5 levels), administered to young people
ETA	European Thyroid Association
FT3	Free Tri-Iodothyronine
FT4	Free thyroxine
g	Gram
GCP	Good Clinical Practice
GD	Graves' Disease
GDPR	General Data Protection Regulations
GP	General Practice
HB Core Antibody	Hepatitis 'B' Core antibody

HBsAg	Hepatitis B Surface Antigen
HCV Antibody	Hepatitis C Virus Antibody
HCRW	Health and Care Research Wales
hr	Hour
HRA	Health Research Authority
HTA	Human Tissue Authority
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
IUD	Intrauterine Device
IV	Intravenous
KREC	Kappa-deleted Recombination Excision Circles
kg	Kilograms
l	Litre
LAM	Lactational Amenorrhoea Method
LFT	Liver function test
m^2	Metres squared

MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
mcg	Microgram
ml	Millilitre
mg	Milligram
NaCl	Sodium Chloride
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NIHR	National Institute for Health Research
NIMP	Non-Investigational Medicinal Product
PAX	PAX gene blood RNA tube
PI	Principal Investigator
PIS	Participant Information Sheet
PML	Progressive Multifocal Leukoencephalopathy
pmol	Picomol
PPI	Patient and Public Involvement
PSS	Personal Social Services
PTU	Propylthiouracil
QA	Quality Assurance
QALYs	Quality-Adjusted Life Years
RAI	Radioactive Iodine
RCT	Randomised Controlled Trial

REC	Research Ethics Committee
RNA	Ribonucleic Acid
RSI	Reference Safety Information
RTX	Rituximab
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SRF	Sample requisition form
SUSAR	Suspected Unexpected Serious Adverse Reaction
TACI	Transmembrane Activator and Cyclophilin Ligand Interactor
TB	Tuberculosis
TBII	TSH-Binding Inhibitor Immunoglobulins
TED	Thyroid Eye Disease
ThyPro-39	Thyroid specific patient reported outcome (questionnaire)
TPO	Thyroid Peroxidase (antibody)
TRAbs	Thyroid-Stimulating Hormone receptor Antibodies
TRECs	T-cell Receptor Excision Circles
TSHR	Thyroid-Stimulating Hormone Receptor
TMG	Trial Management Group
TSC	Trial Steering Committee

TMF	Trial Master File
USM	Urgent Safety Measure
UK	United Kingdom

1. BACKGROUND

Graves' disease (GD) is an autoimmune disease that occurs when the body mistakenly produces thyroid-stimulating hormone receptor IgG autoantibodies (TRAbs) in the thyroid gland and surrounding lymphoid tissue that then bind to and activate the thyroid-stimulating hormone receptor (TSHR) on the thyroid gland. Uniquely for autoimmune endocrinopathies, these autoantibodies directly stimulate the thyroid gland and cause thyrocyte hyperplasia and autonomous thyroid hormone production, resulting in hyperthyroidism. GD is the commonest cause of hyperthyroidism in young people but is still a rare disease in this age group with an annual incidence of 1 in 10,000 adolescents (around 700 per year) in the UK[1]. GD can occur at any age, but the incidence increases with age. Worldwide, the incidence of paediatric GD appears to be rising, with global incidences reported between 1.5 to 6.5 per 100,000[2–4]. It is likely that environmental and immunological stimuli cause disease in genetically predisposed individuals[5].

Consequences of excess thyroid hormone: Excess thyroid hormone has a detrimental impact on a range of organ systems including the heart, bone, brain, liver, and gastrointestinal tract. Symptoms often develop gradually and are non-specific which frequently leads to a delay in the diagnosis being made. The impact on central nervous system function can have profound implications for academic performance, mental health and quality of life in the young[6]. Excess thyroid hormone can reduce bone density, result in myopathy, and cause cardiovascular symptoms and signs such as palpitations, dyspnoea and heart valve defects. Inflammation of the orbital tissues with proptosis (thyroid eye disease (TED)) can be very distressing and challenging to treat, with some cases requiring surgical intervention[7]. Other manifestations of excess thyroid hormone include weight loss, tremor, sleep disturbance and gastrointestinal dysfunction including diarrhoea. Occasionally, patients with severe GD can have a thyrotoxic crisis, a medical emergency with a reported mortality of 10-25% despite early recognition and treatment[8]. GD is, therefore, associated with significant morbidity and potentially mortality which underlines the need for these patients to be treated promptly and effectively.

Current treatment approaches and limitations: There have been no new therapies for GD with proven efficacy for over 60 years and the management pathway has changed little during this time. Conventional treatment options include anti-thyroid drugs (ATD), surgery (total

thyroidectomy) or radioactive iodine (RAI)[9]. Most young patients are commenced on carbimazole (CBZ), a thionamide oral ATD that is taken daily as a means of reducing thyroid hormone concentrations and rendering the patient euthyroid (normal serum thyroid hormone levels). Thionamides act principally by preventing iodination of tyrosine residues and reduce the synthesis of thyroxine. Young people are more likely to experience the side-effects of thionamides than adults, with 20% of patients experiencing problems such as rash, headache, muscle discomfort and joint pain[10–12]. The most concerning side-effect, however, is agranulocytosis, which means that any patient on thionamide who develops a fever or sore throat requires an urgent full blood count. This is a significant limitation of long-term ATD therapy. The only other thionamide available in the UK is propylthiouracil (PTU). This is only prescribed in exceptional circumstances in paediatric practice because of the 1 in 2,000 risk of liver failure in this age-group[11].

The overall remission rate after 2 to 3 years of ATD treatment is lower in young people with GD (20-30%) when compared to adults[13–15]. Whilst there is some evidence to suggest that longer courses of treatment may increase the likelihood of remission, the relationship between remission and duration of treatment is not clear cut. The 70-80% of patients who fail to remit after stopping ATD and who therefore become hyperthyroid again can choose to return to ATD or undergo definitive treatment, either with surgical thyroid gland removal (total thyroidectomy) or thyroid gland ablation using RAI. Thyroidectomy and RAI have well-recognised risks and limitations. Potential problems after thyroidectomy include bleeding, scar formation and voice change due to recurrent or superior laryngeal nerve involvement. Damage to adjacent parathyroid glands can also cause hypoparathyroidism with a potential requirement for long term supplementation with calcium and vitamin D[16]. In addition, the NHS tariff for thyroidectomy surgery is £2,400, making it an expensive procedure. RAI is not ideal in young people because of the potential increase in cancer risk following exposure to ionising radiation[17]. It is also associated with short-term inconvenience because the patient cannot mix with family or peers for 2 weeks following treatment, and because of biochemical instability for around 6 months afterwards. Importantly, both thyroidectomy and RAI therapy result in a requirement for lifelong levothyroxine replacement, which is associated with a reduced quality of life when compared to individuals with normal thyroid gland function[18–22] as well as compliance issues in young people. A recent study also showed that ATD is preferred

to either surgery or RAI[23]. Up to half of respondents in a survey of young people, however, reported that they did not feel recovered from their GD after a year of treatment with ATD, with more than 80% needing ongoing regular contact with healthcare professionals[6]. Missed days of schooling or work can have a significant impact on educational attainment or career opportunities as well as work and financial implications for their family. In addition to management being more complex in young people, the effects of thyroxine on the developing brain remain poorly understood and fluctuating thyroid hormone levels may have adverse long-term outcomes. Novel approaches to management are therefore needed to simplify treatment, improve GD outcome in young people and to increase the likelihood of a life without a requirement for long-term thyroid hormone replacement medication.

Rationale for an immunomodulatory approach to GD treatment: Autoimmune endocrine disease is a logical target for immunotherapy with the potential for agents including biologics to ameliorate the immune targeting of endocrine tissue. Type 1 diabetes is a key example where immunotherapy has been shown to preserve beta cell function with an associated alteration in disease course. In contrast to type 1 diabetes, a proportion of patients with GD can enter long term remission following a course of ATD alone which demonstrates the capacity for the immune system to adapt and tolerate autoantigens. The introduction of immunotherapy in addition to ATD has the prospect of increasing remission rates further. The hyperthyroidism of GD is driven by antibody production from B lymphocyte-derived plasma cells that reside in the thyroid and adjacent lymphoid tissues. A logical approach to managing an autoimmune disorder like GD is to ameliorate the underlying autoimmune process. RTX is a chimeric monoclonal antibody against the B lymphocyte cell-surface protein CD20. RTX removes B cells from the circulation, thyroid, and lymphoid tissues, leading to therapeutic immunomodulation in many autoimmune disorders, thought to be through a combination of mechanisms. These include reducing auto-antibody levels by preventing the generation of new plasma cells, and a reduction in tissue antigen-presentation which has a key role in providing T cell signals that perpetuate the autoimmune response[24]. RTX is an attractive therapeutic option as it has already been used as a safe and readily available licenced product in a range of other autoimmune conditions[25]. RTX has also been used extensively in children and young people for many years in the context of rheumatoid arthritis, idiopathic thrombocytopaenic purpura, haemolytic anaemia, systemic lupus erythematosus and renal

disorders, each with an excellent safety record[25, 26]. As CD20 is not expressed on mature plasma cells, administration of RTX does not affect the production of memory antibodies[27], therefore immune response to previously encountered pathogens remains unaffected. Hypogammaglobulinaemia (typically an isolated reduction in immunoglobulin M; (IgM)) is a possible but very rare side-effect in young people and may reflect an underlying but previously unrecognised immunodeficiency[28]. Following RTX treatment, circulating B-cell numbers recover within six months to two years.

B lymphocyte depleting immunotherapy appears to have disease-modifying activity in adults with GD. RTX administration has been associated with encouraging remission rates in adults with GD. The literature indicates that 53% of thyrotoxic adults (16/30) in case reports and case series have become euthyroid following RTX[29–32]. Many of these patients were selected based on more severe disease with relapsed GD or aggressive orbitopathy. The management of cases where there was no clear response to RTX were characterised by early intervention with either ATD, surgery or RAI within the first year after RTX therapy which may also have obscured a beneficial effect of immunotherapy on thyroid status.

Rituximab in thyroid eye disease (TED): TED is a significant immune manifestation of GD observed in 25-50% of adults. GD and TED have several immunopathogenic features in common, including shared autoantigens. To date there have been 2 double-blind randomised controlled trials (RCTs) of RTX in euthyroid adult patients suffering from TED, with contrasting findings; Salvi et al found a significant improvement in clinical activity score (a scale used to assess the severity of TED) whereas the study by Stan et al, which recruited patients with a longer disease duration, did not[29, 33]. RTX is a second-line treatment for moderate-to-severe and active TED according to recent consensus guidelines[34]. TED is observed in many children but is generally mild and does not usually require any formal treatment.

Rituximab in young people with GD: Our centre (Newcastle University) recently published results from a Medical Research Council funded single arm pilot study, which demonstrated that a single dose of RTX, given alongside ATD, improved remission rates in 27 young people, aged 12-20 years old with GD[35]. Forty-eight percent of these patients were in remission one year after stopping ATD compared to the 20 to 30% expected at 1 to 3 years after stopping ATD, based on the literature. The combination of RTX and ATD was well-tolerated, with no

serious side-effects linked to treatment. Thus, RTX showed a clear signal of efficacy in modulating the natural history of GD in children. To date there have been no RCTs of RTX in young patients with GD. There is currently no recently published or ongoing work in this area according to Clinical Trials websites, PubMed or within guidelines such as the recently published European Thyroid Association (ETA) guideline[9].

Rituximab in combination with standard ATD therapy: A single dose of RTX is not expected to have a significant impact on thyroid function in the weeks following initial presentation when patients are symptomatic because of underlying thyroid hormone excess. Participants would therefore need to receive standard ATD therapy to render them euthyroid in the first weeks post diagnosis. Thionamide ATD also has a specific immunomodulatory effect including reduction in thyroid autoantibody concentrations during treatment[36, 37]. These effects may involve alteration of thyroid antigen structure, inhibition of pro-inflammatory cytokines or inhibition of T lymphocytes by other potential mechanisms[38, 39]. Therefore, an additive or indeed synergistic effect of RTX and ATD is theoretically possible via combined effects on autoantibody generation. Another advantage of the immunomodulatory approach to autoimmune hyperthyroidism is the potential to reduce the likelihood of longer-term hypothyroidism and thus the need for lifelong thyroxine treatment[40, 41].

Key observations from the pilot study that underline the need for an RCT include[35]:

1. Remission rate that supports an impact of RTX on disease course.
2. Relationship between B cell response to RTX and the primary outcome (remission/relapse rate.
3. Marked fall in TRAb concentrations during the first year of the clinical trial.
4. Lower than expected ATD dose towards the end of the first year of treatment.
5. No severe adverse events linked to RTX.

1.1 Rationale

Rationale for the proposed trial: The proposed trial represents an assessment of two well established disease modulating agents being used together over a two-year period in young people for the first time. Before RTX can be recommended as an adjunct to ATD, a placebo-controlled, blinded, RCT to evaluate the efficacy, effect size and tolerability of this adjuvant regimen is required. Furthermore, as 52% of participants still relapsed in the pilot study

(where one dose of RTX was given at the start of 1 year treatment of ATD) we propose to administer ATD for 24 months in total, rather than 12 months. The additional period of ATD offers something additional to GD patients who did not remit in the pilot study. Recent paediatric guidance has recommended ATD for at least 3 years in children although the relationship between ATD duration and outcome beyond 2 years is not established[9, 15]. Young adults are frequently treated with an 18 month to 2-year course of ATD and so a 2-year course of therapy administered to all patients is a realistic, pragmatic treatment in the context of this trial. During the pilot study we noted that the amount of ATD required to maintain a euthyroid state was low with most patients on 10mg CBZ or less by 12 months post diagnosis. There was also an association between B cell number post RTX and increase in remission rate, with those patients with lower B cell numbers more likely to go into remission.

Overall Trial Hypothesis: We hypothesise that depletion of B cells by RTX in newly diagnosed patients with GD, when administered together with a standard course of thionamide ATD, will increase remission rate and long term euthyroidism when ATD is stopped. The clinical course of patients will be related to the immune profile at baseline and at the time that ATD is stopped.

1.2 Risk Assessment

This trial is categorised as Type B = somewhat higher than the risk of standard clinical care

2 TRIAL DESIGN

2.1 Summary of trial design

RiGD2 is a multicentre, randomised, placebo-controlled, single-blinded trial looking to recruit 124 participants aged 12-24 years with newly onset GD who are within 12 weeks of commencing ATD across 26 UK sites (13 paediatric units and 13 adult units) over an 18-month recruitment period. The trial will consist of 24 months of treatment with a 12-month follow-up period. The total trial duration is 6 years.

Patients will be randomised 1:1 to one of two treatment arms:

Arm 1) Standard ATD therapy (usually CBZ but occasionally PTU) daily for 2 years + 1 dose of placebo (250 ml infusion of 0.9% NaCl)

Arm 2) Standard ATD therapy (usually CBZ but occasionally PTU) daily for 2 years + 1 dose of 500mg RTX

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).

2.2 Trial Intervention

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

These 3 additional medications are standard of care to prevent infusion-related reactions to therapeutic antibody infusions including RTX. Participants will then be treated with standard ATD drug therapy for up to 2 years. The standard ATD drug dose will be adjusted to maintain a euthyroid state with normal TSH and thyroid hormone (Free tri-iodothyronine (FT3) and FT4) concentrations. We recommend that ATD should be administered as part of a dose titration (DT) regimen, where the dose of ATD is adjusted to maintain a euthyroid state, thus levothyroxine is not required. Our centre recently published the outcome of a randomised trial that compared the 2 strategies, which showed that the biochemical control with DT was non-inferior to block and replace (BR) with side effects occurring less commonly with the DT regimen[14]. We therefore intend to recommend a DT regimen as part of this trial, although clinicians will have the option of moving to BR if they feel this is appropriate. With BR, endogenous thyroid hormone production is abolished by ATD with levothyroxine then added in a replacement dose. An additional benefit of the DT method is that patients who are hypothyroid on a small dose of ATD can stop treatment altogether. This will be recorded as 'time to stopping ATD' and evaluated as one of the secondary trial outcomes under investigation.

Therapeutic regimen – CBZ/PTU: Patients will have been commenced on CBZ by the clinical team. The CBZ dose will then be titrated according to thyroid function test results for up to 2 years. We will suggest an initial daily dose of 20 to 40mg CBZ (around 0.5mg/kg once daily) in most patients in the initial phase until the patient is euthyroid or FT4 is normal, at which point the dose can be reduced. If patients are becoming biochemically hypothyroid on a small dose of CBZ prior to the end of the 2-year treatment period, then CBZ will be stopped. Guidance on ATD dosing can be found in section 5.10). CBZ is the first choice ATD in this trial but in the event of significant side-effects with CBZ (other than liver dysfunction) then subjects can be switched to PTU. The increased risk of liver dysfunction with PTU will be discussed with participants and their families prior to commencing this treatment. Whilst on PTU, liver function tests (LFTs) will be checked at each clinic visit and PTU stopped immediately if the alanine aminotransferase (ALT) or bilirubin levels are greater than twice the upper limit of the local reference range. If patients cannot tolerate or be treated with either CBZ or PTU during the first 12 months post RTX, then other potential means of maintaining a euthyroid state can be discussed with the clinical and trial management team.

Patients will be contacted within 10 days of each clinic visit and notified of any recommended changes to their ATD (CBZ or PTU) dose.

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 ≥ 16years)
- Methylprednisolone 125mg IV infusion over 30 minutes
- Chlorphenamine 10mg IV injection over 1 minute

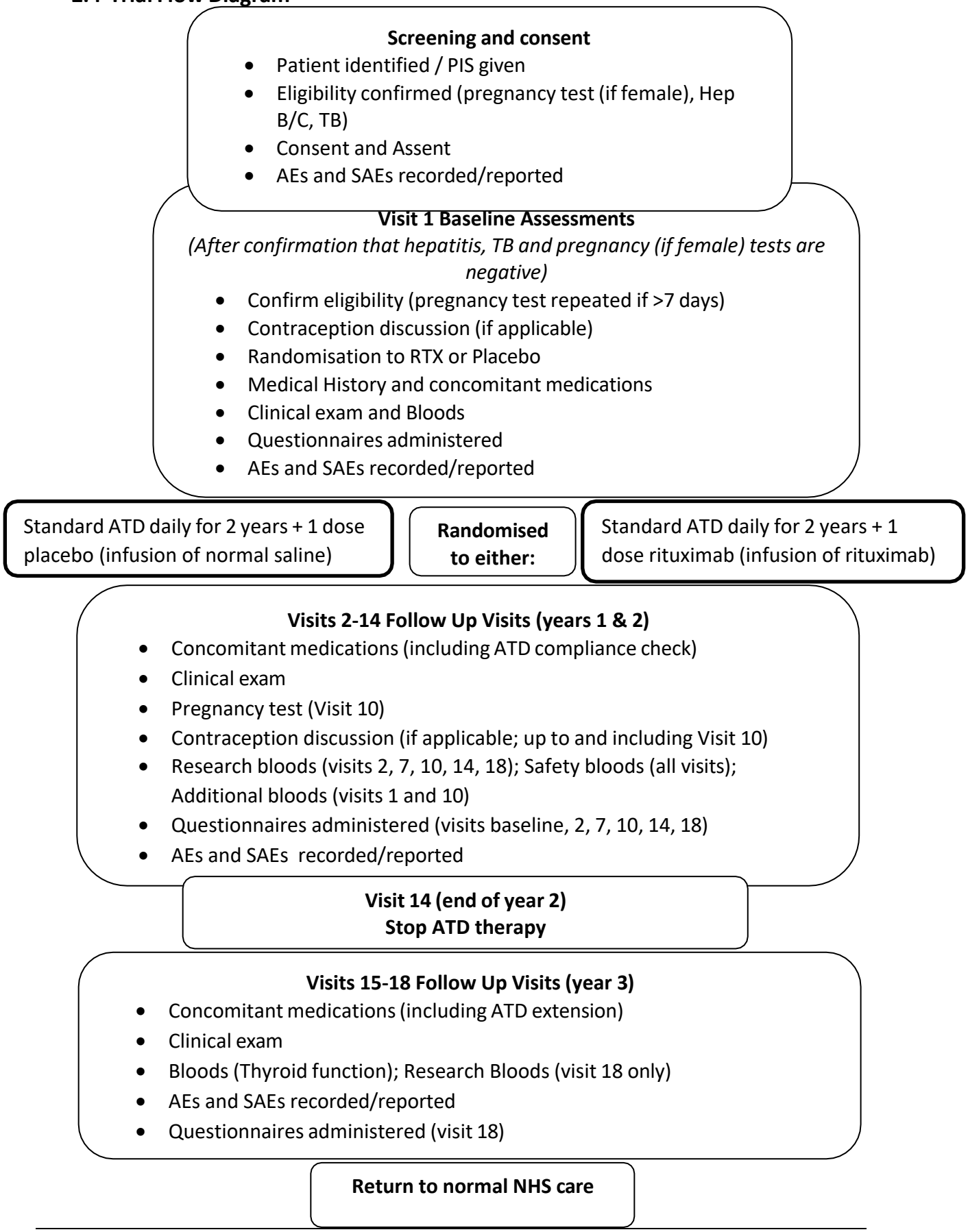
Therapeutic regimen – Rituximab (RTX): The single IV dose of 500mg RTX will be administered up to 12 weeks following start of ATD. It can be given after ATD has started or at initiation of ATD. This dose leads to depletion of the circulating B lymphocyte population (<0.1% of total lymphocytes) lasting for ~6 months in more than 95% of adults with TED[42] and is consistent with local RTX guidelines which were written by the trial co-investigator, Dr McErlane, who

has extensive experience of RTX administration in young rheumatology patients. 500mg of RTX is also the same dose used in our pilot study with young people[35] and in routine NHS practice in adults for TED[43]. By using a modest dose of 500mg that is the same as that used in the pilot study and that has already been shown to provide immunomodulation, we are aiming for maximum effect with minimum side-effects. Side effects are also unlikely because this is a low dose of RTX when compared to many earlier trials, participants are not immunodeficient and have not received other medication that can affect B lymphocyte cell numbers[44]. The rate of infusion will be adjusted according to patient condition but will be approximately 3 hours (Appendix 3 for a suggested infusion schedule).

2.3 Trial Setting

This is a multicentre trial based in 13 paediatric and 13 adult tertiary endocrine units (26 sites).

2.4 Trial Flow Diagram



2.5 Aims and Outcome Measures

2.5.1 Aims

The aim of this clinical trial is to determine whether a single dose of RTX, given in addition to 2 years of daily ATD drug, according to a standard regimen, increases the remission rate in young people with GD.

2.5.2 Objectives and Outcome Measures

2.5.2.1 Primary Objective:

To determine whether 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 (12 months after discontinuing ATD).

2.5.2.2 Secondary Objectives:

1. To determine the relationship between ATD therapy and remission status
2. To examine the relationship between longitudinal immunological markers (time to recovery of B-cell function and concentrations of TRAb antibody levels) and thyroid hormone status
3. To examine the safety of the intervention treatment regimen
4. To examine quality of life in patients in both treatment arms.

2.5.2.3 Exploratory Objectives:

1. To conduct a cost-effectiveness analysis comparing the intervention treatment regimen to the current ATD regimen standard of care offered in the NHS from the perspective of the NHS.
2. To investigate potential relationships between immunological markers and remission or relapse rate.

2.5.2.4 Primary outcome:

The primary estimand will compare the proportion of patients in remission from GD at 3 years (36 months) between randomised groups, in the principal stratum of patients who: initiate randomised treatment; do not withdraw consent during the trial; and remain alive. Patients in remission will be those who have not relapsed. A relapse is defined as: requiring ATD treatment during the third year; receiving RAI or surgical treatment (thyroidectomy) at any

stage of the trial; or the combination of a suppressed (unrecordable) TSH concentrations and a Free T3 above the laboratory reference range at 36 months.

Table 1 Primary Estimand Attributes

Estimand attribute	Description
Treatment	A single dose of RTX versus placebo (infusion of normal saline), given in addition to 2 years of daily ATD drug, according to a standard regimen
Population	Patients aged between 12-24 years of age with a new diagnosis of GD
Outcome variable	Remission rate (i.e., proportion of patients in remission) at 3 years (36 months)
Population-level summary measure	Odds ratio of the remission rate at 3 years between the group which received a single dose of RTX and the placebo group
Strategies used to handle intercurrent events	• Failure to initiate randomised treatment - **principal stratum** • Failure to complete RTX/placebo infusion - **treatment policy** • Failure to comply with ATD treatment regimen during initial 24 months – **treatment policy** • Participant becoming pregnant at any stage of the trial- **treatment policy** • ATD therapy received during the third year - **composite strategy** • RAI or surgical treatment (thyroidectomy) at any stage of the trial – **composite strategy** • Death – **principal stratum** • Withdrawal of all consent with no further data available - **principal stratum**

2.5.2.5 Secondary Outcomes:

1. Comparison of the cumulative ATD dosage at the end of the treatment period, the time to stopping ATD and the dosage of ATD at the end of 24 months between the two treatment arms.
2. Time to recovery of B cell numbers (CD19+ cells) to 1% of total lymphocytes and concentrations of TRAb antibody levels will be compared between both arms at 4

weeks, 28 weeks, 52 weeks, 104 weeks and end of study. These will also be analysed by regimen, in relation to thyroid hormone status and as predictor of relapse.

3. Total number of serious adverse events from the point of consent to participants last visit will be compared between both arms.
4. The mean per patient utility values/scores on the EQ-5D-5L/EQ-5D-Y-5L questionnaires and the mean scores on the Thyroid Specific Patient Report Outcome measure (ThyPRO-39) measured at baseline, 6-, 12-, 24- and 36-months will be compared between the two arms. ThyPRO-39 is a questionnaire used to measure quality of life in patients diagnosed with benign thyroid diseases, such as GD. EQ-5D-5L and the paediatric version EQ-5D-Y-5L are generic measure questionnaires that assesses quality of life in participants, specifically in across the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

2.5.2.6 Exploratory outcomes:

1. The total costs of the intervention and comparator regimens will be estimated through the health resource utilisation questionnaires which allow capture of all relevant costs from a patient, health care (National Health Service (NHS) and Personal Social Services (PSS)) and societal perspective. Costs will be combined with outcome data to estimate the cost-effectiveness of the additional single dose of RTX in combination with standard care compared to standard care alone.

2. A longitudinal study of cytokines (including B-cell activating factor (BAFF) and a proliferation inducing ligand (APRIL), chemokine ligands 5 and 13, T-cell receptor excision circles (TRECs) and Kappa deleted recombination excision circles (KRECs) in response to ATD +/-RTX and between remission and relapse groups. Expression of plasmablast transcriptomic markers (Immunoglobulin J (IgJ), B-cell maturation antigen (BCMA), Transmembrane activator and cyclophilin ligand interactor (TACI)) will be quantified[45].

3 TRIAL PROCEDURES

3.1 Summary of trial visits

Year 1: Screening/consent**,** baseline and intervention visit, 4, 8, 12, 16, 20, 28, 36, 44, 52 weeks (11 visits in total)

Year 2: 65 weeks, 78 weeks, 91 weeks, 104 weeks (4 visits)

Year 3: 117 weeks, 130 weeks, 143 weeks, 156 weeks (4 visits)

There will be a total of 19 visits. Only 2 of these are in addition to the recommended frequency in the ETA guidelines; the screening/consent visit and baseline/RTX visit.

3.2 Recruitment

3.2.1 Patient Identification

Participants will be identified through the screening of newly diagnosed patients under the clinical care of teams within participating NHS paediatric and adult endocrine centres across the UK. Participants may also be identified by referring clinicians via a link on the British Thyroid Foundation (BTF) website and support from the British Society for Paediatric Endocrinology and Diabetes and British Endocrine Society clinician members who may alert centres to potential participants from their hospitals.

3.2.2 Screening

All patients aged between 12-24 years of age with a new diagnosis of GD will be screened for eligibility. Those patients who meet the initial eligibility criteria will be told about the trial and if interested will receive a patient information sheet (PIS) to read through and discuss with family and friends. Adult patients who are lacking capacity but still meet the initial eligibility criteria will be invited to take part in the trial. In this instance the patient's legal representative will be given a legal representative PIS. Participants who are 12 to 15 years old will be given an age-appropriate PIS and their parent/legal guardian will be given a PIS for parent/legal guardian. Patients who are children should be involved in discussions around the trial where appropriate. Patients or their parent/legal guardian/ legal representative will be given at least 24hrs to consider participation in the trial before they are contacted by the research team to discuss the trial further. Those patients interested in taking part in the trial will be asked to attend a hospital appointment prior to the potential baseline visit to discuss the trial (with the parent/legal guardian/legal representative where appropriate) and provide consent and have their eligibility confirmed.

In the case of protocol amendments or if information becomes available which may affect participants' willingness to continue in the trial, it may be necessary to re-consent participants on an updated consent form after necessary regulatory approvals are obtained. If a child who was consented into the trial by a parent/legal guardian turns 16 during their time in the trial, they will need to be reconsented using the 16+ consent form.

3.2.3 Eligibility Criteria

Eligibility must be assessed and confirmed by a medically qualified doctor with the assessment and confirmation documented in the participant's medical notes. Only personnel formally delegated by the Principal Investigator (PI) to assess and confirm eligibility may perform this task.

3.2.3.1 Inclusion Criteria

- Excess thyroid hormone concentrations at diagnosis: elevated FT3 and / or FT4 (based on local assay)
- Suppressed (un-recordable) TSH (based on local assay)
- 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
- 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
- Confirmation of no current pregnancy. Participant must be willing to undergo pregnancy testing, as stipulated in protocol section 3.2.4.
- Willingness to use highly effective forms of contraception for 12 months post-treatment with RTX/placebo (for sexually active patients, see protocol section 3.2.5)
- Able and willing to adhere to a 3-year trial period
- Able to provide informed consent (parent/legal guardian can if <16 years of age or is an adult lacking capacity)

3.2.3.2 Exclusion Criteria

- Previous episodes of autoimmune thyroid disease

- Patients with an active, severe infection (e.g. sepsis and opportunistic infections)
- Severely immunocompromised patients
- Patients with known allergy or contraindication to carbimazole and propylthiouracil
- 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)
- Chromosomal disorders known to be associated with an increased risk of autoimmune thyroid disease including Downs' syndrome and Turners' syndrome
- Currently pregnant or planning to become pregnant during the trial period
- Currently breast-feeding
- Participants with significant chronic cardiac, respiratory or renal disorder or non-autoimmune liver disease
- Participants with known allergy or contraindication to RTX or methylprednisolone
- 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) status
- Participants with evidence of Tuberculosis (TB) infection, assessed by Quantiferon test
- 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
- Participants currently involved in any other clinical trial of an IMP or who have taken an IMP within 30 days or 5 half-lives of the IMP, whichever is longer, prior to trial entry
- Absence of informed consent from parent/legal guardian for participants age <16 years
- Receipt of live vaccines within 4 weeks prior to infusion of either RTX or placebo

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004. PROTOCOL WAIVERS ARE NOT PERMITTED.

3.2.4 Pregnancy Testing

A pregnancy test will be performed as part of screening (either urine or serum βHCG, in line with local clinical practice) and a negative result must be received prior to confirmation of eligibility. This test will be repeated prior to administration of IMP where this is >7 days after the pregnancy test was completed to reconfirm eligibility. Additional pregnancy testing will be performed at the end of year 1. Further pregnancy testing will take place during the trial if the participant is suspected to have become pregnant.

3.2.5 Highly Effective Methods of Contraception

The IMP in this trial has been assessed as having unknown human teratogenicity. Due to the long retention time of RTX in B cell depleted patients, participants who are sexually active should use effective contraceptive methods during and for 12 months following treatment with RTX. After the patient has given consent to take part in the trial, female participants, regardless of menarcheal status, will be required to provide a urine or serum βHCG sample for pregnancy testing to confirm that they are not pregnant. The intervention must then be given within 7 days of the negative pregnancy test. The pregnancy test will need to be repeated on the day of RTX/placebo administration if > 7 days have elapsed since the previous negative pregnancy test was obtained. :

Sexual maturity, for the purposes of this trial, will include all male participants and any female participant who has reached menarche. The need for contraception and related discussions will be reviewed at baseline and all follow up visits up to and including visit 10 (52 weeks). Participants will be reminded that if they become pregnant (or for male participants, their partner) at any point during the trial then they should let the trial team know immediately, because the dose or type of ATD may need to be changed in order to minimise potential harm to the developing foetus.

All male participants who are sexually active and female participants who have reached menarche and are sexually active must agree to use highly effective methods of contraception for 12 months post-treatment with RTX/placebo. Highly effective means they have a failure rate of less than 1% per year when used consistently and correctly. For this trial, the guidance for highly effective forms of contraception in clinical trials as outlined in the Clinical Trials Co-ordination Group Recommendations Version 1.2[46] will be used.

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.

3.3 Consent

Written informed consent will be received by the site PI or other medical doctor delegated to the trial. For patients who are 12 to 15 years old (inclusive) informed consent will need to be given by their parent/legal guardian, in line with The Medicines for Human Use (Clinical Trials) Regulations[47]. Patients 12 to 15 years will be asked to read through and sign an assent form. In instances where the parent and child do not agree about taking part in the trial, the PI or other medical doctor delegated to the trial, will discuss the trial further with the patient and parent/legal guardian to better understand and address any concerns. Patients 16 to 24 years old (inclusive) are classed as adults and will therefore provide informed consent for themselves. If a participant turns 16 years old during their participation in the trial, consent will be reconfirmed using the 16+ PIS and 16+ consent form and recorded.

The original signed consent form will be filed in the Investigator Site File (ISF), a copy will be provided to the patient to take home, and a copy filed in the patient medical notes (or scanned and uploaded to their electronic medical records). Copies of the PIS used will also be filed in the ISF and patient medical notes (or scanned and uploaded to their electronic medical records). Consent must be received prior to any trial-specific assessments including the confirmation of eligibility.

Confirmation of eligibility will need to be completed by a medical doctor delegated to the trial, including the following tests:

- Urine or serum βHCG pregnancy test*
- Blood tests
    - HBsAG
    - HB Core antibody
    - HCV antibody
    - TB infection (assessed by Quantiferon test)

*All females regardless of menarcheal status must provide a urine or serum βHCG sample for pregnancy testing.

If eligibility cannot be confirmed patients will return to NHS standard of care.

Eligibility can be confirmed on the paper version of the eligibility checklist provided in the ISF or direct entered onto the database. Confirmation of eligibility will need to also be

documented in the patient's medical records by a medically qualified doctor delegated to the trial. If the paper version of the eligibility checklist is used a copy must be filed in the patient medical notes (or scanned and uploaded to the patient electronic medical records), which can be used as documentation of confirmation of eligibility. The original completed paper eligibility checklist should be filed in the ISF.

A copy of the completed consent form and confirmation of eligibility will also be sent by site to the secure Newcastle Clinical Trials Unit (NCTU) email address: nctu.rigd2.conf@nhs.net for monitoring purposes. As this document contains patient identifiable information, a nhs.net account must be used to email this document. For sites that do not have nhs.net accounts, another secure method may be used but this must be discussed with and agreed by the NCTU Trial Manager(s) prior to use.

3.4 Randomisation

Participants will be randomised at the baseline visit. Participants will be randomised 1:1 to ATD + placebo or ATD + a single dose of RTX. Treatment allocation will be performed in permuted blocks (size concealed), stratified for sex (at birth), age at diagnosis (≥ 16 years) and initial serum FT4 level (≥50pmol/l) at diagnosis.

Patients will be randomised to one of two treatment arms:

Arm 1) Standard ATD therapy (usually CBZ but occasionally PTU) daily for 2 years + 1 dose of placebo (250 ml infusion of 0.9% NaCl)

Arm 2) Standard ATD therapy daily for 2 years + 1 dose of 500mg RTX (diluted in 250ml of 0.9% NaCl)

3.4.1 Randomisation System

Randomisation will be carried out by a delegated member of the research team using Ennov™'s randomisation system, which is a central, secure, 24-hour web-based randomisation system.

If the online randomisation system is not accessible, the site team should contact the NCTU data management team within normal working hours (9am – 5pm Monday to Friday, excluding bank holidays and Newcastle University closures https://www.ncl.ac.uk/regulations/term-dates/):

nctu.database.support@newcastle.ac.uk

Randomisation system web address:
https://saas7007.ennov.com/EnnovClinical/login

The system is available 24 hours a day, 7 days a week

3.5 Blinding

This is a single-blinded trial where participants will be blinded to their allocation and will not be aware of whether they are receiving an IV RTX infusion or a placebo (normal saline infusion). Both arms of the trial will receive paracetamol (500mg oral if 12-15 years old, 1g oral if ≥16 years old), methylprednisolone 125mg IV injection, and chlorphenamine 10mg IV injection.

The Trial Management Group (TMG) will remain blinded to the participants intervention arm. This will not include Trial Managers in order to facilitate monitoring of sites.

The trial statisticians will remain blinded until version 1.0 of the Statistical Analysis Plan has been written and approved. The lead/methodologist statistician (Prof James Wason) will remain blinded throughout.

3.6 Unblinding

Unblinding in the clinical setting should only occur for valid medical or safety reasons where it is necessary for the participant to know whether they have received RTX. As the trial is single-blinded, the treatment arm to which the participant is randomised will be documented in the participants medical notes and visible in Ennov™, the CDMS and randomisation system to all site research staff who have been delegated access. Ennov™ is accessible 24 hours a day, 7 days a week. We anticipate the requirement to unblind participants will be rare as only 1 dose of RTX is being given at the outset and the dose used is no higher than that already used in paediatric clinical practice at the lead site (The Newcastle upon Tyne Hospitals NHS Foundation Trust (NUTH); where repeated doses are often given). RTX was well tolerated during the pilot study[35]. Potential scenarios include:

- In the event of a potential Suspected Unexpected Serious Adverse Reaction (SUSAR) unblinding will be undertaken in accordance with the regulatory requirements for safety reporting in Clinical Trials of Investigational Medicinal Products (CTIMPs)
- At the request of a senior clinician responsible for the care of the trial participant if knowing whether RTX was received by the participant may impact the clinical care received (for example if admitted to hospital with an unrelated condition)

3.7 Site Staff Training and Delegation

All site staff must be trained in protocol requirements and appropriately delegated the tasks they will be carrying out before they perform any trial related activities. For staff involved at the commencement of site set-up, a Site Initiation Visit (SIV) will be scheduled prior to granting of site green light. This session will train staff in the trial protocol and provide a thorough overview of all site tasks involved throughout the duration of the trial. Attendance will be documented via SIV attendance log for each of member of staff.

For those not able to attend the SIV or for new staff members that join later in the trial, training will be provided via trial videos, and these include the same information provided within the SIV. Completion of this training will be documented via a training checklist for each of member of staff.

Signed and dated CVs and (where applicable) in date GCP* certificates must be held within the ISF and provided to NCTU as part of the off-site monitoring. These documents provide evidence that staff are trained by education, experience and training to perform the activities delegated to them.

A completed entry on the trial Delegation Log, and sign off by the PI, must be in place for each staff member before they commence the trial related activities assigned to them.

**GCP certificates – there may be instances where GCP certificates are not required for every staff member delegated tasks on the delegation log for example if the staff member is performing a task that follows their day-to-day clinical role and nothing additional to this. In these instances, seek sponsor advice first to ensure the approach to GCP requirements is pragmatic while in keeping with regulations.*

3.8 Baseline Assessments

The baseline visit can only take place once it has been confirmed that the Hep B/C and TB results are negative and confirmation the participant is not pregnant. The negative results of these tests must be confirmed by a medical doctor delegated to the trial. If the patient is unwell with an acute viral illness (e.g. cough or cold) they may need to delay their baseline visit until they are feeling well again.

The following assessments will take place at baseline:

(Visit 1) Baseline Visit- approximately 6 hours duration

The patient will be randomised at this appointment by a delegated member of the research team.

3.8.1 Pre- Intervention

- Pregnancy test (only applicable if the urine or serum βHCG pregnancy test used to confirm eligibility at Visit 0 was > 7 days prior to intervention)
- Medical history
- Concomitant medications (including current dose of ATD)
- Clinical examination including:
    - Pulse
    - Blood pressure
    - Cardiac, respiratory and abdominal exam
    - Goitre size (size recorded as 0 to 3, size 0 = neither palpable nor visible. Size 1 = palpable only, not visible. Size 2 = Palpable and visible. Size 3 = Large goitre and hence easily seen from several feet away)
- Height and weight
- Blood tests (obtained prior to intervention):
    - Full blood count (haemoglobin, platelets and white cells – neutrophils and lymphocytes)
    - Liver function tests (including albumin and ALT)
    - Thyroid function tests (TSH, FT3 and FT4)
    - Thyroid peroxidase (TPO) and TSH receptor (TRAb) antibodies

  - Lymphocyte subset tests; T cells (CD3, CD4, CD8), B cells (CD19) and class switch B cells (CD27+ve)
  - Serum immunoglobulin levels (IgG, IgM, IgA)
  - Specific antibody levels - tetanus, Hib, pneumococcus, varicella, measles
- Administer questionnaires
  - EQ-5D-5L/EQ-5D-Y-5L
  - ThyPro-39
  - Health Resource Use
  - Time to Travel
- An extra 10mls of blood will be collected. This will be spun to provide approximately 5ml serum which will be stored in a -40°C freezer or lower until samples are transferred to Newcastle (1ml serum will be used for TSH, FT4, FT3 and TRAb determination and the remainder will be stored for potential additional serology and exploratory analyses as described in exploratory objectives and analysed separately from the main trial).
- A further 2.5mls will be collected in a PAX gene tube for RNA analysis. This will also be stored in a -40°C freezer or lower until samples are transferred to Newcastle University laboratories.
- **For Newcastle patients only**: a 2.0mls sample will also be collected for DNA analysis. This sample cannot be frozen.

3.8.2 Intervention Given

- 500mg RTX/placebo administered by IV infusion with paracetamol (500mg oral if 12-15 years old, 1g oral if ≥16 years), methylprednisolone 125mg IV, and chlorphenamine 10mg IV
- Vital signs and blood pressure measured every 30 minutes during RTX/placebo IV infusion for first hour, then hourly for remainder of infusion and for 30 minutes after (see Section 5.3 and Appendix 3)
- Recording of any adverse events/ serious adverse events

3.8.3 Post Intervention

- Patients contacted within 10 days after the visit and notified of any changes to their ATD (CBZ or PTU) dose.

3.8.4 Post-Baseline Assessments

3.8.4.1 Post-Baseline Visits

The trial has 17 post-baseline visits which take place every 4 weeks (Visit 2 to Visit 6), then every 8 weeks (Visit 6 to Visit 10) and finally every 12 or 13 weeks (Visit 10 to Visit 18).

3.8.4.2 Post Baseline Additional Bloods

As with baseline (visit 1) an additional 10mls of blood will be collected at 4 weeks (visit 2), 28 weeks (visit 7), 52 weeks (visit 10), 104 weeks (visit 14), 156 weeks (visit 18). This will be spun to provide approximately 5ml serum which will be stored in a -40°C freezer or lower until samples are transferred to Newcastle laboratories (1ml serum will be used for TSH, FT4, FT3 and TRAb determination and the remainder will be stored for potential additional serology and exploratory analyses as described in exploratory objectives and analysed separately from the main trial).

As with baseline (visit 1) a further 2.5mls will be collected at 52 weeks (visit 10) in a PAX gene tube for RNA analysis. This will also be stored in a -40°C freezer or lower at site until samples are transferred to Newcastle University laboratories.

As with baseline (visit 1) for Newcastle patients only 2.0mls sample will be collected at 52 weeks (visit 10), for DNA analysis. This sample cannot be frozen.

3.9 Follow Up Visits

(Visit 2) Week 4 after visit 1 (+/-14 days)

- ATD compliance check – record any missed dosage
- Concomitant medications including current dose of ATD
- Adverse events including signs of infection such as cold, sore throat, cough
- Serious Adverse Events

- Enquire about neurological function and cognitive state- gait abnormalities, memory or speech/language problems (rare side effect of RTX- progressive multifocal leukoencephalopathy (PML))
- Clinical examination including:
    - Pulse
    - Blood pressure
    - Cardiac, respiratory and abdominal exam
    - Goitre size (size recorded as 0 to 3, size 0 = neither palpable nor visible. Size 1 = palpable only, not visible. Size 2 = Palpable and visible. Size 3 = Large goitre and hence easily seen from several feet away)
- Height and weight
- Blood tests:
    - Full blood count (haemoglobin, platelets and white cells – neutrophils and lymphocytes)
    - Liver function tests (including albumin and ALT)
    - Thyroid function tests (TSH, FT3 and FT4)
    - Thyroid peroxidase (TPO) and TSH receptor (TRAb) antibodies
    - Lymphocyte subset tests; T cells (CD3, CD4, CD8), B cells (CD19) and class switch B cells (CD27+ve)
    - Serum immunoglobulin levels (IgG, IgM, IgA)
    - Specific antibody levels - tetanus, Hib, pneumococcus, varicella, measles
- Administer questionnaires.
    - EQ-5D-5L/EQ-5D-Y-5L
    - ThyPro-39
- An extra 10mls of blood will be collected. This will be spun to provide approximately 5ml serum which will be stored in a -40°C freezer or lower until samples are transferred to Newcastle (1ml serum will be used for TSH, FT4, FT3 and TRAb determination and the remainder will be stored for potential additional serology and exploratory analyses as described in exploratory objectives and analysed separately from the main trial).

- Patients will be contacted by telephone within 10 days after the visit and notified of any changes to their ATD (CBZ or PTU) dose.

(Visit 3) Week 8 after visit 1 (+/-14 days)

- ATD compliance check – record any missed dosage
- Concomitant medications including current dose of ATD
- Adverse events including signs of infection such as cold, sore throat, cough
- Serious Adverse Events
- Enquire about neurological function and cognitive state- gait abnormalities, memory or speech/language problems (rare side effect of RTX- progressive multifocal leukoencephalopathy (PML))
- Clinical examination including
    - Pulse
    - Blood pressure
    - Cardiac, respiratory, and abdominal exam

  Goitre size (size recorded as 0 to 3, size 0 = neither palpable nor visible. Size 1 = palpable only, not visible. Size 2 = Palpable and visible. Size 3 = Large goitre and hence easily seen from several feet away)
- Height and weight
- Blood tests
    - Full blood count (haemoglobin, platelets, and white cells – neutrophils and lymphocytes)
    - Liver function tests (including albumin and ALT)
    - Thyroid function tests (TSH, FT3 and FT4)
- Patients contacted within 10 days after the visit and notified of any changes to their ATD (CBZ or PTU) dose.

(Visit 4) Week 12 after visit 1 (+/-14 days)

Repeat as per Visit 3.

- Patients contacted within 10 days after the visit and notified of any changes to their ATD (CBZ or PTU) dose.

(Visit 5) Week 16 after visit 1 (+/-14 days)

Repeat as per Visit 3

- Patients contacted within 10 days after the visit and notified of any changes to the ATD (CBZ or PTU) dose.

(Visit 6) Week 20 after visit 1 (+/-14 days)

Repeat as per Visit 3

- Patients contacted within 10 days after the visit and notified of any changes to the ATD (CBZ or PTU) dose.

(Visit 7) Week 28 after visit 1 (+/-14 days)

Repeat as per Visit 2.

In addition:

- Health Resource Use questionnaire
- Time to Travel questionnaire
- Patients contacted within 10 days after the visit and notified of any changes to their ATD (CBZ or PTU) dose.

(Visit 8) Week 36 after visit 1 (+/-14 days)

Repeat as per Visit 3

- Patients contacted within 10 days after the visit and notified of any changes to the ATD (CBZ or PTU) dose.

(Visit 9) Week 44 after visit 1 (+/-14 days)

Repeat as per Visit 3

- Patients contacted within 10 days after the visit and notified of any changes to the ATD (CBZ or PTU) dose.

(Visit 10) Week 52 after visit 1 (+/-14 days)

Repeat as per Visit 2

In addition:

- Urine or serum βHCG pregnancy test. All females regardless of menarcheal status must provide a sample for pregnancy testing.
- A further 2.5mls will be collected in a PAX gene tube for RNA analysis. This will also be stored in a -40°C freezer or lower until samples are transferred to Newcastle University laboratories.
- **For Newcastle patients only**: a 2.0mls sample will also be collected for DNA analysis. This sample cannot be frozen.
- Health Resource Use questionnaire
- Time to Travel questionnaire
- Patients will be contacted within 10 days after the visit and notified of any changes to the ATD (CBZ or PTU) dose.

(Visit 11) Week 65 after visit 1 (+/-14 days)

Repeat as per Visit 3

- Patients contacted within 10 days after the visit and notified of any changes to the ATD (CBZ or PTU) dose.

(Visit 12) Week 78 after visit 1 (+/-14 days)

Repeat as per Visit 3

- Patients contacted within 10 days after the visit and notified of any changes to the ATD (CBZ or PTU) dose.

(Visit 13) Week 91 after visit 1 (+/-14 days)

Repeat as per Visit 3

- Patients contacted within 10 days after the visit and notified of any changes to the ATD (CBZ or PTU) dose.

(Visit 14) Week 104 after visit 1 (+/-14 days)

The patient must stop ATD treatment at this visit.

- Repeat as per Visit 2

In addition:

- Health Resource Use questionnaire
- Time to Travel questionnaire

(Visit 15) Week 117 after visit 1 (+/-14 days)

- Concomitant medications
- Record if ATD was required beyond Visit 14 (week 104)
- Details of any definitive treatment since stopping ATD.
- Adverse Events including signs of infection such as cold, sore throat, cough
- Serious Adverse Events
- Enquire about neurological function and cognitive state- gait abnormalities, memory or speech/language problems (rare S/E of RTX- progressive multifocal leukoencephalopathy (PML))
- Clinical examination including
    - Pulse
    - Blood pressure
    - Cardiac, respiratory, and abdominal exam
    - Goitre size (size recorded as 0 to 3, size 0 = neither palpable nor visible. Size 1 = palpable only, not visible. Size 2 = Palpable and visible. Size 3 = Large goitre and hence easily seen from several feet away)
- Height and weight
- Blood tests
    - Thyroid function (TSH, FT4, FT3)

(Visit 16) Week 130 after visit 1 (+/-14 days)

Repeat as per Visit 15

Visit 17 Week 143 after visit 1 (+/-14 days)

Repeat as per Visit 15

Visit 18- week 156 (36 months after visit 1) (+/-14 days)

- Record if ATD was required beyond Visit 14 (week 104)
- Details of any definitive treatment since stopping ATD
- Adverse events including signs of infection such as cold, sore throat, cough
- Serious Adverse Events
- Enquire about neurological function and cognitive state- gait abnormalities, memory or speech/language problems (rare side effect of RTX- progressive multifocal leukoencephalopathy (PML))
- Clinical examination including:
    - Pulse
    - Blood pressure
    - Cardiac, respiratory, and abdominal exam
    - goitre size (size recorded as 0 to 3, size 0 = neither palpable nor visible. Size 1 = palpable only, not visible. Size 2 = Palpable and visible. Size 3 = Large goitre and hence easily seen from several feet away)
- Height and weight
- Blood tests:
    - Full blood count (haemoglobin, platelets, and white cells – neutrophils and lymphocytes)
    - Liver function tests (including albumin and ALT)
    - Thyroid function tests (TSH, FT3 and FT4)
    - Thyroid peroxidase (TPO) and TSH receptor (TRAb) antibodies
    - Lymphocyte subset tests; T cells (CD3, CD4, CD8), B cells (CD19) and class switch B cells (CD27+ve)
    - Serum immunoglobulin levels (IgG, IgM, IgA)
    - Specific antibody levels - tetanus, Hib, pneumococcus, measles, varicella

- Administer questionnaires:
    - EQ-5D-5L/EQ-5D-Y-5L
    - ThyPro-39
    - Health Resource Use questionnaire
    - Time to Travel questionnaire
- An extra 10mls of blood will be collected. This will be spun to provide approximately 5ml serum which will be stored in a -40°C freezer or lower until samples are transferred to Newcastle (1ml serum will be used for TSH, FT4, FT3 and TRAb determination and the remainder will be stored for potential additional serology and exploratory analyses as described in exploratory objectives and analysed separately from the main trial).

3.10 End of Trial

The definition of the end of trial is the last patient, last visit date or completion of the transfer and analysis of samples associated with exploratory objectives, whichever comes latest.

3.11 Post-Trial Care

Participants will return to their routine clinical care on completion of the trial. After the trial, participants can find out what arm they had been allocated to during the trial if they wish to know. The local clinician would be able to provide this information.

3.12 Withdrawal Criteria

3.12.1 Right to Withdraw

Participants have the right to withdraw from the trial at any time, including during the single infusion of RTX/placebo, without giving a reason.

3.12.2 Uninitiated RTX/placebo infusion

If a participant is randomised to the trial but does not receive any part of their infusion (RTX or placebo) a withdrawal form must be completed. The form will outline why the infusion was not initiated. The completed withdrawal form should be emailed to the confidential inbox (mailto:nctu.rigd2.conf@nhs.netnctu.rigd2.conf@nhs.net).

3.12.3 Participant Discontinuation of Trial Procedures/full withdrawal After Infusion

If a participant withdraws (or the parent/carer/legal representative withdraws the participant) from the trial during the follow-up period, then every effort will be made to obtain follow-up data, with the permission of the participant (or the parent/carer/legal representative). The participant (or the parent/carer/legal representative) will be asked to complete the discontinuation of trial procedures/withdrawal form which will confirm if the participant (or the parent/carer/legal representative) has agreed for the trial team to continue collecting the participant's data throughout the trial. The completed form should be emailed to the confidential inbox (mailto:nctu.rigd2.conf@nhs.netnctu.rigd2.conf@nhs.net).

3.12.4 Clinician Led Withdrawal

A clinician delegated to the trial may withdraw a participant from the trial at any time if they consider it necessary for any reason including (but not limited to):

- Participant/parent/legal guardian withdrawal of consent
- Significant protocol deviation or non-compliance
- Clinician's discretion that it is in the best interest of the participant to withdraw
- An adverse event that renders the participant unable to continue in the trial
- Termination of the clinical trial by the sponsor

In the case of a clinician withdrawing a participant from the trial, the participant (or the parent/carer/legal representative) will be asked to complete the discontinuation from trial follow-up procedures/withdrawal form which will confirm if the participant (or the parent/carer/legal representative) has agreed for the trial team to continue collecting the participant's data throughout the trial. The completed form should be emailed to the confidential inbox (mailto:nctu.rigd2.conf@nhs.netnctu.rigd2.conf@nhs.net).

3.12.5 Replacement of Withdrawn Participants

Participants who withdraw from the trial will not be replaced.

3.13 Discontinuation of Trial Treatment

This trial involves a single dose administration (RTX or placebo) and as such it is not anticipated that the investigator would discontinue treatment during the infusion. However, if the RTX/placebo infusion must be stopped completely and cannot be recommenced, then site will be asked to record the amount of RTX/placebo that was administered on an IMP discontinuation form and on the database. The IMP discontinuation form must be emailed to the confidential inbox nctu.rigd2.conf@nhs.net. A participant who does not receive the full infusion will still continue in the trial, attending all follow up visits as normal, unless they choose to discontinue follow-up procedures or fully withdraw from the trial (please see section 3.12.3).

13.14 Out of Hours Contact

If the patient is experiencing an acute event they should be advised to attend their nearest Emergency department informing the staff there that they are taking part in the RiGD2 trial. Patients should be advised to have the RiGD2 trial Patient Safety Card with them.

For all other trial related issues which are urgent and require clinical guidance please contact the Chief Investigator for the trial Dr Claire Wood via DECT 0191 2821813 or via the Royal Victoria Infirmary (Newcastle upon Tyne) Switch Board on 0191 233 6161. If Dr Claire Wood is not available please ask Switch Board to connect you to Professor Simon Pearce or Professor Tim Cheetham. In the event that none of these doctors are contactable please ask Switch Board to connect you with the ‘on-call paediatric endocrinology consultant’.

4 Schedule of Events

	V0 Screen-ing and Consent	V1 Base-line	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18
	Wk -1	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 28	Wk 36	Wk 44	Wk 52	Wk 65	Wk 78	Wk 91	Wk 104	Wk 117	Wk 130	Wk 143	Wk 156
		- 7 days	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day	+/- 14 day
Eligibility assessed	x																		
Informed Consent and Assent (if applicable)	x																		
Pregnancy test[a]	x [b]	(x) [b]									x								
Contraceptive discussion [c]	x	x	x	x	x	x	x	x	x	x	x								
HBsAG, HB Core antibody, HCV antibody, Quantiferon	x	(x)																	

Record of TFT result at time of diagnosis	x																		
Confirm Eligibility	x	X																	
Randomisation RTX or Placebo[d]		X																	
Medical History		X																	
Concomitant medications (including current dose of ATD)		X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Current ATD regimen		X																	
Clinical Examination (completed by doctor or nurse) • Pulse • Blood pressure • Height and weight		X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical Examination (completed by doctor or nurse specialist ONLY) • Cardiac, respiratory		X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

and abdominal pain • Goitre size																			
Full blood count[ef]		X	x	x	x	x	x	x	x	x	x	x	x	x	x				x
Liver function tests [eg]		X	x	x	x	x	x	x	x	x	x	x	x	x	x				x
Thyroid function tests [eh]		X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Thyroid peroxidase (TPO) and TSH receptor (TRAb) antibodies[e]		X	x					x			x				x				x
Lymphocyte subset tests [ei]		X	x					x			x				x				x
Serum immunoglobulin levels [ej]		X	x					x			x				x				x
Specific antibody levels[ek]		X	x					x			x				x				x
Additional 10mls blood (gold top tube)[l]		X	x					x			x				x				x
Additional 2.5mls blood (PAX gene tube)[m]		X									x								

Additional 2.0mls (EDTA tube)[n]		X									x							
EQ-5D-5L/ EQ-5D-Y-5L		X	x					x			x				x			x
ThyPro-39		X	x					x			x				x			x
Health resource use questionnaire		X						x			x				x			x
Travel time questionnaire		X						x			x				x			x
RTX or placebo infusion given		X																
Adverse and Serious Adverse Event check		X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ATD Dose adjustment[o]		X	x	x	x	x	x	x	x	x	x	x	x	x	x			
ATD Compliance check			x	x	x	x	x	x	x	x	x	x	x	x	x			
Neurological function and cognitive state [p]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ATD stop treatment															x			
Check if ATD treatment extended																x	x	x
Check treatment since stopping ATD																x	x	x

[a]All females regardless of menarcheal status must provide a urine or serum βHCG sample for pregnancy testing
[b] A pregnancy test result must be confirmed as negative within 7 days prior to the RTX infusion. Hence a test will need to be repeated on the day of RTX administration if more than 7 days has elapsed since the screening visit or a negative pregnancy test.
[c] The need for this will be reviewed if patient has reached sexual maturity and has confirmed, or it is suspected they could be, sexually active.
[d] Administer Rituximab infusion as per protocol
[e] Bloods taken at baseline visit should be taken prior to intervention
[f] Full blood count (haemoglobin, platelets and white cells – neutrophils and lymphocytes)
[g] Liver function tests (including albumin and ALT)
[h] Thyroid function tests (TSH, FT3 and FT4)
[i] Lymphocyte subset tests; T cells (CD3, CD4, CD8), B cells (CD19) and class switch B cells (CD27+ve)
[j] Serum immunoglobulin levels (IgG, IgM, IgA)
[k] Specific antibody levels - tetanus, Hib, pneumococcus, measles, varicella
[l]10mls blood (5mls of serum) at visit 1, 2, 7, 10, 14 and 18 to be sent for central analysis.
[m] 2.5mls blood at visit 1 and 10 to be sent for central analysis
[n]2.0mls blood at visit 1 and 10 to be sent for central analysis for **Newcastle patients only**
[o] Patient to be contacted within 10 days after each study visit V1-14 and adjust ATD dose as per protocol
[p] check for rare side effect of RTX- progressive multifocal leukoencephalopathy

5 Trial Intervention

5.1 Description of Intervention

One dose of RTX (500mg) will be given to patients newly diagnosed with GD and who are within 12 weeks of commencing ATD. It can be given after ATD has started or at initiation of ATD. RTX is a chimeric monoclonal antibody against the B lymphocyte cell-surface protein CD20. RTX removes B cells from the circulation, thyroid and lymphoid tissues, leading to therapeutic immunomodulation. It is an attractive therapeutic option as it has already been repurposed as a safe and readily available licenced product for a range of other autoimmune conditions and has been used extensively in children and young people for many years in the context of rheumatoid arthritis, idiopathic thrombocytopaenic purpura, haemolytic anaemia, systemic lupus erythematosus and renal disorders, each with an excellent safety record[25, 26] .As CD20 is not expressed on mature plasma cells, administration of RTX does not affect the production of memory antibodies[27] .

5.2 Rationale for Intervention

The 500mg single dose of RTX leads to depletion of the circulating B lymphocyte population (<0.1% of total lymphocytes) lasting for ~6 months in more than 95% of adults with TED[42] and is consistent with our local RTX guidelines which were written by Dr McErlane (co-investigator) who has extensive experience of RTX administration in young rheumatology patients. This dose of RTX is the same dose used in the pilot study[35] and in routine NHS practice in adults for TED[34]. The rate of infusion will be gradually increased as per protocol, and slowed if necessary, according to participant condition (see Appendix 3), but will be approximately 3 hours. By using a modest dose of 500mg that is the same as that used in the pilot study and that has already been shown to provide immunomodulation, we are aiming for maximum effect with minimum side-effects.

5.3 Dosing and Administration for RTX

The originator biologic of RTX is MabThera. There are now several biosimilars available including Rixathon, Truxima and Ruxience. For this trial, any brand of RTX can be used as the IMP.

RTX will be administered intravenously as a single dose at 500mg within 12 weeks of commencing ATD therapy for newly diagnosed GD patient.

The participant will be cannulated and will then receive (in this order):

1. 500mg (12 to 16 years of age) or 1g (>16 years) of paracetamol (taken orally)
2. 125mg methylprednisolone (by IV injection over 30 minutes)
3. 10mg chlorphenamine (by IV injection over 1 minute)
4. 500mg of Rituximab (by IV infusion over approximately 3 hours)

The prepared RTX solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus. It should not be mixed with any other medication product.

RTX start rate should be 50mg/hr (25ml/hr) increasing by 50mg/hr (25 ml/hr) every half hour if tolerated, otherwise the infusion should be maintained at current rate or stopped and then restarted after 30 minutes. If the RTX infusion is tolerated and the infusion rate increased as above, then the infusion will take 2 hours 55 minutes if the patient weighs > 50kg. The RTX infusion may take several additional hours to be completed if it is not tolerated optimally and hence the infusion rate is not increased as described above.

Examples of symptoms which are considered intolerable are:

- angioedema
- hypotension
- Breathing difficulties.

If any of these symptoms are observed the treatment must be stopped immediately and clinical care instigated as required. Only restart the infusion once the symptoms have resolved (please refer to relevant RTX Summary of Product Characteristics (SmPC) and Appendix 3 for an example infusion protocol.)

Vital signs, including blood pressure will be measured every 30 minutes during the RTX intravenous infusion and for 30 minutes afterwards.

5.4 Dosing and Administration for Placebo

The placebo used in this trial is normal saline (0.9% NaCl). The normal saline will be administered intravenously as a single dose at 250ml within 12 weeks of commencing ATD therapy for newly diagnosed GD patients.

The participant will be cannulated and will then receive (in this order):

1. 500mg (12 to 16 years of age) or 1g (>16 years) of paracetamol (taken orally)
2. 125mg methylprednisolone (by IV injection over 30 minutes)
3. 10mg chlorphenamine (by IV injection over 1 minute)
4. 250ml of saline (0.9% NaCl by IV infusion over 3 hours)

The normal saline solution should be administered as an intravenous infusion over 3 hours, through a dedicated line. It should not be administered as an intravenous push or bolus. It should not be mixed with any other medication product.

Vital signs, including blood pressure will be measured every 30 minutes during the saline intravenous infusion and for 30 minutes afterwards.

5.5 Treatment for Overdose of RTX

Overdose information (available only from the Truxima SmPC[48] suggests that limited experience with doses higher than the approved dose of intravenous RTX formulation is available from clinical trials in humans. The highest intravenous dose of RTX tested in humans to date is 5g (2250 mg/m^2), tested in a dose escalation study in patients with chronic lymphocytic leukaemia. No additional safety signals were identified. In the post-marketing setting 5 cases of RTX overdose have been reported. Three cases had no reported adverse event. The 2 adverse events that were reported were flu-like symptoms, with a dose of 1.8g of RTX and fatal respiratory failure, with a dose of 2g of RTX.

Patients who experience overdose should have immediate interruption of their infusion and be closely monitored. If there are trial drug errors defined as errors in administration or the administered dose, these must be reported immediately to NCTU and the CI and documented as a protocol deviation. A brief description of the event must be provided in the deviation report with any potential associated symptoms.

5.6 Preparation/Storage/Handling/Accountability

5.6.1 Preparation and Labelling

RTX is available as MabThera, Rixathon, Ruxience, Truxima, or other biosimilars. RTX will be prepared according to SmPC or local preparation protocol. RTX is available as 100mg in 10ml and 500mg in 50ml vials. For this trial we require sites to only use 500mg in 50ml vials. It needs to be further diluted for administration. See appendix for example infusion protocol. Aseptically withdraw the necessary amount of RTX and dilute to a calculated concentration of 2 mg/mL RTX into a 250 ml infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution. For mixing the solution, gently invert the bag to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Once the infusion bag is prepared for administration it will be labelled according to Annex 13 regulations of EU directive[49] thus turning it into an IMP prior to administration. The IMP should be reconstituted as soon as practicable before administration.

5.6.2 Storage and supply

RTX will be sourced and stored at 2-8 ºC as per standard hospital procedures.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

5.6.3 Handling

According to section 6.3 of the SmPC (MabThera 500mg Concentrate for Solution for Infusion[50]); the prepared infusion solution of RTX in 0.9% sodium chloride solution is physically and chemically stable for 7 days at 2 - 8 °C and subsequently for a further 24 hours at ≤ 30 °C. Clinical staff who may be pregnant should refer to the local Pregnant Workers Policy. For other biosimilars please see local preparation protocol.

5.6.4 Accountability

Waste medication products from RTX should be disposed of in the designated waste yellow bag with a purple stripe or a rigid, yellow, leak proof container with a purple lid. For more information see your local Policy for the Handling, Segregation and Disposal of Cytostatic and

Cytotoxic Waste. The RTX carton/container should be returned to local site pharmacy for accountability and destruction.

5.7 Known Drug Reactions

The Reference Safety Information (RSI) for RTX can be found in the appropriate section of the SmPC[50].

Serious Adverse Reactions (SARs) that are thought to have a causal relationship to RTX must be assessed for expectedness against the RTX RSI. In the event of a SAR that is thought to have occurred due to a reaction between the IMP and another medication, please also ensure to check appropriate section of the SmPC.

RTX may result in a clinically significant fall in immunoglobulin levels although this is much less likely in patients who have not had immunosuppressive treatment before and who are only receiving one dose of RTX. Clinicians should still be aware that the use of RTX in this context might occasionally result in an increased risk of severe infections (such as pneumonia) and/or recurrent infections. Appropriate surveillance in patients receiving RTX is needed with patients being considered for antibiotic prophylaxis and/or intravenous immunoglobulin replacement therapy if they have a pertinent history in the context of low B cells (less than the lower end of normal range for age) and low serum IgG levels (less than lower end of normal range for age/gender). These events are expected to be of a very low frequency and decisions about antibiotic therapy, prophylaxis or immunoglobulin replacement therapy will be reached on each individual patient following careful assessment by the clinician in charge.

Progressive multi-focal leukoencephalopathy (PML) has been reported in association with RTX typically in adult patients who have had previous immunosuppressive therapy or malignant disease. It has not been reported in young people without this complex background. However, subjects treated with RTX should be monitored for cognitive, neurological, or psychiatric signs and symptoms, and referred immediately for specialist neurological assessment if such features are suspected. RTX therapy is generally very well tolerated and there were very few adverse events (AEs) in the pilot study[35]. In total 6 serious adverse events (SAEs) were reported; 5 were unrelated to treatment and 1 was determined to be unlikely to be related to treatment. Immunoglobulin levels, specific antibody levels and lymphocyte subsets will be measured at intervals during the trial.

5.8 Concomitant Medications

A complete list of all concomitant medication received during the data collection period will be recorded.

5.9 Compliance

At each visit in the first 2 years, participants will be asked whether they have missed ATD medication, and clinicians will be asked to rate compliance on a scale of high, medium, or low, where >80% of ATD taken on the correct day is classified as high compliance, <80-50% medium and <50% low[51] Visit windows of +/- 14 days should ensure visit attendance. Non-attendance for trial visits will prompt follow-up by text, email, or telephone by a delegated member of the research team.

5.10 NIMPs

5.10.1 Name and description of NIMP

ATD therapy- CBZ and PTU

The non-investigational medicinal product (NIMP) for this trial will be one of two thionamide oral anti-thyroid drugs (ATD) given to patients with GD. Most young patients are commenced on CBZ. The only other thionamide available in the UK is PTU. This is only prescribed in exceptional circumstances in paediatric practice because of the 1 in 2,000 risk of liver failure in this age-group.

CBZ and PTU must be given as per standard local Trust protocols. When given for therapeutic purpose they must be delivered as per the UK licensed indication. Any information provided below about these NIMPs are given for reference only.

Please note: Any SUSARs related to CBZ or PTU, where there is a possibility of an interaction with the IMP, must be reported as a SUSAR.

5.10.2 Treatment Dose of NIMPs

The CBZ dose will be titrated against prevailing thyroid function tests at the discretion of the local clinician as per standard local Trust protocols. A guideline is also provided in Table 2, which is meant to assist the managing team and does not have to be followed 'to the letter' if it is felt that a different dose of ATD is more appropriate. PTU can be administered on the basis that 5mg of CBZ is equivalent to 50mg PTU. If patients become hypothyroid (with an

elevated TSH and low FT4/FT3 level) on the smallest daily dose of CBZ (5mg) or PTU (50mg) then the ATD can be administered on alternate days. If patients are still hypothyroid then the ATD (CBZ or PTU) will be stopped before 12 months has elapsed following RTX administration.

Adverse reactions to CBZ usually occur in the first eight weeks of treatment. The most common minor reactions are nausea, frequently occurring reactions are nausea, headache, arthralgia, mild gastric disturbance or distress, skin rashes and pruritus. These reactions are usually self-limiting and may not require withdrawal of the drug.

Bone marrow depression including neutropenia, eosinophilia, leucopenia, and agranulocytosis has been reported. Fatalities with carbimazole-induced agranulocytosis have been reported. Rare cases of pancytopenia/aplastic anaemia and isolated thrombocytopenia have also been reported. Additionally, very rare cases of haemolytic anaemia have been reported.

Patients should always be warned about the onset of sore throats, bruising or bleeding, mouth ulcers, fever and malaise and should be instructed to stop the drug and to seek medical advice immediately. In such patients, white blood cell counts should be performed immediately, particularly where there is any clinical evidence of infection.

All participants who develop unacceptable toxicity to CBZ (notably neutropenia with a neutrophil count less than 0.5 $x10^9$/l) will stop ATD immediately. Participants with a neutrophil count between 0.5 and 1.0 can remain on ATD if well. The neutrophil count should be repeated after approximately 1 to 2 weeks or as clinically indicated to confirm that it has not fallen to less than 0.5 $x10^9$/l. If in doubt discuss with the CI. If patients develop ATD side-effects other than neutropaenia then the options include dividing the ATD dose (CBZ is usually administered once daily), switching to PTU (only if liver function tests are normal) or stopping the ATD on the basis that the underlying hyperthyroidism may be resolving.

Isolated cases of myopathy have been reported. Patients experiencing myalgia after the intake of CBZ should have their creatine phosphokinase levels monitored.

PTU can be commenced as a replacement ATD in the case of adverse events that do not involve hepatic dysfunction or neutropenia. The increased risk of liver dysfunction on PTU will be discussed with participants and their families prior to commencing PTU. Check liver

function at each visit if on PTU and stop the PTU if ALT or bilirubin elevated (2 x above the upper limit of normal).

If patients are unable to tolerate ATD, other potential means of maintaining a euthyroid state can be discussed with the trial management team, such as the addition of a beta-blocker.

5.10.3 Duration of NIMP Treatment

ATD treatment will be given for 24 months in total. The exception to this is if a patient becomes hypothyroid on a very low dose of CBZ/PTU (i.e., 5mg CBZ alternate days or 50mg PTU alternate days) then the ATD will be stopped before 24 months has elapsed. The timing of this will be recorded at the next trial visit so that cumulative dosing can be calculated.
After 24 months, patients who are thyrotoxic as evidenced by the combination of a suppressed TSH and elevated FT3 will be deemed to have relapsed and will return to standard care. Standard care may involve further clinic visits (in addition to those scheduled as per the protocol) and will typically involve treatment with further ATD, radioiodine or surgery.

5.10.4 Dose Modification of NIMP(s)

The ATD regimen is designed to ensure that the risk of ATD side-effects is as low as possible. Clinicians will be advised to follow a dose titration regimen when administering ATD to patients enrolled into this clinical trial. The managing clinician can elect not to follow this framework if their assessment of the overall clinical picture suggests that this is in the patient's best interests. The rationale for changing the ATD regimen will be documented by the clinician or research nurse. The below is given as guidance only (if using PTU assume that 5mg CBZ = 50mg PTU):

Table 2 Treatment Regimens for NIMPs

Dose titration regimen
CBZ is usually commenced at 0.75 mg/kg/day until child is euthyroid up to max of 40mg/day. (CBZ available in 5mg and 20mg tablets). In the case of mild Graves' hyperthyroidism (e.g. FT3 < 10pmol/l) clinicians may use a smaller initial dose.
Then reduce the dose to 0.25 mg/kg/day, aiming to maintain FT4/FT3 and TSH concentrations in normal range. The TSH takes longer to normalise so be guided primarily by FT4 and FT3 initially.
If patient is **hypothyroid** (low FT4/FT3) then reduce CBZ by 5mg/day for those patients under 30 kg and 10 mg/day for those over 30kg.

If the patient is **hyperthyroid** (high FT3/FT4) increase CBZ by 5mg/day for those patients under 30 kg and 10 mg/day for those over 30kg
Block and replace regimen
CBZ is usually commenced at 0.75 mg/kg/day until the child is euthyroid up to max of 40mg/ day.
As the intention is to completely block endogenous thyroxine production, wait until the patient becomes euthyroid and then FT4 drifts to lower end of normal range and then add thyroxine in a replacement dose. When FT4 levels are <15pmol/l start thyroxine in a low replacement dose such as 75 mcg/m^2.
If TSH is suppressed and FT4 is low or in the bottom part of the normal range in the initial phase of treatment (the first 4 months) then thyroxine should still be commenced (as TSH level can lag behind).
If FT4 levels remain elevated above the reference range 2 months into treatment or TSH remains suppressed, an increase of CBZ dose to 1 mg/kg may be needed.
Treatment regimen may not require adjustment if FT4 is relatively high but the TSH is normal.
If compliance is not a concern and dose of thyroxine is not greater than 75 mcg/m^2 then a suppressed TSH beyond the first 4 months of therapy should be managed by increasing the dose of CBZ in the first instance.
If patient becomes thyrotoxic with a suppressed TSH when it has previously been normal– check compliance and consider increasing dose of CBZ by 5 mg/day. It is unlikely that a child will require more than 40mg daily of CBZ, so consider compliance issues if larger doses appear necessary.
If patient subsequently develops a high TSH then increase the dose of thyroxine up to 100 mcg/m^2 /day or by 12.5 to 25 mcg increments (12.5 mcg <30kg, 25 mcg for >30kg).

5.10.5 Compliance of NIMP(s)

Compliance will be assessed by direct questioning at each visit and classified as high, medium or low, where ≥80% of ATD taken on the correct day is classified as high, <80-50% medium and <50% low compliance. Visit windows of +/- 14 days should ensure visit attendance; non-attendance for study visits will result in prompt follow-up by text, email or telephone from a delegated member of the research team to the participant (or their parent/legal guardian). Bloods will be taken for safety purposes, even if the study visit is outside of the 14 days allocated to each study visit (please refer to schedule of events).

5.11 Procedure for Samples

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the Data Protection Act 2018, UK's implementation of the General Data Protection Regulations (GDPR)[52]. Biological samples

collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act[53] and 2006 Human Tissue (Scotland) Act[54].

5.11.1 General Sampling Notes

All routine blood and urine samples will be collected according to standard local policy and analysed in the routine clinical laboratories of the local hospital Trust following their standard laboratory procedures. Results will be reported back according to local policy to the site. The site research team will access these results to record in the electronic case report form (eCRF). Remaining sample will be destroyed in accordance with local laboratory procedures and policy.

Blood and urine samples should be collected as per the schedule of events in the current approved version of the RiGD2 protocol.

The site's local NHS Trust standard procedure for urine pregnancy testing and venepuncture (equipment, personal protective equipment, process, mixing of vacutainer contents) should be followed. Where necessary, site staff should ensure that any mandatory NHS Trust training relating to urine and blood sample collection and transportation is up to date.

5.11.2 Sample Collection

Urine βHCG samples will be collected at site for eligibility confirmation purposes. The urine sample will be disposed of immediately after testing, in line with local site policies.

Blood samples will be collected via venepuncture. At each visit blood samples will be collected and analysed locally as per visit schedule. In addition, at visits 1, 2, 7, 10, 14 and 18 an extra 10ml of blood will be collected which will require 5ml of serum to be stored in a -40 °C freezer or lower until samples are transferred to Newcastle laboratories. Samples should be collected in tubes specified in the RiGD2 laboratory manual. At visits 1 and 10, 2.5ml of blood will be collected in a PAX tube and frozen at -40 °C or lower separately for RNA analysis. In Newcastle only, at visits 1 and 10 2.0ml of blood will be collected for DNA analysis, as this cannot be frozen.

A full chain of custody should be maintained for all samples throughout their lifecycle. The site is responsible for keeping full traceability of biological samples from the time the samples are collected from the participant, whilst in storage at the site until shipment. Trial sample tracking logs will be provided; however, sites may use their own sample tracking logs with prior approval by the NCTU.

All samples must be labelled as required (see RiGD2 Laboratory Manual). Samples should be logged on the trial sample tracking logs. On shipping to the central laboratory (Newcastle University laboratories), the sample tracker should be updated, and a sample requisition form (SRF) completed for each sample shipped. Sites must ensure there is no patient identifiable information on the sample tube or SRF.

Documentation to confirm receipt of samples shipped to central laboratory should be retained at site. Please refer to the RiGD2 Laboratory Manual for further details.

For samples that are inadequate or not received within the appropriate shipping timeframe, the patient may be asked to provide repeat/additional samples for that assessment time point.

5.11.3 Transfer and processing of samples

Blood samples from all visits that require local analysis should be transported to the local NHS site laboratory as per the local NHS laboratory guidelines. Samples should be sent to the local laboratory the same day as collection.

The additional 10mls of blood samples collected at visits 1, 2, 7, 10 ,14 and 18 will be transported to the central laboratory at Newcastle University for processing. This transfer will be arranged by the central laboratory in collaboration with the NCTU trial management team (please see laboratory manual for details). Samples should be spun and frozen (-40^{o} C) before transferring to the central laboratory.

5.11.4 Analysis of samples

Blood samples will be analysed at site's local laboratory analysed as per local policy. Samples will be analysed for full blood count (haemoglobin, platelets and white cells – neutrophils and lymphocytes), liver function tests (including albumin and ALT), thyroid function tests (TSH, FT3

and FT4), thyroid peroxidase (TPO) and TSH receptor (TRAb) antibodies, lymphocyte subset tests; T cells (CD3, CD4, CD8), B cells (CD19) and class switch B cells (CD27+ve), serum immunoglobulin levels (IgG, IgM, IgA), specific antibody levels - tetanus, Hib, pneumococcus, measles, varicella.

Of the 5ml of serum sent to the Newcastle laboratory, 1ml serum will be analysed for TSH, FT4, FT3 and TRAb determination and 1 ml will be stored for potential additional serology. The remaining sample will be used for exploratory analyses as described in exploratory objectives and analysed separately from the main trial. The additional 2.0ml (collected in EDTA tube) and 2.5ml (collected in PAX tube) will be processed at Newcastle laboratory for DNA and RNA analysis (DNA samples will only collected for Newcastle patients as samples cannot be frozen).

5.11.5 Storage of samples

Samples for local analysis will be stored at the local site laboratory in line with their local policies (samples will be kept for 1 week after receipt in Newcastle upon Tyne Hospitals Trust laboratories).

The additional blood samples collected at visits 1, 2, 7, 10 ,14 and 18 will be stored in a -40 ^{o}C freezer or lower at Newcastle laboratory. Any remaining sample from these additional bloods will be stored and used for exploratory analyses as described in exploratory objectives and analysed separately from the main trial.

5.11.6 Destruction of samples

After analysis at local laboratories, samples will be destroyed in line with local site destruction policies.

The additional blood samples collected at visits 1, 2, 7, 10 ,14 and 18 which are analysed and stored at the Newcastle University laboratory will be destroyed in line with local destruction policies. Please refer to the lab manual for specific destruction requirements.

6 INTERNAL PILOT

The trial includes an internal pilot which will run for 9 months from the start of the recruitment period and will include an evaluation of trial progress.

6.1 Evaluation of trial progress

The NCTU will review screening logs and recruitment and retention rates, as well as data capture, completeness, and quality throughout the trial to address unforeseen recruitment

barriers. Data relating to overall site opening, recruitment and retention rates will be reviewed on an ongoing basis by the TMG. Recruitment at individual sites will also be reviewed by the TMG and lessons learned from high recruiting sites can be shared at regular site delivery meetings with the local site teams.

6.2 Internal pilot progression criteria

Projected recruitment is informed by the number of sites participating in the trial, previous experience of recruiting to the original RiGD trial, staged opening of sites, and a lag period prior to full recruitment per site. We anticipate recruitment rates to increase as the number of sites open increases. At the end of the internal pilot, recruitment within the green criteria will indicate transition to full trial; recruitment within the amber range will result in the construction of a time bounded mitigation plan with our trial steering committee (TSC), including implementing contingencies (e.g., protocol changes / additional sites) for funder (NIHR-EME Fellowship) consideration. Should recruitment fall within the red criteria, this will result in a discussion with the TSC and funder about expediting recruitment or consideration of study closure.

Table 3, below, summarises the funder approved progression criteria and includes a monthly recruitment target per site to demonstrate the feasibility of recruitment; all green progression criteria are set at 100% with amber and red thresholds set appropriately and in line with relevant publications[55].

Table 3Stop/Go Progression Criteria for Trial

Parameter	Progression criteria at 9 months of recruitment		
	Green % (n)	**Amber % (n)**	**Red % (n)**
Total number of participants recruited	100% (34)	60-99% (20-33)	<60 (<20)
Number of participants recruited per site per month (with lag period to full recruitment per site)	100% (0.5)	60-99% (0.3-0.49)	<60% (<0.3)
Total number of participants who drop out before 9 months	<10% (<3)	10-20% (3-7)	>30% (>7)
Number of sites opened	100% (17)	60-99% (10-16)	<60% (<16)
Related actions/outcomes	Proceed with the main trial	Consider mitigations with oversight groups and propose a recovery plan to Funder	Closure options to be discussed with Funder.

7 PHARMACOVIGILANCE

7.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward or unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

	The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions
Reference Safety Information (RSI)	The RSI is a list of medical terms detailing the ARs that are expected for an IMP and must be referred to when assessing a SAR for expectedness.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation. • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences. * - life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable

	probability to be due to one of the trial treatments, based upon the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the approved Reference Safety Information.

7.2 Recording of AEs

- All AEs occurring from point of consent to end of trial participation must be recorded on the trial database, as well as documented in the participant's medical records, except for events specified in section 7.2.1.
- The documentation of each AE should include a description of the event, event duration (start and stop dates), details of any action taken or treatment in response to the event, and results of any assessments conducted in relation to the event. Each AE must undergo a documented assessment for severity (7.2.2), seriousness (7.1) and, after administration of IMP/NIMP, for causality (7.2.3) by a medically qualified doctor delegated this task.
- Out of range laboratory results that are deemed to be clinically significant should be reported as AEs unless excluded from reporting as per section 7.2.1.

7.2.1 Protocol Specific AE Recording Exclusion

The following events will not be recorded as AEs for this trial:

- Out of range laboratory results for TSH, FT4 and FT3, TRAB levels as these are consistent with the disease process.
- Events judged by the investigator responsible for patient care to be consistent with either GD or ATD Treatment. Disease progression will be recorded as an AE **only if** it is more severe than expected in the trial population.
- AEs that are expected, either because of GD or ATD treatment and are therefore non recordable include:
    - Nausea or vomiting
    - Headache
    - Arthralgia
    - Abdominal pain/gastric disturbance

- Rash and/or pruritus
- Neutropenia/ Agranulocytosis
- Goitre
- Bruit
- Tachycardia or bradycardia
- Tremor
- Weight loss, weight gain
- Change in scalp hair (people always complain about this)
- Pancreatitis
- Fatigue/ daytime somnolence
- Change in menstrual periods
- Thyroid eye disease

- Treatment that was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications.

AEs excluded from recording as per protocol will still be documented in patient's medical records as part of standard care. If any of the above AEs are found to meet SAE criteria (see section 7.1) then they should be recorded in the eCRF as an AE and marked as serious but do not require expedited reporting to NCTU using the SAE reporting form.

7.2.2 Assessment of Severity

A delegated medically qualified doctor should make an assessment of severity for each AE as mild/moderate/severe.

Table 4 Assessment of Severity

Mild	Minor adverse event, not requiring medical intervention. May be asymptomatic and is likely to be a clinical or diagnostic observation only; or may be a symptomatic but minor, or transient event, with no necessity for medical intervention. This might include asymptomatic laboratory or radiographic findings. A mild adverse event is likely to have only marginal clinical relevance.
Moderate	An adverse event which may require some medical intervention (local/non-invasive), and which is symptomatic to patient. May affect activities of daily living.
Severe	An adverse event that requires urgent intervention or may have life threatening consequences. Death related to the adverse event.

7.2.3 Assessment of Causality

The relationship between the use of IMP/NIMP and the occurrence of each AE must be assessed and categorised by a delegated medically qualified doctor using clinical judgement to determine the causal relationship. Other factors such as medical history of underlying diseases, concomitant therapy and any other relevant risk factors should be considered.

Table 5 Assessment of Causality Categories and Definitions

Category	Definition
Definitely related	The event is considered related to the IMP/NIMP
Probably related	It is probable that the event is related to the IMP/NIMP
Possibly related	It is possible that the event is related to the IMP/NIMP
Unlikely to be related	It is unlikely that the event is related to the IMP/NIMP
Not related	The event is not considered related to the IMP/NIMP

If after review of the information the PI/delegated clinician is unable to determine if the event is related to the IMP this should be assessed as possibly related.

If the participant is on placebo and the event is considered associated with the placebo (e.g. a reaction to an excipient or impurity within the formulation) such cases must also be assessed as related.

7.3 SAE Reporting

When an AE is assessed as serious and is not excluded from expedited reporting (see section 7.1 and 7.2.1), as well as documenting in the participant's medical notes and recording in the trial database (as described in section 9), it must also be reported as an SAE as soon as possible (at least **within 24 hours** of awareness of a member of the trial team) by completion and sending of an SAE report form.

All SAEs occurring from the point of consent to the end of trial participation must be reported. In addition, any SAR that comes to the attention of the trial team must be reported up until the point of trial closure.

Please send completed SAE report forms via secure email to: nctu.rigd2.sae@nhs.net within 24 hours of awareness of the event. *No personal identifiable data should be documented on the SAE report form*

Nctu.rigd2.sae@nhs.net is a distribution list to ensure that all relevant individuals (CI, NCTU trial management, NCTU Quality Assurance (QA) and Sponsor) are informed of the event in a timely manner. All confirmed SAEs will be allocated a unique SAE number and confirmation of receipt returned to the sender. SAEs will be recorded by NCTU personnel on the trial's safety database.

Preliminary reporting to NCTU via email or telephone is acceptable to meet the 24-hour reporting timeline, where circumstances do not allow for immediate completion of the SAE form. However, the SAE form should be completed with as much information as is available at the time and submitted as soon as possible after the initial notification to comply with reporting timelines.

For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)

- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator

Any change of condition or other follow-up information should be submitted by completion of an SAE follow-up form as soon as possible or at least within 24 hours of the information becoming available. Please send completed follow-up forms to nctu.rigd2.sae@nhs.net. Events will be followed up until the event has resolved or a final outcome has been reached until the end of the trial.

7.3.1 Protocol Specific SAE Reporting Exclusions

Adverse events associated with RTX infusion (limited to 6 hours from start of infusion)

AEs that may be expected because of a mild reaction to the RTX infusion include:

- Flushing
- Itch
- Nausea
- Dizziness, shivers/shakes
- Tachycardia, hypotension/hypertension
- Headache
- Myalgia/ Aches and pains, 'flu-like symptoms
- Cough, coryza, sneezing, wheezing
- Tiredness, somnolence

If the above AEs meet SAE criteria (see section 7.1), they should be recorded as serious in the eCRF but do not require expedited reporting to NCTU on the SAE reporting form.

Pre-planned hospitalisations (e.g., for elective thyroidectomy or radioactive iodine treatment) or scheduled treatment for pre-existing conditions that are not associated with clinical deterioration do not need to be reported as SAEs.

7.3.2 Recording and Reporting SUSARs

All SAEs assessed as **related** to the IMP and assessed as unexpected, in accordance with the approved RSI, will be reported to the Medicines and Healthcare Products Regulatory Agency (MHRA) as SUSARs. All SUSARs occurring from first administration of RTX until 1 year post treatment (Visit 10) must be reported to the MHRA and the Research Ethics Committee (REC). The NCTU will perform this reporting on behalf of the Sponsor.

The assessment of expectedness will be performed by the CI against the approved RSI for the trial. The RSI is contained within section 4.8 of the RTX SmPC used at site.

Fatal and life-threatening SUSARS must be reported no later than 7 calendar days after the NCTU has first knowledge of the event. Any relevant follow-up information must be sought and reported within a further 8 calendar days.

Non-fatal SUSARs must be reported no later than 15 calendar days after the NCTU has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

The reporting timeframe starts at day 0 when the NCTU is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- Patient trial number and date of birth
- Name of IMP
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g. Principal Investigator)

Sites should follow the SAE reporting instructions in section 7.3 to alert Sponsor, NCTU and the CI to the event. The site is expected to fully cooperate with the NCTU in order that a full and detailed report can be submitted to the MHRA within the required timelines.

SARs thought to be related to a NIMP must be expedited if:

- The event might be linked to either a NIMP or IMP but it is not possible to attribute causality
- The event may be linked to an interaction between a NIMP and the IMP
- The reaction due to the NIMP is likely to affect the safety of the trial subjects

For other serious adverse reactions which are assessed as unexpected and related (e.g. to a NIMP or other medicinal product) but not related to the IMP, the REC will be notified by email, including what the event was, what circumstances caused it to occur, what the implications were for the safety of the trial participants were and how these were addressed. PIs will be informed of all SUSARs by the NCTU.

7.4 Responsibilities

Principal Investigator

- Checking for AEs and ARs when participants attend for treatment or follow-up.
- Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness of events using the Reference Safety Information relevant to the SmPC for the RTX used at site.
- Ensuring that all SAEs and SARs, including SUSARs, are recorded and reported within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.

- Using medical judgement in assigning seriousness, causality, and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Using medical judgement in assigning expectedness to SARs in line with the RSI.
- Immediate review of all SUSARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.
- Review/assignment of Medical Dictionary for Regulatory Activities (MedDRA) or body system coding for all SAEs and SARs.
- Preparing the clinical sections and final sign-off of the Development Safety Update Report (DSUR).

Sponsor

- Data collection and verification of AEs, ARs, SAEs, SARs and SUSARs onto a database (may be delegated to NCTU).
- Reporting safety information to the independent oversight committees for the ongoing assessment of the risk/benefit ratio throughout the life of the trial (may be delegated to NCTU).
- Assessment of expectedness of any SUSARs (may be delegated to the CI)
- Expedited reporting of SUSARs to the CA and REC within required timelines
- Notification of all investigator sites of any SUSAR that occurs (may be delegated to NCTU).
- Reviewing RSI at least annually and notification of PIs of any required updates (may be delegated to NCTU).
- Preparing tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC (may be delegated to NCTU).

TSC/IDMC

- Review of safety data collected to date to identify any trends.

7.5 Notification of Deaths

All deaths will be reported as SAEs irrespective of the cause of death and reported to the sponsor. All deaths will be reported to the Independent Data Monitoring Committee (IDMC).

7.6 Pregnancy Reporting

Pregnancy itself is not classified as an AE. In the event of a trial participant or the partner of a male trial participant becoming pregnant within 12 months of receiving IMP/placebo, the site must notify NCTU, the CI and the Sponsor representative within 24 hours of becoming aware of the pregnancy by completion of a pregnancy reporting form and sending via secure email to nctu.rigd2.sae@nhs.net. Initial notification can be by telephone to the trial manager, but this must be followed up by a completed form as soon as possible.

7.6.1 Procedure for pregnancy follow-up

A participant who becomes pregnant after infusion of RTX/placebo will continue on the trial, attending all follow up visits, as normal, unless they choose to withdraw. If a female participant or the partner of a male participant becomes pregnant at any point in the trial, the participant will be unblinded.

A delegated member of the site team must approach the pregnant participant or the pregnant partner of a male participant to provide them with a pregnant participant/ pregnant partner patient information sheet. The site team must then request consent using the pregnancy monitoring consent form to follow the pregnancy to completion and for 12 months after the birth to ensure there are no congenital abnormalities. If the pregnant participant or the pregnant partner of a male participant is younger than 16 years old, then the information sheet must be given to, and consent must be requested from, their parent/carer or legal representative . In all instances of a participant, or partner of a male participant, younger than 16 years old becoming pregnant, sites must initiate local safeguarding policies.
The site will need to submit the completed pregnancy monitoring consent form to NCTU via secure e-mail to nctu.rigd2.conf@nhs.net or using appropriate secure transfer methods.

The pregnancy should be followed until completion (i.e., termination, miscarriage, stillbirth or live birth). This will include documentation of the outcome of the pregnancy, and for pregnant participants, any adverse events obtained at participant visits. For both pregnant participants and pregnant partners of male participants this will include a review of their medical notes.

If the pregnancy results in a live birth, then the child will need to be followed up for 12 months to ensure there are no congenital abnormalities. If a congenital abnormality is detected for either a live or stillbirth child, then this will need to be reported as an SAE.

7.7 Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the Sponsor, CI and NCTU must be notified immediately and details of the USM given. The Sponsor must inform the MHRA and the NHS REC within 3 days of the USM taking place in accordance with the Sponsor's standard operating procedures.

7.8 Development Safety Update Reports

A DSUR will be submitted to the MHRA and NHS REC once a year on the date of Clinical Trial Authorisation (CTA) of the trial. The Trial Manager must ensure that the report is submitted within 60 days of the end of the reporting period. The TMG must contribute to the compilation of the DSUR with the CI being involved in completion of the relevant sections requiring medical input and assessment of any newly identified risks and the summary of benefit-risk considerations. The CI must review and authorise the final report before it is ready for submission. The DSUR should also be reviewed by the NCTU QA Manager and Sponsor Representative prior to submission. NCTU staff will prepare and submit DSURs for the trial, in accordance with NCTU SOPs.

8 STATISTICAL CONSIDERATIONS

8.1 Analysis Population

The analysis population includes patients aged between 12-24 years of age with a new diagnosis of GD who meet the inclusion and exclusion criteria.

8.2 Statistical Analyses

Statistical analysis: Principal statistical analyses will be carried out on an intention-to-treat basis. All analyses will be described in a Statistical Analysis Plan, version 1.0 of which should be approved prior to trial statisticians receiving any unblinded data.

8.2.1 Analysis of the Primary Outcome Measure

For the analysis of the primary outcome, we will use the augmented binary method[56] ,which will fit a latent variable model to jointly model the TSH level, the FT3 level and a binary component representing non-remission for another reason. The model will include parameters representing treatment effect, effect of baseline measurement of the respective component (for TSH and FT3) and stratification variables. The model will be used to estimate the odds ratio of the remission rate between arms. The delta method will yield the standard error which will allow forming a 95% confidence interval and a Wald test for testing the null hypothesis of no difference between arms. As a secondary analysis we will also analyse the remission rate as a binary outcome using a logistic regression with the same parameters.

8.2.2 Analysis of Secondary Outcome Measures

Continuous secondary outcomes will be analysed with linear mixed effects models, adjusting for baseline. Binary secondary outcomes will be analysed with a logistic regression model.
If there are non-negligible missing outcome data (>5% loss to follow-up), we will use a suitable missing at random analysis strategy, such as multiple imputation.

8.3 Sample Size Calculations

Twenty endocrinologists from key centres were surveyed to determine what would be the minimum proposed improvement in remission rate after a 1- or 2-year course of treatment that would justify or warrant discussing the trial with their newly diagnosed GD patients. More than 60% of those surveyed felt that an improvement of 10-20% was clinically meaningful, with the mode response chosen being an improvement of 20%.

As the primary outcome (remission at 36 months) is defined by dichotomised continuous components (TSH and FT3 levels) and a binary component (not requiring ATD after 3 years; receiving RAI or thyroidectomy at any point during the trial) we will utilise the augmented binary method[56]. This method allows estimating the difference in remission rates between arms (together with a confidence interval and p-value for testing difference) but utilises the continuous components to improve efficiency. Resampling data from the pilot study allowed us to investigate the reduction in sample size using this method would allow. Assuming 90% power to detect a 24% difference in remission rate (24% remission with ATD (from systematic review data[15]) to 48% with ATD +RTX (from pilot study[35], 56 patients will be needed in each

arm (reduced from 82 per arm required for a standard binary analysis), therefore 112 altogether. 124 participants will be recruited in total to allow a 10% drop out rate.

8.4 Health Economic Analysis

The economic evaluation will include both a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA)[57]. The CEA will be undertaken using the primary outcome measure at 36 months and/or ThyPro-39 scores. An appropriate regression model (e.g., general linear model; the precise nature of the regression model will depend on the data collected from the trial) will be fitted to estimate marginal costs and outcomes whilst controlling for baseline covariates (e.g., age, EQ-5D-(Y)-5L utility scores), where appropriate, consistent with the statistical analysis described above. The results of the CEA will be presented in the form of incremental cost-effectiveness ratio (ICER), graphically represented on a cost-effectiveness plane. Uncertainties associated with the ICER will be explored by conducting stochastic analysis with the results presented using a cost-effectiveness acceptability curve (CEAC) [58, 59]. The CEAC will show the probability that the intervention is cost-effective compared with the standard treatment, given the observed data, for a range of maximum monetary values that decision makers may be prepared to pay for unit change in the primary outcome measure (often referred to as willingness-to-pay thresholds). The CUA will follow the similar approach to CEA and will compare changes in health-related quality of life based on participant responses to the EQ-5D-5L or EQ-5D-Y-5L at baseline, 4 weeks, 6, 12, 24 and 36 months across both arms of the trial[60]. The data collected using EQ-5D-5L will be combined with participant life years to generate quality adjusted life years (QALYs). The results of the CUA will be presented in the form of incremental cost per QALY and graphically using the cost-effectiveness plane. Uncertainties in the incremental cost per QALY estimates will be explored by conducting stochastic analysis and illustrated using CEAC as per the CEA. Both the CUA and CEA will be conducted from the perspectives of the NHS and personal social services. However, we will conduct further analyses that take a societal perspective by incorporating the time and travel costs, out of pocket expenses for health care borne by patients and their families as well as lost productivity. Health resource utilisation questionnaires will be used to collect data at baseline, 6, 12, 24 and 36 months, across both arms of the trial. NHS resource use data will include secondary care contacts and prescribed drugs collected via the eCRF, extracted from patient records or via participant questionnaires. Patient costs will be collected via a time to

travel questionnaire alongside the health resource use questionnaire. This will include questions relating to travel time and costs (e.g. to attend general practice, health clinics), time away from employment or education and time spent providing care (if appropriate). Costs will be calculated as quantities of resource use contacts multiplied by appropriate unit costs (e.g. NHS Reference Costs, PSS Research Unit[61] All costs will pertain to a specific price year, to be determined at the point of analysis.

The costs and outcomes of the intervention may extend well beyond the 36 months' time frame of the trial. Long-term cost-effectiveness will be estimated through the development of a decision model extrapolating trial data over a patient's lifetime incorporating evidence from the published literature as required following guidance for best practice[62, 63]. The model will most likely be a Markov model with states defined in terms of treatment received and relapse. The transition probabilities, costs and utilities associated with each model state will be determined at the point of model construction. The results of the model will be expressed in the form of incremental cost per QALY. Uncertainties in the model parameters will be explored within the deterministic sensitivity analyses and probabilistic sensitivity analysis. CEACs, cost-effectiveness plane and tornado diagrams will be used to illustrate the impact of uncertainties in the model. A value of information analysis will be conducted on the decision model to identify whether future research to reduce uncertainty in decision making between the two treatment arms is likely to be worthwhile.

9 DATA HANDLING

9.1 Data

Clinical and safety data for all trial participants will be collected by the PI or their delegated nominees and recorded in the eCRF of Ennov™, the clinical database management system (CDMS). Participant identification on the eCRF and paper documentation will be through a unique participant number. A record linking the participant's name to the unique participant identifier will be held within the ISF and is the responsibility of the PI. As such, participants cannot be identified from the eCRF's (see sections on data handling and data protection and confidentiality below).

Further information is available in the trial Data Management Plan.

9.2 Data Collection Tools and Source Document Identification

Data collection and entry at hospital sites will be performed by appropriately trained and delegated members of the team. The team will access source data within the hospital records and general practice (GP) records where accessible.

Patient completed questionnaires will be completed either directly into the study database or on paper and entered by site staff. Where questionnaires are completed electronically the data in the trial database will be the source data and will not be editable. Site staff will have access to the completed patient reported outcomes via the trial database.

The trial-specific (eCRF) will be set up using Ennov™. Participant identification on the eCRF will be through a unique trial identifier. Participants cannot be identified from eCRFs or paper data collection tools. The participant's name will be linked to their unique trial identifier via a record filed within each site's ISF, which will be stored in a locked room at site.

A Source Data Agreement will be completed prior to each site opening to screening and recruitment activity; this will document agreed sources of data.

9.3 Data Handling and Record Keeping

The CI has overarching responsibility for collection, quality and retention of data. Data will be collected by an appropriately qualified and delegated member of site personnel. Data will be handled, computerised and stored in accordance with the UK Data Protection Act 2018 and the UK GDPR as amended on 01 January 2021 by regulations under the European Union (Withdrawal) Act 2018[64] , to reflect the UK's status outside the European Union , the latest GCP Directive (2005/28/EC)[65] and local site policy. Paper copies of trial-related documentation will be annotated, signed, dated and filed in the Investigator Site File. Copies of the Summary PIS, PIS, completed written consent form, eligibility forms and letter to GP will be filed in the participant's medical records. Data contained in paper case report forms (CRF)s, data relevant to the trial that has been recorded in participant's medical notes or electronic medical records will be transcribed into the eCRFs on the Ennov™ database.

The CI or designated nominees will continuously monitor completeness and quality of data collected on the trial database. Monitoring will include regular correspondence with site staff to ensure missing data is collected wherever possible and ensuring continuous high quality of

data capture. Data completeness and progress reports will be generated for regular review at TMG meetings.

9.4 eCRF Data Collection

Trial clinical data will be entered into an eCRF, maintained within a CDMS. CDMS users will be assigned role-based permissions specific to their site and study role with a connection via a secure strong password. All access to and modifications of the database are logged in an audit trail. When completing the eCRF, local investigators will be prompted for any missing data items. Data submitted will be reviewed and if ambiguous or incomplete, data queries will be issued.

The CDMS used for the eCRFs in this trial is fully compliant with all regulatory frameworks for research of this nature. The CDMS is Ennov Clinical V8.2 supplied by Ennov™ and ISO certified for information security management systems ISO 27001 and quality management ISO 9001:2015. The application servers that host the application and customer data are backed up daily to two other remote data centres in the UK. It uses a secure web-based interface for data entry, no data is stored on computers at site. The data is protected by an application firewall, a network firewall and isolated on an independent virtual network (see Data Management Plan for further details).

AE coding will be done using the MedDRA with the same version of MedDRA used throughout the trial[66].

9.5 Data Protection and Patient Confidentiality

The trial will be run in accordance with the UK Data Protection Act 2018 and the UK GDPR as amended on 01 January 2021 by regulations under the European Union (Withdrawal) Act 2018 [64], to maintain the confidentially of trial participants and trial data integrity.

Participant identification on the eCRF and paper documentation will be through a unique participant number. A record linking the patient's name to the unique participant ID will be held within the ISF. Fields containing data which may be personally identifiable such as postcode, date of birth and email addresses to facilitate the provision of links to electronic questionnaires will be marked as such in the trial database set-up and will have 'reduced visibility'. This means that users with data entry permissions can enter data into and view data

contained within these fields at their own site, but data in these fields are not visible to other user roles, and do not appear in any downloads of data from the database.

Personal data will be regarded as strictly confidential. All trial files will be securely stored, and access restricted to staff involved in the trial. Access to the CDMS will be password protected and limited to staff at research sites or those employed by Newcastle University who are involved in the trial.

All investigators and trial site staff must comply with the requirements of the applicable legislation with regards to the collection, storage, processing, and disclosure of personal information and will uphold the core principles of the legislation. Explicit consent must be obtained via the informed consent form from each trial participant to allow data sharing to occur.

Overall responsibility for data collection lies with the CI. Data will be handled, computerised, and stored in accordance with the UK Data Protection Act 2018 and the UK GDPR as amended on 01 January 2021 by regulations under the European Union (Withdrawal) Act 2018[64]. Paper copies of trial related documentation will be annotated, signed, and dated, and filed in the patient medical notes or scanned and uploaded to the electronic medical records. The overall quality and retention of trial data is the responsibility of the Chief Investigator. All trial data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy[65].

9.6 Data Analysis and Transfer

All trial analyses will be performed on pseudonymised data. Data analysis will be performed by statisticians and health economists based at the NCTU. Prior to analysis outstanding data queries with sites will be reconciled and the database will be locked. The data will be downloaded and transferred to the trial statistics and health economics team via shared folder on the Newcastle University network.

9.7 Access to Data

The site PI and staff formally delegated to do so will have access to source data and the ISF to conduct the trial. Access to Ennov^{TM} database will be password protected and restricted to a user's particular role and will be limited to a site's PI and their delegated research team

members. NCTU's trial management team will have monitor role access to the trial's database for all sites for monitoring purposes.

NCTU trial management staff, trial oversight committees, representatives of the host institution, Sponsor and the MHRA will be granted access to the source data, ISF and trial database for the purposes of monitoring, audit, and inspection respectively. Consent will be sought from the participant for access to their medical records and trial data for the purposes of monitoring, audit, and inspection.

Data may be securely downloaded from the trial database and released to the Trial Statistician for analysis, including, as needed, for reports to the IDMC. Data may be downloaded where required to contribute to the mechanistic analyses. Data release will only take place after documented agreement from key members of the TMG. The full trial dataset will not be shared outside the TMG prior to the final publication. Site staff, including the PI may not disclose or use for any purpose other than conduct of the trial any data, record or other unpublished confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said information to other parties.

9.8 Archiving

Electronic data from the trial database will be provided for the Sponsor TMF and to sites in an appropriate format (to be determined at the time in accordance with latest guidance and SOPs). The trial site is responsible for archiving their trial ISF.

Trial data and the Trial Master file (TMF) will be archived for a minimum of 5 years in accordance with Sponsor and NCTU SOPs. Archiving will be authorised by the Sponsor following submission of the end of trial report. The archiving facility designated by the Sponsor will be used for storage of the TMF, which contains the essential documents that individually and collectively permit the evaluation of the data produced.

Authorisation will be requested from the Sponsor to destroy the documentation at the end of the archiving period.

10 MONITORING, AUDIT & INSPECTION

10.1 Trial Oversight

10.1.1 Trial Management Group

The TMG will be responsible for the day-to-day running of the trial and will consist of the CI, members of NCTU, statistician(s), Sponsor and, as required, other members of the co-applicant team. The TMG will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. TMG meetings will occur approximately 4-8 weekly. Progress will be monitored proactively according to agreed trial timelines and any issues addressed. The TMG will liaise with the Trial Steering Committee (TSC), providing updates on trial progress and highlighting any issues arising.

10.1.2 Trial Steering Committee (TSC)

The TSC will be established to provide overall independent oversight of the trial and will oversee trial conduct and progress. The TSC will consist of an independent chair, together with at least two other independent members, a Patient and Public Involvement (PPI) representative and the CI. The TSC will meet approximately 6-monthly throughout the trial and meetings may be attended by non-voting observers including those from the NCTU, co-applicant team, Sponsor and Funder.

10.1.3 Independent Data Monitoring Committee (IDMC)

The IDMC will consist of at least three independent members including an Independent Chair, an Independent Statistician and an Independent Clinician. The IDMC will make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate changes to the trial. The IDMC will meet approximately 6-monthly throughout the trial.

10.1.4 Principal Investigator

Each site will be led by a PI who will be responsible for trial conduct. They will be supported by research nurses and site staff will be GCP trained (except where this is unnecessary such as site staff performing tasks that are part of their usual role responsibilities). The Principal Investigator will be responsible for the oversight of day-to-day trial conduct at site. The NCTU

will provide day-to-day support for the site and training, site initiation activities and routine monitoring activities.

10.2 Monitoring

A trial monitoring plan will be developed, based upon the trial risk assessment, and agreed by the TMG, NCTU QA representative and the Sponsor. The monitoring plan will be reviewed and amended during the trial, based on changes to the protocol and identified or perceived risks.

All monitoring activity will be detailed in the monitoring plan. Monitoring of trial conduct and data collected will be performed by a combination of central review, off-site, remote, and on-site monitoring, to ensure the trial is conducted in accordance with GCP and appropriate regulations. Trial site monitoring will be undertaken by NCTU trial personnel as indicated in the monitoring plan.

All monitoring findings will be reported and followed up with the appropriate personnel in a timely manner. Sites will be expected to assist the Sponsor in monitoring the trial e.g. hosting monitoring visits, providing information for on- and off-site monitoring and responding to monitoring findings within the timeframes requested, wherever possible.

The CI or designated nominees will continuously monitor completeness and quality of data collected on the trial database. Monitoring will include regular correspondence with site staff to ensure missing data is collected wherever possible and ensuring continuous high quality of data capture. Data completeness and progress reports will be generated for regular review at TMG meetings.

The trial may be subject to audit by representatives of the Sponsor or inspection by MHRA and Human Tissue Authority (HTA). Each investigator site will permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial.

11 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Research Ethics Committee Review and Health Research Authority Approval

The NCTU will obtain Health Research Authority (HRA) and Health and Care Research Wales (HCRW) approval which includes a favourable ethical opinion from an NHS REC prior to the

start of the trial. All parties will conduct the trial in accordance with this ethical opinion and approval.

The NCTU will notify the REC and HRA of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion and HRA HCRW approval will not be implemented until HRA HCRW approval is confirmed. The NCTU will notify the REC of any serious breaches of GCP or the protocol, urgent safety measures or fatal/life threatening SUSARs that occur during the trial.

The NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines, as well as submitting the final report.

11.2 Peer Review

The trial was independently reviewed as part of application for funding. The protocol will be reviewed by the IDMC and TSC as part of the peer review process. The protocol has been reviewed and authorised by the Sponsor, Chief Investigator, Senior Trial Manager, Trial Statistician, and Data Manager.

11.3 Public and Patient Involvement

To refine the trial design the team liaised with a public panel from the Research Design Service North-East and held two focus groups involving young people with GD. A Public Involvement Fund grant was awarded to compensate contributors for their time. These individuals will also be invited to contribute to the ongoing study.

Ongoing PPI in the trial will be provided by a Young Person's Advisory Group that will meet regularly to support the trial team by providing input to all participant-facing trial documentation, review progress and assist with dissemination of results.

The Trial Management Group will include a PPI representative, Ms Julia Priestley Chief Executive Officer of the BTF, which is the largest UK thyroid patient organisation. The Trial Steering Group will also include a PPI representative.

11.4 Regulatory Compliance

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments[47]. All parties must abide by these regulations and the ICH GCP guidelines[65].

The NCTU will obtain a CTA from the MHRA prior to the start of the trial and will notify the MHRA of any substantial amendments that require review by the competent authority. These substantial amendments will not be implemented until the MHRA have issued an acceptance of the amendment.

The Sponsor will notify the MHRA of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

The Development Safety Update Report will be submitted each year to the MHRA by the NCTU until the end of the trial.

The NCTU will notify the MHRA of the early termination or end of trial in accordance with the required timelines.

11.5 Protocol Compliance

It is the responsibility of the CI to ensure that the trial is run in accordance with GCP and the protocol. Trial tasks may be delegated to a suitably qualified or experienced member of the trial team, but the CI and PI will retain overall responsibility for adherence to protocol and GCP. The trial will be monitored by NCTU staff, to measure protocol compliance and manage deviations.

Site staff are responsible for compliance with the protocol in their everyday trial activities and must report anything that they feel constitutes an AE, SAE, SUSAR, protocol deviation, serious breach, anything that requires an USM, or anything else that should be reported and documented between monitoring visits. Protocol deviations, violations, non-compliances or breaches are departures from the approved protocol. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used. The CI will not implement any deviation from the protocol without agreement from the Sponsor, except where necessary to eliminate an immediate harm to trial participants.

Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events must be documented on the protocol deviation log, including the relevant Corrective and Preventive Actions (CAPA) required. Protocol violations are a consistent variation in practice from the study protocol that could potentially impact on study participant's rights/safety or affect the scientific value or

outcome of a study. The PI will sign off each deviation and decide whether this is a deviation or violation. Violation documentation must be completed within 3 days of the violation being discovered using the violation reporting form.

11.5.1 Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

The sponsor must be notified immediately of any incident that may be classified as a serious breach. Sponsor will notify the MHRA and the NHS REC within the required timelines in accordance with the Sponsor SOP.

11.6 Indemnity

The Sponsor will provide indemnity in the event that trial participants suffer negligent harm due to the management of the trial provided under the NHS indemnity arrangements for clinical negligence claims in the NHS.

The substantive employers of the protocol authors will provide indemnity in the event that trial participants suffer negligent harm due to the design of the trial.

The trial sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site. For NHS Organisations this indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements. Trial staff without NHS contracts e.g., General Practitioners or Dentists will provide their own professional indemnity.

11.7 Amendments

It is the responsibility of the Sponsor to determine if an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI, Sponsor and the TMG.

Substantial amendments will be submitted to the HRA and REC as well as MHRA (as appropriate) and will not be implemented until this approval is in place. It is the responsibility

of the NCTU to submit substantial amendments following authorisation of the amendment tool by Sponsor.

Non-substantial amendments will be submitted to the HRA and will not be implemented until authorisation is received.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS Research & Development Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will provide to sites by the NCTU.

11.8 Access to the Final Trial Dataset

Ownership of the data arising from this trial resides with the Sponsor. On completion of the trial, the trial data will be analysed and tabulated, and a final report will be prepared.

12 DISSEMINATION POLICY

12.1 End of Trial Reporting

We will use traditional methods of publications and conference presentations to share the results with other researchers, clinicians and people living with Graves' hyperthyroidism and their families. There are no plans to report individual results back to participants.

A final report of the trial will be provided to the Sponsor, REC, and the trial funder within 1 year of the end of the trial.

12.2 Authorship Policy

Ownership of the data arising from this trial resides with the trial team and their respective employers. On completion of the trial, the trial data will be analysed and tabulated, and a clinical trial report will be prepared.

Authorship eligibility for each manuscript arising from this trial will be determined by the Trial Management Group. All co-applicants, plus the senior trial manager, trial managers, data manager and trial statisticians, will be eligible for authorship on papers reporting the protocol and main trial results, subject to fulfilling the International Committee of Medical Journal Editors (ICMJE) authorship criteria[67]. Authorship for other conference abstracts and scientific papers arising from this work will be decided by the TMG.

All outputs from this programme of work will acknowledge the NIHR Efficacy and Mechanism Evaluation (EME) as funder and will specifically acknowledge the NCTU, Newcastle University, and Newcastle Upon Tyne Hospitals NHS Foundation Trust as Sponsor.

12.3 Publication

Findings will be published in high impact peer-reviewed academic journals, ensuring that all publications are open access. Results will be publicised at national and international conferences irrespective of the results, as it is important even for negative results to be in the public domain. Results will also be presented at a range of both paediatric and adult endocrinology conferences to ensure that the results are widely publicised. The results will be shared with the UK thyroid patient community through the BTF website, membership newsletter and social media.

It is anticipated that the results will have a major impact on clinical practice. If positive, then RTX could be implemented into the next ETA guidelines for the treatment of GD.

12.4 Making Results Publicly Available

The trial will be prospectively registered on the International Standard Randomised Controlled Trial Number (ISRCTN) trial database prior to enrolment of the first participant.

12.5 Access to Final Data Set

Until publication of the trial results, access to the full dataset will be restricted to the TMG and to authors of the publication. Anonymised or pseudonymised data from this trial may be available to the scientific community in accordance with ethical approval obtained for the trial. Requests for data should be directed to the lead author/CI and NCTU in line with any applicable data sharing policies.

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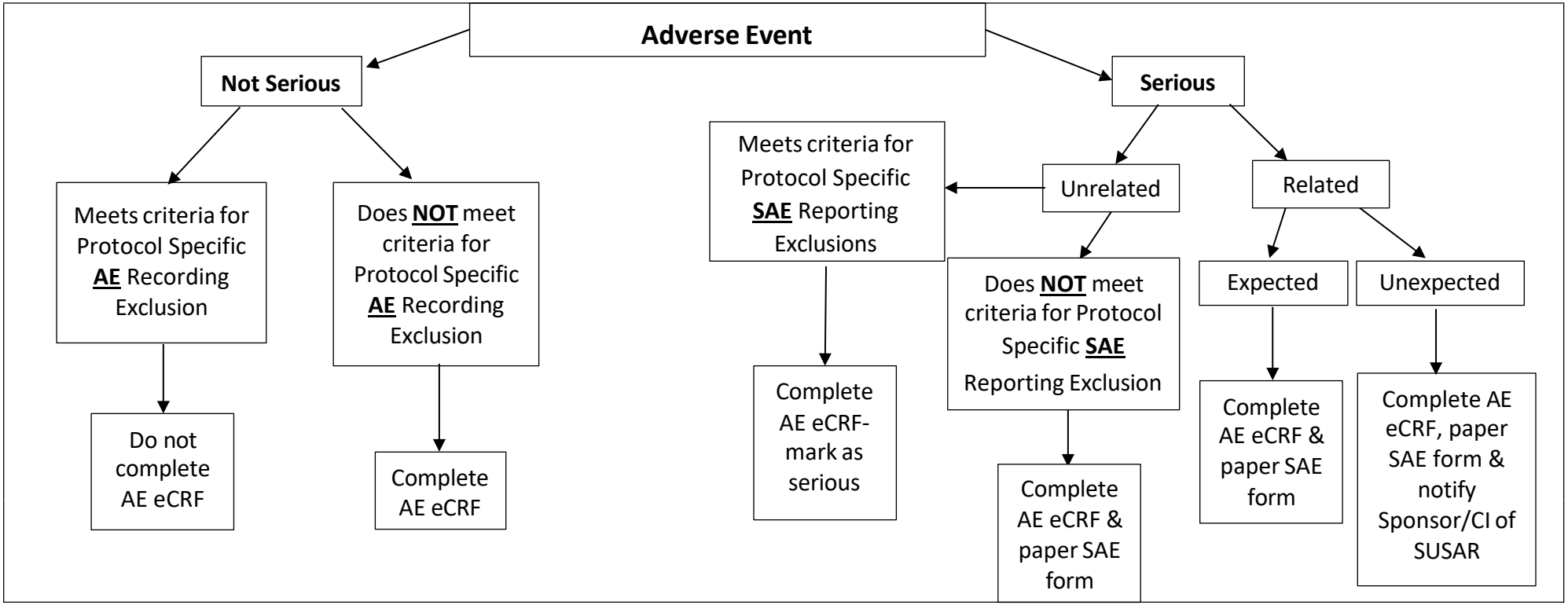
14 APPENDICES

Appendix 1 - Safety Reporting Diagram



Contact details for reporting SAEs & SUSARS

Please send SAE forms via secure email to nctu.rigd2.sae@nhs.net within 24hrs of becoming aware of the event

Appendix 2 – Amendment History

Amendment Number	Non-Substantial/ Substantial	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

Appendix 3 -Example infusion protocol for administration of Rituximab (RTX)

Example of infusion protocol for a patient weighing >50kg if patient tolerates infusion with no problems:

Time (minutes)	Rate (mls/hour)	Amount infused (mls)	Total infusion volume (mls)
0-30	25	12.5	12.5
31-60	50	25	37.5
61-90	75	37.5	75
91- 120	100	50	125
121- 150	125	62.5	187.5
151-175	150	62.5	250

Total infusion time: 2 hrs 55 mins (total infusion = 250 ml)

Calculation Example				
Patients dose	No. of vials of Rituximab needed	Conc. of Rituximab solution	Volume to be removed from the infusion bag	Volume of Rituximab solution to be added to infusion bag
500mg	1	2mg/mL	50mL	50mL