

A randomised study of two anti-thyroid drug treatment regimens in young people with thyrotoxicosis

A study devised and co-ordinated by the British Society for Paediatric Endocrinology and Diabetes.

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Introduction

Thyrotoxicosis is a relatively uncommon disorder in childhood and adolescence with an incidence of 1-8/100,000 in Europe.^{1,2} There are no reliable UK incidence data although the disorder is becoming more common in some parts of the world.³ Most patients with thyrotoxicosis have Graves disease which develops because of thyrotropin (TSH) receptor stimulation by autoantibodies. Patients with Hashimoto's thyroiditis can also be thyrotoxic in the early phase of the disease and occasionally thyrotoxicosis develops because of activating mutations of the TSH receptor. Many general paediatricians have experience of managing patients with thyrotoxicosis but national guidelines to assist in patient care have not been produced to date.

There is no ideal therapy for thyrotoxicosis in children and adolescents.⁴ The three treatment modalities for thyrotoxicosis – anti-thyroid drugs, surgery and radioiodine all have significant disadvantages. Particular considerations when managing young people include:

1. Low remission rates following a course of anti-thyroid drug therapy.^{5,6}
2. Concerns about the morbidity associated with thyroidectomy.
3. Inadequate data regarding the long term safety of radioiodine.

Children and adolescents presenting with autoimmune thyrotoxicosis in the UK are usually treated with antithyroid drugs from diagnosis for 1 - 4 years.⁷ Treatment is then stopped and patients who relapse return to anti-thyroid drugs or are offered more definitive treatment with surgery or radioiodine. Life long thyroid hormone replacement will be required if the thyroid gland is removed by surgery or ablated by radioiodine.

Hyperthyroidism and anti-thyroid drug treatment.

Excess thyroid hormone can have a major detrimental impact on cognitive function as well as cardiovascular and skeletal health.¹⁰⁻¹³ The maintenance of a clinically and biochemically euthyroid state is therefore highly desirable.

There are two possible approaches when treating patients with anti-thyroid drugs.^{8,9}

- 'Block and replace' (combined) therapy - where thyroid hormone production is prevented by anti-thyroid drugs and thyroxine is then added in a replacement dose;
- 'Dose titration' (adaptive) therapy - where the dose of anti-thyroid drug is adjusted so that hormone production is normalised.

Both strategies are used by adult endocrinologists but it is unclear which of these approaches is the most appropriate in the young person.

Potential advantages of the 'block and replace' regimen include:

- Improved stability with fewer episodes of hyper or hypothyroidism.
- A reduced number of venepunctures and visits to hospital.⁸
- Improved remission rates following a larger anti-thyroid drug dose.⁹

Potential advantages of the dose titration approach include:

- Fewer side effects with a lower anti-thyroid drug dose^{9,14}
- Improved compliance on one rather than two medications.

It is possible to partially block thyroid gland function and add thyroxine in a relatively low dose but this investigation is not designed to assess this strategy.

A prospective, multi-centre study is therefore proposed which aims to establish which regimen - block and replace or dose titration - is the most appropriate medical therapy for thyrotoxicosis during childhood and adolescence.

Study objectives

Primary objectives

1. To determine whether a 'block and replace' anti-thyroid drug regimen or 'dose titration' therapy provides more stable biochemical control. This will be determined by measuring the proportion of thyroxine and TSH concentrations that are outside the laboratory normal range and by measuring the standard deviation of thyroxine and TSH measurements.
2. To establish whether the remission rates post therapy are affected by the treatment regimen. This will be determined by measuring the proportion of individuals with normal thyroid function off anti-thyroid drug therapy at the end of the of the study period.

Secondary objectives

3. An analysis of remission rates according to disease characteristics including baseline biochemistry, thyroid volume and antibody titres.

- 4 To establish which anti-thyroid drug regimen is more acceptable to patients. This will be reflected by the incidence of drug side-effects and by the proportion of patients changing to a different treatment during the study period. This will be discussed in more detail later in the protocol.
- 5 To assess the role of genetic factors in the development and natural history of thyrotoxicosis in childhood and adolescence.

Study design

Subjects will be randomised centrally to receive one of two standard antithyroid treatments using random blocks and minimisation based on age (>10 or <10 years), free T4 levels (\leq 50pmol/l or $>$ 50pmol/l), gender and region. Randomisation will be performed using the minim program and will be carried out by the British Society for Paediatric Endocrinology and Diabetes (BSPED) Clinical Trials Unit located in the Department of Paediatrics, University of Cambridge. Patients will be allocated a unique study reference number which will be used throughout.

Randomised Groups

Group 1

'Block and replace' regimen for 36 months.

Carbimazole will be commenced in a dose of 0.75 mg/kg/day. The intention is to completely prevent endogenous thyroxine production. Thyroxine is then added in a replacement dose as the patient becomes eu and then hypothyroid.

Group 2

Dose titration for 36 months with carbimazole alone.

Carbimazole is commenced in a dose of 0.75 mg/kg/day until euthyroidism is established. The dose is then reduced to 0.25 mg/kg/day with the intention of maintaining a euthyroid state. The dose of carbimazole will be adjusted up or down depending on the prevailing biochemistry. If the patient is hypothyroid then the daily carbimazole dose will be reduced by 5mg (10 mg in the older child) and if hyperthyroid then it will be increased by 5mg (10 mg in the older child).

Registration of patients

Patients will be registered at each centre and the Baseline & Randomisation Form (Visit 1) faxed to the BSPED CTU (01223 336886). Randomisation will be performed by the BSPED CTU and the results faxed immediately back to the centre in question.

Study population

Number of patients

The standard deviation of the proportion of TSH measurements above or below the laboratory normal range (one of the primary outcome measures) on block and replace and dose titration regimens (n=12) is approximately 0.2 (unpublished data from Newcastle-upon-Tyne and Glasgow).

A clinically important difference in means between the two study groups is 0.1

128 patients (2 groups of 64 patients) will therefore be required to detect a mean difference in control of 0.1 with 80% power at the 5% level.

Assuming an incidence of 3 per 100,000 (children and adolescents)

~ 120 patients per year in the UK

Recruitment completed over a 3-4 year period.

Inclusion criteria

All patients with Graves' disease 2-16 years at the time of diagnosis. Graves' disease will be diagnosed by the paediatrician on the basis of the clinical picture and the biochemistry (suppressed TSH with high thyroid hormone levels).

Exclusion criteria

1. Known toxic adenoma / toxic hyperplasia (germline activating TSHR mutation)
2. Previous episodes of thyrotoxicosis

Study Outcome

Outcome in each group

The optimal anti-thyroid drug regimen which will be determined by:

1 Biochemical control

Biochemical stability will be assessed in two ways:

- By determining the proportion of thyroxine concentrations that are above or below the laboratory normal range and by measuring the standard deviation of free thyroxine levels.
- By determining the proportion of TSH levels that are above or below the laboratory normal range (greater than 2SD above or below the mean).

2 Disease course

The impact of the treatment regimen on remission rate after 4 years. This will be 1 year after the anti-thyroid drug treatment has been stopped. Remission is defined by the presence of normal thyroid function tests off anti-thyroid drug therapy.

Other outcome measures

3 Prognostic factors

- An analysis of remission rates according to disease characteristics which are baseline biochemistry, thyroid volume and antibody titres.

4 Acceptability and Safety

- The frequency and severity of side effects during the 3 year period of drug therapy.
- The number of patients/families and physicians electing to change to another treatment modality or drug regimen during the 3 year treatment period. If patients opt for another medical treatment regimen or for definitive treatment (surgery or radio-iodine) then data will continue to be collected from them for the study duration. They will then be included in the analysis on the basis of intention to treat.

5 Genetics

- An analysis of the genetic loci implicated in the development of Graves disease and their relationship with clinical and biochemical details and natural history of the disease (page 9).

Patient details and investigations

At diagnosis -

Family History

First and second degree relatives with thyroid and other autoimmune disease

Clinical details

- Systemic enquiry
- Height and weight
- Pubertal status (Tanner staging)
- Cardiovascular status
- Eye examination

Biochemistry

- Thyroid function TSH, FT4 (and T3/FT3 where available).
- Thyroid antibodies - thyroid receptor, microsomal and thyroglobulin antibodies. These will be measured centrally on samples transported by post. This analysis will not be affected by the 24-48 hour transit time.

Other investigations

- Assessment of thyroid volume by ultrasonography (where available) at baseline and at the end of years 3 and 4.
- Technitium (Tc^{99m}) or iodine (¹²³I) uptake scan at baseline (if this is usually part of the initial assessment).
- Bone age assessment at baseline and the end of years 3 and 4

Molecular genetics. Blood sample obtained at baseline

- EDTA sample from patient and parents for central analysis

At subsequent assessments -

Clinical details

- Systemic enquiry
- Height and weight
- Cardiovascular status
- Eye examination

Biochemistry

- Thyroid function TSH, FT4, (T3/FT3 where available).

Annual assessment -

Clinical details

- Systemic enquiry
- Height and weight
- Pubertal status
- Cardiovascular status
- Eye examination

Biochemistry

- Thyroid function TSH, FT4, (T3/FT3 where available).
- Thyroid antibodies - thyroid receptor, microsomal and thyroglobulin antibodies (measured centrally)

Other investigations

- Bone age assessment (end of years 3 and 4)
- Thyroid Ultrasound at the end of years 3 and 4

Treatment aims and guidelines

i) Block and replace regimen

The primary objective of treatment is to maintain free thyroxine concentrations in the normal laboratory range (mean $-2SD < \text{FreeT4} < \text{mean} + 2SD$) with a TSH that is also within the normal laboratory range (neither elevated nor suppressed).

Carbimazole is commenced in a dose of 0.75 mg/kg/day (propylthiouracil – see below). The intention is to completely prevent endogenous thyroxine production. Thyroxine is then added in a low replacement dose as the thyroid hormone levels fall into the lower half of the laboratory normal range.

- The carbimazole dose of 0.75 mg /kg/day will block the production of thyroid hormone in most patients.
- If thyroxine values remain elevated ($> 2SD$) at 2 months into treatment or beyond with a suppressed TSH then consider increasing the dose to 1 mg/kg. It may also be appropriate to discuss the importance of compliance at this stage.
- When Free thyroid hormone levels are in the lower half of the laboratory normal range or below start thyroxine in a low replacement dose ~ 75 micrograms / m^2 .
- If the TSH is suppressed and the free thyroxine 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.
- The treatment regimen may not require adjustment if the free thyroxine is relatively high but the TSH is normal.
- If compliance is not a concern and if the dose of thyroxine is not greater than 75 micrograms / m^2 then a suppressed TSH beyond the first 4 months of therapy should be managed by increasing the dose of carbimazole in the first instance.
- If the patient becomes thyrotoxic with a suppressed TSH when the biochemistry has been normal at an earlier stage of therapy – check compliance and consider increasing the dose of carbimazole by 5 mg/day.
- If the patient subsequently develops a high TSH then increase the dose of thyroxine up to ~ 100 micrograms / m^2 /day or by 12.5 to 25 microgram increments (12.5 micrograms under 30 kg, 25 micrograms for those over 30kg).

ii) Dose titration regimen

The primary objective of treatment is to maintain free thyroxine concentrations in the normal laboratory range (mean -2SD < FreeT4 > mean + 2SD) with a TSH that is also within the normal laboratory range (neither elevated or suppressed).

Carbimazole is commenced in a dose of 0.75 mg/kg/day until thyroid hormone levels fall into the local laboratory normal range. The dose is then reduced to 0.25 mg/kg/day with the intention of maintaining a euthyroid state as reflected by a free thyroxine and TSH within the normal range.

- The dose of carbimazole will be adjusted up or down depending on the prevailing biochemistry.
- If the patient is hypothyroid then the carbimazole dose will be reduced by 5mg/day for those patients under 30 kg and 10 mg for those over 30kg.
- If the patient is hyperthyroid then it will be increased by 5mg for those patients under 30 kg and 10 mg for those over 30kg.
- Be primarily guided by the thyroid hormone value (not the TSH) in the first 4 months after diagnosis.
- Be guided by both the TSH and free T4 thereafter; if the TSH is suppressed in the presence of normal free T4 values then consider reducing the dose of carbimazole as detailed above.
- The treatment regimen may not, therefore, need to be adjusted if the TSH is suppressed and the free thyroxine is normal in the initial phase of treatment (the first 4 months).
- The treatment regimen may not need to be adjusted if the free thyroxine is relatively high but the TSH is normal (analogous to the congenital hypothyroid patient who may have a normal TSH but a relatively high free T4 when on T4 replacement).

Propylthiouracil

Most paediatricians in the UK commence thyrotoxic children on carbimazole rather than propylthiouracil. Patients who are going to be treated with propylthiouracil can also be recruited and randomised. The guidelines detailed above can be used in the knowledge that 1mg of carbimazole is *approximately* equivalent to 10 mg of propylthiouracil.

Treatment Failure

If patients opt for another medical treatment regimen, or for definitive treatment (surgery or radio-iodine) either electively or because of treatment side effects resulting in anti-thyroid drugs being stopped, (see appendix I) then data will continue to be collected from them for the study duration. They will then be included in the analysis on the basis of intention to treat. Data on those who opted out will also be analysed separately if there are sufficient numbers.

Management and outcome during therapy with regimens 1 and 2

- Patients are treated with anti-thyroid drug for 3 years. Data including biochemistry, disease course at 4 years and treatment side-effects will be available for analysis.
- Patients opt for definitive treatment part-way through the 3 year course of medical therapy. The reasons for this will be documented as well as the treatment selected. Data collection will continue until the end of year.
- Patients opt for a different treatment (surgery, radioiodine or propylthiouracil) because of the side-effects of carbimazole (part-way through the 3 year course of medical therapy). The reasons for this will be documented as well as the treatment selected. Data collection will continue until the end of year 4.
- Patients opt for definitive treatment because of compliance difficulties part-way through the 3 year course of medical therapy. The reasons for this will be documented as well as the treatment selected. Data collection will continue until the end of year 4.
- Patients relapse during the final year of the study having stopped anti-thyroid drugs at the end of year 3 (as per the protocol). They will then have the option of returning to anti-thyroid drug treatment or opting for definitive treatment (surgery or radioiodine). Data collection will continue until the end of year 4.

Ethics approval

This study has ethical approval (MREC Ref No 04/12/015).

Steering group

The BSPED clinical trials unit will act as the study steering group.

Study Management

This study will be conducted under the auspices of the British Society for Paediatric Endocrinology and Diabetes (BSPED) Clinical Trials Unit (CTU) in compliance with the protocol, GCP and the applicable regulatory requirements. The CTU is based within the University of Cambridge, Department of Paediatrics. This centre has extensive previous experience in clinical trial management, in line with GCP regulations. This team will organise all aspects of data management for the study including: randomisation, data entry, database management, trial monitoring, site visits, and support the preparation of regulatory and ethical submissions.

Quality control and assurance

The trial will be monitored by an independent Data and Safety Monitoring Committee (DSMC). No member of the Trial Steering Committee or any clinician (investigator) responsible for the clinical care of trial participants may be a member of the DSMC. The DSMC will monitor the trial in all its aspects.

Routine monitoring of data will be undertaken by the BSPED clinical trials unit to confirm that:

- Eligibility criteria are met and signed consents are in place.
- That data collected are consistent with adherence to the trial protocol.
- That accurate assessment of outcome information has occurred.
- To collect any important missing data.

Direct access to source data

Principal investigators will be responsible for the security of data at each local site according to the requirements of their employing authorities. Only data required for the trial will be forwarded to Clinical Trials Unit where only Unit support staff will have access to the data.

On entry to the study each participant will be randomised to treatment by the CTU and allocated a unique study number by which the participant will be identified. Personal identifiers or contact details for subjects will not be recorded on the Case Record Forms, ensuring direct contact cannot occur.

Paper copies of the anonymised Case Record Forms are kept in a locked filing cabinet within the CTU in Cambridge, the Department itself being accessed using a "swipe card" system.

Investigators will grant permission to all necessary regulatory authorities for direct access to the data to examine, analyse, verify and reproduce records and reports that are important to the evaluation of the trial. They will take all

reasonable precautions to maintain the confidentiality of subjects' identities.

Statistical Analysis

John Matthews, Professor of Medical statistics was closely involved in the study design including the power calculation detailed above (section on page 6). He will also be involved in data analysis.

Finances and indemnity

This study only requires a small amount of funding because it is a trial of 2 established treatment regimens with little that is not routine clinical care. A local fund is available to pay for the costs of postage, DNA extraction and storage and for the TBII assay.

The chief investigator has NHS indemnity and is a member of the Medical Defence Union (no. 3055261). Participating BSPED members will also be members of the MDU/Medical Protection Society.

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Appendix (i)

Adverse event reporting – thyrotoxicosis study

MREC Ref No: 04/12/015

Information regarding adverse events will be forwarded to, and reviewed by the Principal investigator (See page 35 of data forms). Investigators will also be expected to abide by the standard 'Yellow Card' reporting system.

Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product

Adverse reaction of an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship

Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria.

Serious adverse event or serious adverse reaction

Any untoward medical occurrence or effect that:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients' hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect.

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Expected adverse drug reactions

In order to minimise unnecessary work, it is recommended that all expected adverse drug reactions and all expected serious adverse events are listed in the protocol (otherwise they will have to be reported as SUSARs).

Sometimes, unexpected adverse drug reactions and unexpected serious adverse events become 'expected' during the trial, in which case the protocol should be amended and such events would not need reporting. The Sponsor² and Chief Investigator and Data Monitoring Committee, if applicable, should determine whether any events become 'expected' during the course of the trial and apply for MHRA and Ethics Committee approval for a substantial amendment.

Expected Serious Adverse Events

In order to minimise unnecessary work, it is recommended that all expected adverse drug reactions and all expected serious adverse events are listed in the protocol (otherwise they will have to be reported as SUSARs).

Recording and evaluation of adverse events

Individual adverse events should be evaluated by the investigator and, where indicated, they should be reported to the sponsor for evaluation. This includes the evaluation of its seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the adverse event.

The sponsor has to keep detailed records of all AEs reported to him by the investigator(s) and to perform an evaluation with respect to seriousness, causality and expectedness.

Assessment of seriousness

- Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated
- Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity
- Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and / or the subject's life is at risk from the event.

Assessment of causality

- Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and

there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product.

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible.

Anti-thyroid drugs. Expected adverse events

1a Carbimazole - Expected adverse drug reactions

Nausea,
Mild Gastro-intestinal disturbance
Headache
Rashes and pruritis
Arthralgia

1b Carbimazole- Expected serious adverse events

Bone marrow suppression including:
leucopenia,
neutropenia,
pancytopenia,
agranulocytosis

2a Propylthiouracil - Expected adverse drug reactions

Nausea, mild Gastro-intestinal disturbance
Headache
Rashes and pruritis
Arthralgia

2b Propylthiouracil - Expected serious adverse events

Vasculitis
Hepatitis
Hepatic necrosis
Encephalopathy
Lupus erythematous-like syndrome
Bone marrow suppression including neutropenia pancytopenia,
agranulocytosis

Appendix (ii)

Genetic studies

Graves' disease in childhood/ adolescence represents an important subgroup for genetic study as the disease (by definition) has earlier onset and thus is likely to have a stronger genetic basis than that found in adulthood. Furthermore, the established immunomodulatory therapy (Carbimazole) is less efficacious in childhood and adolescent GD, consistent with a more aggressive autoimmune disease (as seen in adult males with GD). A 5-10 ml EDTA blood sample from each of the 128 subjects would be sufficient for genetic studies, which would take place in parallel to similar analyses in adult Graves' populations. Obtaining an additional 5ml EDTA blood sample from each parent would be an enormous advantage, as this would allow transmission disequilibrium testing (TDT), which would provide a much more stringent and robust analysis. Samples would be sent by first-class post to the Institute of Human Genetics, Newcastle in mail-safe plastic containers. Receipt of the specimens would be acknowledged. Mutation screening for *de-novo* activating TSHR mutations (exon 10) would be batched and carried out by denaturing-HPLC (95% sensitivity) 3 times per year. This will give important prognostic information, as all such cases are predicted to relapse after discontinuation of antithyroid drugs. The prevalence of this genetic abnormality in an unselected cohort of childhood hyperthyroidism is unknown and its elucidation would be an important secondary endpoint.

Currently two loci have been unequivocally established for GD, namely the MHC (chromosome 6p21) and CTLA4 (2q33), together accounting for about 50% of the inherited susceptibility to Graves'. The Newcastle group, and others, have been involved in identifying a further a further six putative GD loci by linkage studies using anonymous (short tandem repeat/ microsatellite) genetic markers, with evidence suggestive of linkage to GD on chromosomes 5q31-q33, 14q31, 18q21, 20q11, Xp11 and Xq21.¹⁵⁻²⁰ We are currently involved in fine-mapping a Graves' locus on chromosome 18q21 and would plan to use the samples to confirm the findings in adults. However, this would be a unique sample resource and aliquots of the DNA samples would be freely available to all members of the UK endocrine community for appropriate analyses, subject to steering committee approval.

Appendix (iii)

Biochemical ranges

The local centre laboratory biochemical range for TSH and Free thyroxine level will be used where possible. This is where TSH and thyroid hormone concentrations will be measured. The biochemical assessment of TSH is relatively consistent from one laboratory to another and standard deviation scores based upon local normal ranges can be used in the analysis.

The laboratory ranges for Newcastle Upon Tyne Hospitals
TSH normal range: 0.3 to 4.7 mIU/l pmol/l

Free Thyroxine normal range: 11 to 23 pmol/l

Free T3	0 – 3 years	3.5 – 8.3 pmol/l
	4 – 7 years	3.5 – 7.8 pmol/l
	8 – 11 years	3.5 – 7.1 pmol/l
	12 – 15 years	3.5 – 6.8 pmol/l
	16 + years	3.5 – 6.5 pmol/l

Auxology

UK reference data will be used when assessing SD scores for height and weight. Blood pressure will be compared with appropriate sex, age and height adjusted reference data.

Appendix (iv)

Study Summary

1. Diagnosis of thyrotoxicosis made at DGH or tertiary unit
2. Patient can be commenced on carbimazole 0.75mg/kg (± propranolol).
3. Explanation and information leaflet downloaded and follow-up arranged with endocrinologist in ~ 2 weeks
4. **Visit 1 (~2 weeks):** Patient / family would like to participate– Consent.
5. Patient details recorded (including thyroid function at diagnosis).
6. Baseline bloods taken and imaging arranged if not performed already (ultrasound +/- isotope study).
7. **Randomisation.** This will be undertaken at the BSPED Clinical Trials Unit located in the Department of Paediatrics, University of Cambridge. Patients will be randomised to one of two standard antithyroid treatments (block and replace or dose titration) using the minim program according to age (< or > 10 yrs), free T4 levels (≤ 50pmol/l or > 50pmol/l), gender and region. Patients will be assigned a unique study reference number.
8. Treatment – ‘Block and Replace’ regimen or ‘Dose Titration’
9. **Visit 2 – 4 weeks post diagnosis:** Bloods for central analysis (antibodies and EDTA) taken at this venepuncture if not already collected
10. Assessment at 4 weeks, 8, 12, 16, 26 weeks – follow guidelines
11. ~3 monthly review with annual assessment there-afterwards
12. Try and keep to visit schedule if at all possible.
13. Extra visits if thought to be indicated by clinician – complete ‘additional visit’ sheet (page 40/41).
14. **Annual assessment:** information as per 3 monthly review except that pubertal staging documented (end of years 1,2,3) and thyroid ultrasound and bone age required (end of year 3).
15. Treatment for 36 months then stop therapy
16. 3 monthly review with bloods off therapy
17. Outcome at 4 years including pubertal status, thyroid U/S, bone age.

18. Patients requiring definitive therapy (radio-iodine or surgery) will be followed up with data collected as per the protocol.

Appendix (v)

Study protocol – Summary

Investigations at diagnosis

1. Bloods (analysed locally)

- Thyroid function tests TSH, FT4, (and FT3 or total T3 if available).

2. Bloods (to be analysed centrally – these can be taken at visit 2)

- Antibodies – 2mls clotted
- Blood for genetic studies - patient (4mls EDTA)
- parents (4ml EDTA)

Forward to: Children's Out Patients, Royal Victoria Infirmary,
Newcastle-upon-Tyne, NE1 4LP

3. Imaging

- Thyroid imaging – ultrasound and / or isotope scan (^{123}I or $\text{Tc}^{99\text{m}}$)
- Bone age

	Exam ⁿ	Possible effects incl. throats	side incl. sore throats	Thyroid function	Antibodies	Bone age	Thyroid U/S	Other
Diagnosis: 0 wks	*			*				
Visit 1 - Consent & randomisation	*	*				*	*	• Isotope scan
Visit 2: 4 wks	*	*		*	* (Analysed centrally)			• Genetic Studies (any time in the first weeks of therapy)
Visit 3: 8 wks	*	*		*				
Visit 4: 12 wks	*	*		*				
Visit 5: 16 wks	*	*		*				
Visit 6: 6 mths	*	*		*				
Visit 7: 9 mths	*	*		*				
Visit 8: :12mths	*	*		*				
Visit 9: 15 mths	*	*		*				
Visit 10:18 mths	*	*		*				
Visit 11: 21 mths	*	*		*				
Visit 12: 24 mths	*	*		*				
Visit 13: 27 mths	*	*		*				
Visit 14: 30 mths	*	*		*				
Visit 15: 33 mths	*	*		*				
Visit 16: 36 mths	*	*		*	*	*	*	
Visit 17: 39 mths	*			*	* (Analysed centrally)			
Visit 18: 42 mths	*			*				
Visit 19: 45 mths	*			*				
Visit 20: 48 mths	*	*		*	* (Analysed centrally)	*	*	

Appendix (vi)

Extra visits

Patients participating in the study should be assessed according to the study schedule (see page 23 of the protocol).

However they can also be brought for 'extra visits' if, for example, the interval between visits is considered to be too long. An extra visit sheet is on pages 29/30 of the data forms.

If the patient has thyroid function tests checked between visits but is not seen by a clinician then this information can be recorded on the scheduled appointment sheet at the next clinic visit.

Appendix (vii)

Frequently asked questions

1. Patients will be randomised whilst they are on carbimazole (0.75 mg/kg).
2. TSH and Free thyroxine are required in all patients. T3 and FT3 only if available.
3. Serious drug side effect – please contact Tim Cheetham (Direct dial 0191-282-9562) or by air call (0191-282-9562 then ask switchboard to air-call Tim Cheetham) or alternatively contact Chris Kelnar at Edinburgh (0131-536-0821).
4. Patients who stop taking antithyroid drugs – for whatever reason – should remain in the study with regular thyroid function tests / data collection, provided they are happy to do so.
5. Most people would not advise patients who have become neutropaenic on one drug (eg Carbimazole) to be switched to the other (eg Propylthiouracil).
6. If patients receive definitive therapy then this can be entered on the data collection sheets in the 'treatment/other' section.
7. Please have a low threshold for discussing the protocol or patient treatment with the study co-ordinators.