The TABLET Trial: A Randomised Controlled Trial of the Efficacy and Mechanism of Levothyroxine Treatment on Pregnancy and Neonatal Outcomes in Women with Thyroid Antibodies

PROTOCOL

There is a strong and statistically significant association between thyroid peroxidase antibodies and miscarriage and preterm birth. Pregnancy may trigger progression to a relative hypothyroid state in women with thyroid peroxidase antibodies, which can be counteracted by levothyroxine treatment. The two existing randomised trials show substantial reductions in miscarriages (52% relative risk reduction) and preterm births (69% relative risk reduction) in women taking levothyroxine compared to placebo. Such reductions need to be confirmed in a large, high quality study.

The TABLET Trial is a large, double blind, placebo controlled trial that will test the hypothesis that in euthyroid women with thyroid peroxidase antibodies, levothyroxine (50mcg, oral, once daily), started pre-conceptually and continued to the end of pregnancy, increases live births at or beyond 34 completed weeks of gestation by at least 10% compared with placebo. We will also explore the effects of levothyroxine in prognostic subgroups including maternal age, number of previous miscarriages, women undergoing infertility treatment, and initial thyroid stimulating hormone concentration. Over 4500 women who have miscarried will be screened for thyroid peroxidase antibodies in around 20 UK early pregnancy assessment and recurrent miscarriage clinics. In addition we will screen women who are having infertility treatment. It is anticipated over 900 will be randomised into the TABLET Trial.

Should the TABLET Trial demonstrate a significant benefit, it would represent a major breakthrough in the treatment of two common, serious and costly conditions. There is a high prevalence of thyroid autoantibodies, and thus a large number of women would be expected to benefit from levothyroxine treatment if effectiveness is established. Given that levothyroxine treatment is cheap, safe and convenient, and the financial impact of miscarriage substantial, even a small improvement in outcome is likely to cost-effective.

In order to obtain the large number of patients needed to provide reliable answers, and to maximise the clinical relevance of the findings, the trial is designed to fit in with routine practice as far as possible and to impose minimal additional workload by keeping extra clinic-based tests and evaluations to a minimum. Because the success of the trial depends entirely on the whole-hearted collaboration of many doctors and midwives, publication of the main result will be in the name of the collaborative group and not those of the central organisers.

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Sponsor and Sponsor Roles

University of Birmingham is the sponsor. Professor Arri Coomarasamy is the Chief Investigator.

The University of Birmingham is responsible for obtaining necessary approvals and for pharmacovigilance. The Trial Management Group is jointly responsible for overseeing GCP. The investigators are responsible for obtaining informed consent and care of the participants.

Signatures

The investigators and the sponsor have discussed this protocol. The investigators agree to perform the investigation and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

Chief Investigator	Signature	Date
Trial Statistician	Signature	Date
Sponsor(s) Representative	Signature	Date

Abbreviations

ABPI	Association of the British Pharmaceutical Industry
ABHI	Association British Healthcare Industries
ACU	Assisted Conception Unit
AE	Adverse event
AR	Adverse reaction
ASR	Annual Safety Report
BCTU	Birmingham Clinical Trials Unit at the University of Birmingham
BMI	Body Mass Index
CA	Competent Authority
CI	Chief Investigator
CTA	Clinical Trial Authorisation
DMC	Data Monitoring Committee
EPAU	Early Pregnancy Assessment Unit
ERPC	Evacuation of Retained Products of Conception
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
IMMQAS	Immunology Quality Services
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
MHRA	Medicines and Healthcare Products Regulatory Authority
MRC	Medical Research Council
MREC	Multicentre Research Ethics Committee
PI	Principal Investigator – the local lead investigator for the TABLET Trial
PIS	Participant Information Sheet
QP	Qualified Person for release of trial drug
RCOG	Royal College of Obstetricians and Gynaecologists
RR	Relative Risk
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TPO	Thyroid Peroxidase
TSC	Trial Steering Committee
TSH	Thyroid Stimulating Hormone
TVUS	Transvaginal Ultrasound
USS	Ultrasound Scan

Contents

1. BACKGROUND

1.1. Clinical background

Miscarriage, the loss of a pregnancy before 24 weeks of gestation, affects 1 in 5 women who conceive, making it the commonest complication of pregnancy. It substantially impacts on physical and psychological wellbeing: research shows that the level of distress associated with miscarriage can be equivalent to that of a stillbirth of a term baby. An estimated 140,000 women per year miscarry in the UK, costing the NHS over £350 million/ year.

In addition, preterm birth, delivery of a baby between 24 and 37 completed weeks of gestation, occurs in 6-10% of pregnancies. Preterm birth is responsible for up to 85% of new-born deaths. Of those who survive, approximately 10% suffer long-term disability. The human cost of preterm birth is therefore enormous; the financial cost of preterm birth is estimated at £939 million/year in the UK. This includes healthcare costs (including neonatal care), education, and costs to the parents.

The prevalence of measurable circulating antithyroid autoantibodies to thyroglobulin or thyroperoxidase (TPO) in women of childbearing age in the developed world is 5-15%; that of overt hypothyroidism is estimated at 0.3-0.5% and subclinical hypothyroidism at 2-3%(1;2). Prevalence rates are similar during pregnancy (3;4).

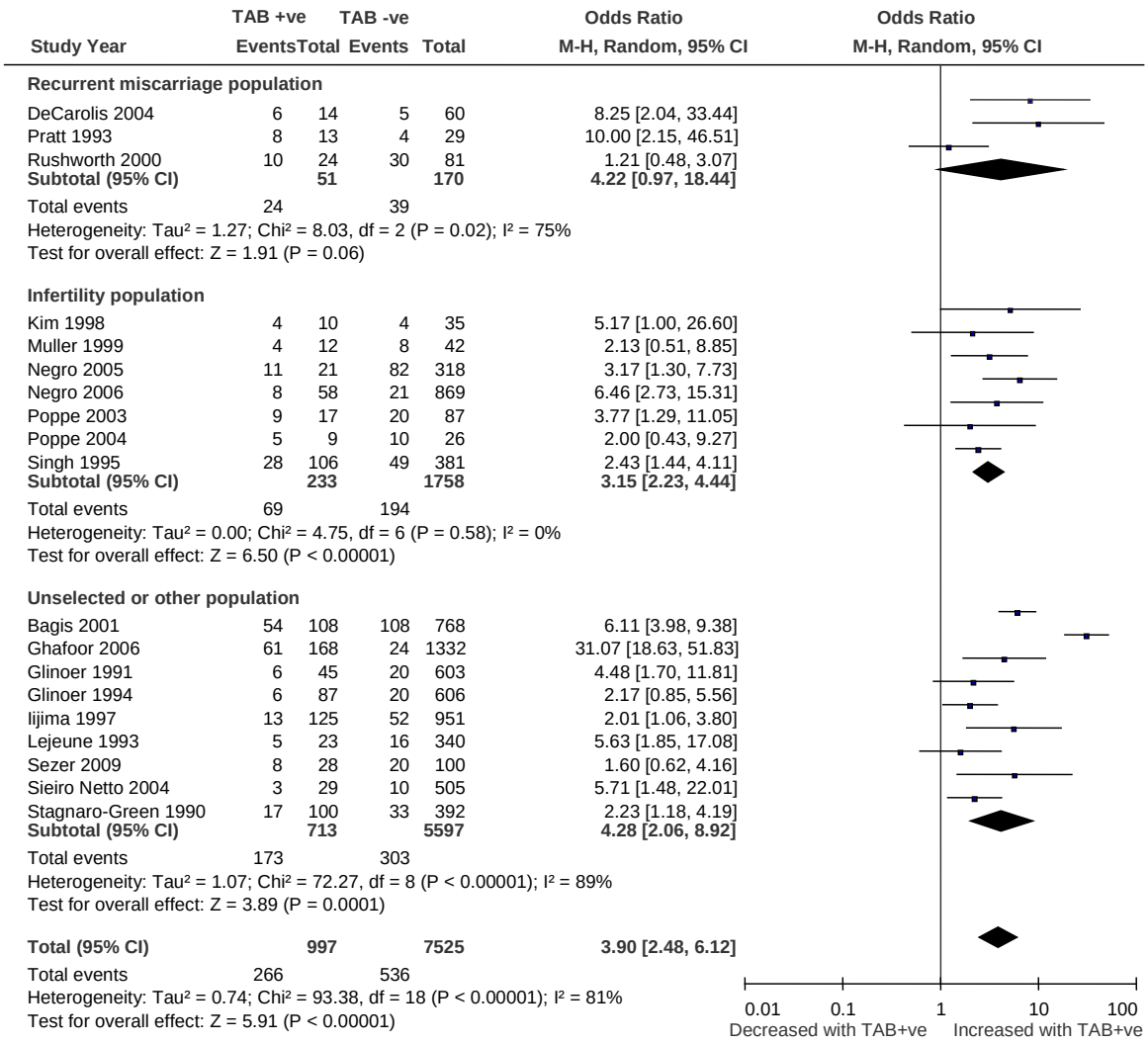
Pregnancy may trigger progression to a relative hypothyroid state in women with TPO antibodies. This is because of an increased demand for thyroid hormone during pregnancy and women with thyroid autoimmune disease are less able to sustain this increased demand.

To understand the relationship between thyroid autoantibodies and adverse outcomes, systematic reviews of the literature were conducted.

1.2. Association between thyroid antibodies and miscarriages

A systematic review, published in the British Medical Journal (5) identified 31 studies, including a total of 12,126 women and three reviews. Thirteen studies were in recurrent miscarriage populations, nine were in infertile populations and nine were in unselected or other populations. The quality of the studies was judged to be generally good on Newcastle-Ottawa Scale (6), with most studies (22/29, 76%) establishing good comparability of the antibody positive and negative cohorts. Of the 31 studies, 28 showed a positive association between thyroid antibodies and miscarriage. Meta-analysis of results from 19 cohort studies showed more than a tripling in the odds of miscarriage in the presence of thyroid antibodies (OR: 3.9, 95% CI: 2.48 to 6.12) (Figure 1). This strong and statistically significant association between thyroid antibodies and miscarriage was observed in all three population subgroups. A "dose-response" relationship between thyroid antibody positivity and the number of miscarriages was observed. There was also a similar magnitude of increased risk of miscarriage in each of the three subpopulations identified.

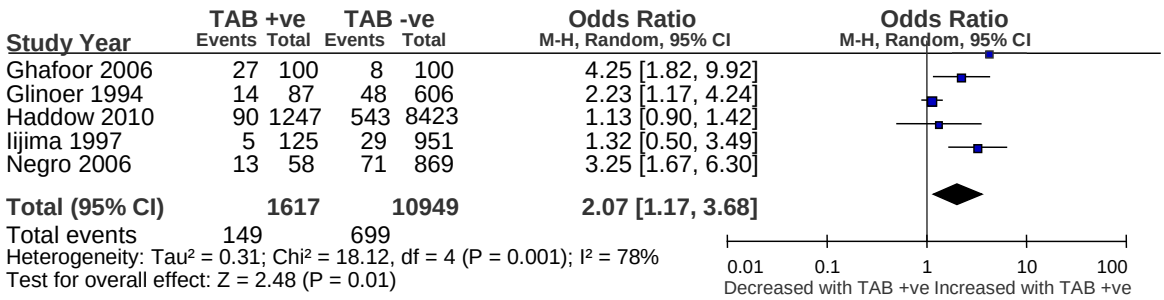
Figure 1. Association between thyroid auto-antibodies (TAB) and miscarriage
Cohort Studies



1.3. Association between thyroid antibodies and preterm births

A systematic search of the literature identified five studies, including a total of 12566 women and one review. All five were cohort studies, and all were judged to be of good quality on Newcastle-Ottawa Scale.(6) All studies showed a positive association between the presence of thyroid antibodies and preterm births. Meta-analysis showed a more than two fold increase in the odds of preterm birth in the presence of thyroid antibodies (OR: 2.07, 95% CI: 1.17, 3.68; see Figure 2).

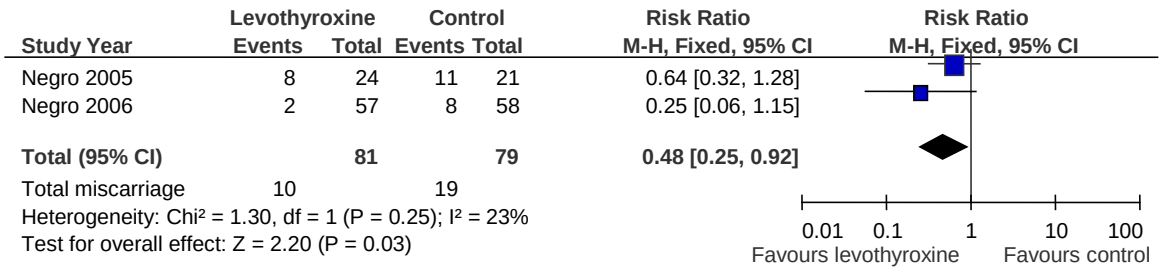
Figure 2. Association between thyroid auto-antibodies (TAB) and preterm births



1.4. Effectiveness of levothyroxine treatment

Two randomised studies, including a total of 187 women, were identified in a systematic search. Both studies were in euthyroid women with thyroid autoantibodies, one was in unselected women (7) and the other in women scheduled to have IVF treatment (8). 1mcg/kg/day of levothyroxine was used in one study (8), and the other study (7) used a titrated dose of levothyroxine. The quality of the studies was satisfactory (Jadad Quality Scores 5/5 and 3/5). Both studies showed a reduction in miscarriage rates (36% and 75% relative reductions), and when the results were pooled, there was a statistically significant 52% reduction in miscarriages with levothyroxine treatment (RR: 0.48, 95% CI: 0.25, 0.92). One of the two studies reported on preterm birth (7): this study (n=115) found a 69% reduction in preterm births with levothyroxine treatment (RR: 0.31; 95% CI:0.11, 0.90; see Figure 3).

Figure 3. Effect of levothyroxine treatment in reducing miscarriage in euthyroid women with thyroid auto-antibodies



1.4.1 Risks and benefits

Levothyroxine is a commonly used drug in obstetric-endocrine clinics, and has a well-established safety profile. The two randomised studies (7;8) described in Section 1.3 did not find any safety concerns for the mother or the baby. Specifically, there were no instances of hyperthyroidism (from overtreatment with levothyroxine). However, as the randomised trials were small (with a total of 187 women randomised), and the follow-up was only to the end of pregnancy, these trials would not have been suitable for assessing rare or long-term adverse events. We therefore carried out a literature search to identify studies of potential harm of levothyroxine treatment in pregnancy by using MeSH terms and keywords to capture adverse events and combined this with search terms to capture levothyroxine and pregnancy studies. This safety review identified 1026 studies, of which 191 were reviews. Most studies evaluated the use of levothyroxine in hypothyroid pregnant women, and found no clear or consistent evidence of serious adverse effects on the mother or the baby, provided there was appropriate monitoring and dose titration (9;10). A comprehensive literature review, which was interpreted and graded by an international panel of endocrinologists, found that the potential risk of treating subclinical hypothyroidism with levothyroxine was limited to the development of subclinical hyperthyroidism (11). Although this review may not directly apply to the *euthyroid* population, the absence of any serious side effects in this review provides reassurance on the safety of levothyroxine, particularly at the proposed dose of 50µg per day.

1.5. The pathophysiological consequences of thyroid antibodies

The exact mechanisms to explain the observed associations between thyroid antibodies and miscarriages or preterm birth are largely unknown. Two mechanisms have been postulated.

It could be suggested that the presence of thyroid antibodies may reflect a generalized activation of the immune system and specifically, a dysregulated activity of the immune system at the fetal-maternal interface. The presence of TPO antibodies in several non-thyroidal autoimmune diseases supports this hypothesis of global immune dysfunction (12). Furthermore, there is evidence that there is an alteration in cytokine expression by peripheral T-lymphocytes in TPO positive individuals outside of pregnancy (13).

Alternatively, the presence of thyroid antibodies in euthyroid women could be associated with a subtle deficiency in thyroid hormone availability (a fall in circulating free thyroid hormones within the reference ranges) or a lower capacity of the thyroid gland to adequately rise to the increased

demand for augmented synthesis of thyroid hormones required in pregnancy. Indeed, the mean serum TSH values, while being within normal range, are significantly higher in thyroid antibody positive women compared with women without thyroid antibodies (TSH in TPO positive: 2.14 mU/L +/-0.84 vs TPO negative 1.33 mU/L +/- 0.32) (14).

1.6. How may levothyroxine alter the pathophysiology?

Higher concentrations of thyroid hormones within the normal reference range can directly enhance innate and adaptive immunity in normal healthy individuals (15). Pregnancy is an inflammatory process involving a shift in the regulation of cytokine networks within the local placental-decidual environment. Dysregulation of local inflammatory processes may be associated with miscarriage and premature delivery (16). The main regulators of inflammation within the decidua are a whole host of cells of 'bone marrow lineage' (17). In particular, uterine natural killer (uNK) cells, which are a major source of angiogenic growth factors and cytokines, have been shown to regulate vascular remodelling (18). Thyroid hormones can potentially influence (i) angiogenic growth factor and cytokine production (19;20) as well as (ii) trophoblast proliferation, survival and invasion (21;22).Thus thyroid hormones may influence the maternal immune regulation in general and at the fetal-maternal interface as well as specifically affect trophoblast and decidual cell behaviour.

1.7. Rationale

The two existing randomised trials (7;8) (Section1.3) show substantial reductions in miscarriages (52% relative risk reduction) and preterm births (69% relative risk reduction). Such reductions need to be confirmed in a large, high quality, randomised, placebo-controlled and multi-centre study. This would represent a major breakthrough in the treatment of two common, serious and costly conditions (miscarriages and preterm births, together costing the NHS £1.2 billion per year). There is a high prevalence of thyroid autoantibodies, and thus a large number of women would be expected to benefit from thyroxine treatment if effectiveness is established. Given that thyroxine treatment is cheap, safe and convenient, and the financial impact of miscarriage substantial, even a small improvement in outcome is likely to cost-effective.

Furthermore, we postulate that exogenous thyroxine treatment may correct any relative deficiency of thyroid hormones, and impact upon both systemic immune regulation and the local placental-decidual environment. A parallel study with longitudinal cytokine profiling assessment of inflammatory responses within the decidua and placental morphology following thyroxine treatment will address this mechanistic hypothesis.

1.8. Aims and Objective

The primary aim of the TABLET Trial is

1. To test the hypothesis that in euthyroid women with TPO antibodies, levothyroxine (50mcg, oral, once daily), started pre-conceptually and continued to the end of pregnancy, compared with placebo, increases the proportion of women who attain a live birth at or beyond 34 completed weeks of gestation by at least 10%.

Additional **secondary aims** are:

2. To test the hypothesis that levothyroxine improves secondary outcomes such as on-going pregnancy at 12 weeks, gestation at delivery and survival at 28 days of neonatal life.

3. To explore subgroup effects of levothyroxine in prognostic subgroups (including maternal age, number of previous miscarriages, initial serum TSH concentration and women who are having infertility treatment).

4. To test the hypothesis that levothyroxine, compared with placebo, does not incur substantial adverse effects to the mother or the neonate.

The parallel mechanistic study which will be detailed in a separate protocol aims:

5. To evaluate if women with TPO positivity display evidence of altered immune responses and if these are altered by levothyroxine treatment, by a) comparing the circulating levels of specific cytokines implicated in miscarriage and preterm birth, and b) evaluating cytokine and angiogenic growth factor production by decidual cells at the maternal-placental interface.

6. To study if placentae obtained from women with TPO positivity show morphological differences and whether these are altered by levothyroxine treatment, by performing villous placental stereology (so as to aid elucidation of underlying mechanisms).

This parallel study will be detailed further in a separate protocol and be conducted in a limited number of hospitals. Blood, decidual and placental samples will be collected through the University of Birmingham Biomaterials Resource Centre.

1.9. Support for the TABLET Trial

The TABLET trial is supported by a patient survey: 78 women from Early Pregnancy Assessment Unit (EPAU) at Birmingham Women's Hospital were consulted about various aspects of the trial, including the need for the trial, acceptability of blood tests, duration of treatment and choice of outcomes. There was unanimous support for the study.

A clinician survey supports the study: We conducted a clinician survey in the UK (n=183), and found that 8% (15/183) of clinicians use or intend to use levothyroxine for the prevention of miscarriages in thyroid antibody positive women; 85% (155/183) reported that they were willing to recruit into a The study is supported by the following bodies, including the RCOG Early Pregnancy – Clinical Studies Group, the Miscarriage Association, the British Thyroid Association, British Thyroid Foundation, the Association of Early Pregnancy Units and the RCOG – Consumer Forum and Infertility Network UK.

2. TRIAL DESIGN

2.1. Design

A randomised, double-blind, placebo-controlled multicentre study of levothyroxine in euthyroid women with TPO antibodies to determine if levothyroxine can reduce miscarriage and premature births in women.

3. ELIGIBILITY

The TABLET Trial will recruit women who have miscarried, or who are having infertility treatment in a two-step process. First, women will be invited to be screened for TPO antibodies and TFTs. Those who are found to be positive for TPO antibodies, with normal thyroid function, will then be introduced to the TABLET randomised controlled trial.

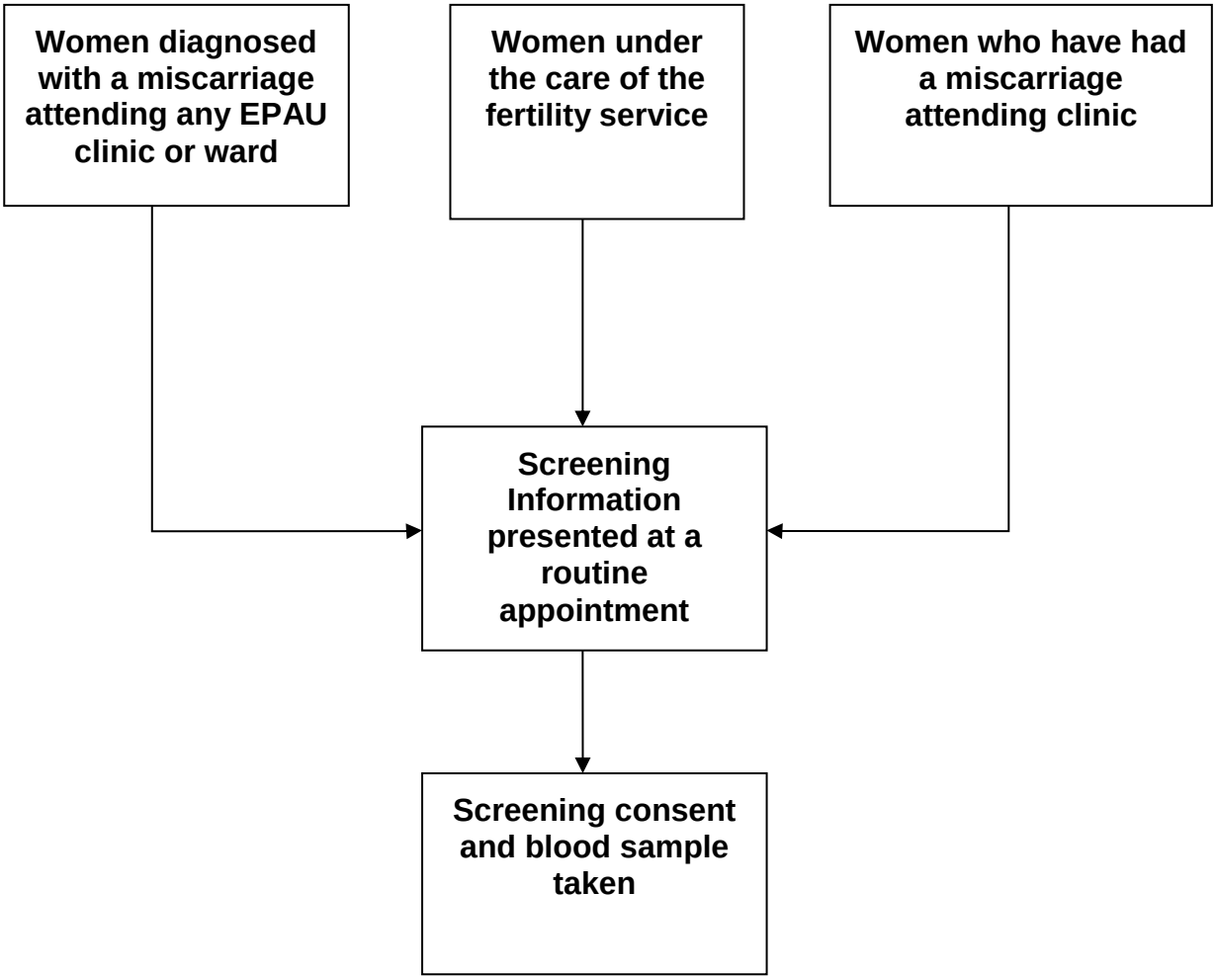
3.1. Source and screening of potential participants

Potential participants will be identified and approached by clinic doctors, nurses, and research nurses in the EPAU's, Miscarriage Clinics, and Infertility Clinics in the participating NHS hospitals. They will be clearly advised that participation in the study is entirely voluntary with the option of withdrawing from the study at any stage, and that participation or non-participation will not affect their usual care. All women will be approached by appropriately trained GCP staff who will have also been specifically trained in taking consent for this trial. Consent will be documented in the medical notes and 3 copies of the consent form will be produced: 1 to the patient, a 2nd copy will be filed in the medical notes and a 3rd copy will be kept in the site file for the trial.

For women who have had a miscarriage, the initial approach will be after the miscarriage has been confirmed. For women who are having fertility treatment the initial approach will be made at a routine clinic appointment. The timing of the approach is described in Figure 4. Potential participants will be provided with a short Screening Patient Information Sheet (Appendix A) and given time to consider their involvement and ample time to ask any questions.

We aim to approach women at the optimum point, before their subsequent conception. For women who have miscarried this will be at the time of diagnosis. For women attending infertility clinics, this would be at a routine appointment. The rationale for the TABLET trial is that TPO positive women may be in a relative hypothyroid state and provision of levothyroxine whilst trying to conceive may be beneficial.

Figure 4. Routes of initial approach for screening



3.2. Eligibility for screening

To be invited for screening, the woman must be willing and able to give informed consent (Appendix B) to provide a small (10 ml) blood sample for thyroid antibody and thyroid function testing and be between 16 and 40 years of age. The likelihood of miscarriages due to chromosomal aberrations is higher in older women; such miscarriages are unlikely to be prevented by thyroxine therapy.

Women taking amiodarone or lithium, which can significantly affect thyroid function, are ineligible for the TABLET study. Women who have any previous or current heart disease will also be ineligible. These women will not be offered screening.

Women with a current diagnosis of any thyroid disorder requiring treatment will not be approached for screening. Women who have previously been treated for thyroid disorders should be considered on a case-by-case basis. It should be the discretion of the principal investigator and/or the chief investigator whether a woman with a history of thyroid disorder can be safely offered participation in the trial. The rationale for exercising this discretion is that women who may have received very short term treatment a significant time ago and whom have since had normal thyroid function and not required treatment long term should not be automatically discounted from participation in the study, as clinically it is not unsafe for these woman to participate if TPO positive. Women with a family history of thyroid disease or another autoimmune disease are also eligible for screening. Eligible women will be determined by the medical staff at each unit and specific training will be performed to ensure the medical staff are fully aware of eligibility criteria.

Women eligible and giving informed consent for screening will have blood samples taken for testing of TPO antibodies and measurement of serum TSH and free T4. Consent will be recorded on the screening consent form, which must be retained in the site file.

3.2.1 Thresholds for thyroid function tests

Various assays for TPO antibodies are available, each with different detection limits and thresholds for test positivity, which are pre-determined by the assay manufacturer. These variations are an accepted part of normal practice in the UK. Quality assurance for assays in the laboratories for all the participating centres is provided by UK IMMQAS, which shows over 99% concordance in the classification of samples as either positive or negative for TPO antibodies across all assays. Therefore the TABLET protocol will not define a threshold for TPO positivity but accept the classification provided by the laboratories servicing the participating centres.

For TFT and Free T4 testing, use of an analyser which has been approved by the TMG.

To be eligible, a TPO woman who has miscarried or who will be having fertility treatment.

1. TSH level at or above a lower limit of 0.44mU/L and at or below an upper limit of 3.63mU/L using the appropriate analyser.

This is the normal range for women of the reproductive age for the Roche assay based on studies performed by the manufacturer (23).

2. Free T4 at or above a lower limit of 10.0 and at or below an upper limit of 21.0 pmol/L.

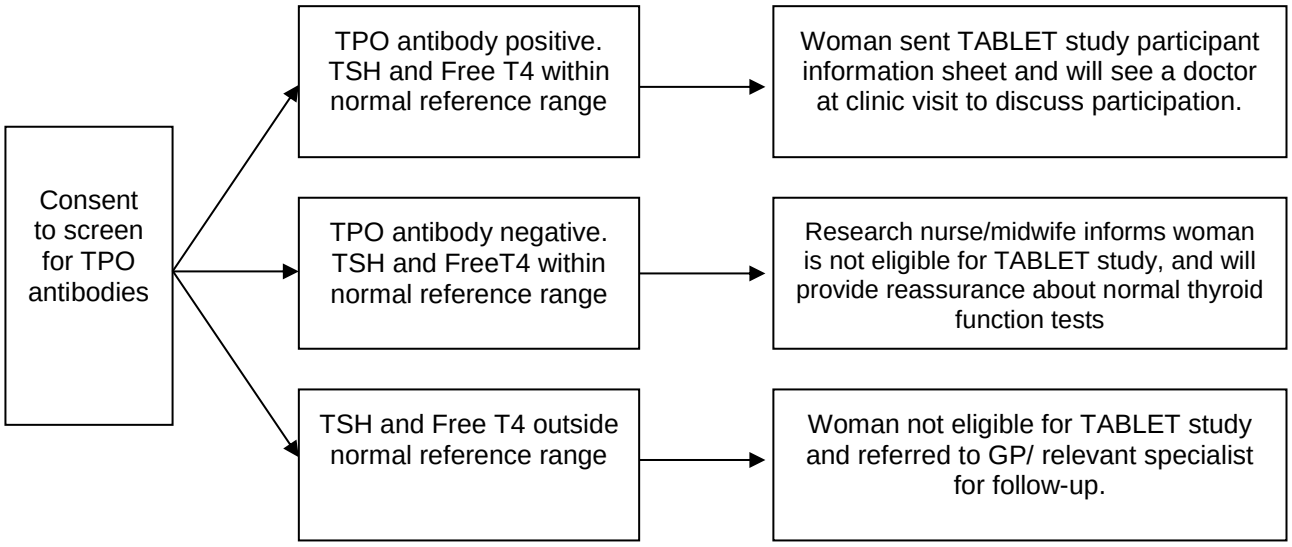
3.3. Eligibility for the TABLET Randomised Trial

Figure 5 shows the potential outcomes from the thyroid function test screening of potential participants. The results are anticipated to be available within 7 days of taking the blood sample. The coordinating midwife/nurse at each centre will be responsible for contacting TPO negative women to inform them that they are ineligible for the TABLET trial, and provide reassurance about normal thyroid function tests. There will be a small number of asymptomatic women who have abnormal thyroid function tests regardless of the TPO antibody status, identified fortuitously by the

screening test. These women will be referred to a maternal medicine specialist for management of the thyroid dysfunction.

If TPO antibodies are positive, TSH and free T4 concentrations are within the normal range for the trial, the woman will be sent a TABLET study participant information sheet (Appendix C) along with an appointment to discuss participation at a subsequent clinic visit.

Figure 5 Screening of potential participants for the TABLET study



For women with TPO antibodies and normal TSH and free T4 levels, the subsequent clinic visit will provide an opportunity to discuss the TABLET trial and final eligibility checks to be performed (summarised in Section 3.4). For women who have had a miscarriage the woman's desire to conceive again should be explored and only those who indicate they intend to try should be invited to participate. It should be made clear that she can change her mind at any time. Consent must be confirmed in writing and countersigned by the investigator at that time. (Appendix D)

3.4. Summary of eligibility for the TABLET Study

3.4.1 Inclusion Criteria:

1. Women trying to conceive
2. History of one or more miscarriage(s) or Primary or Secondary infertility
3. Age 16 - 40 years at randomisation.
4. Biochemically euthyroid ([TSH 0.44 - 3.63 mU/L; Free T4 10.0 – 21.0 pmol/L using the appropriate analyser.)
5. TPO Antibody positive according to local laboratory reference ranges.
6. Willing and able to give informed consent

3.4.2 Exclusion Criteria:

1. Current treatment for any thyroid disorder; past treatment will be considered on an individual case basis (see 3.2 for rationale)
2. Taking amiodarone or lithium therapy.
3. Contraindications to thyroxine therapy:

- thyrotoxicosis
- hypersensitivity to thyroxine, or any of its excipients

.

4. Participation in any other blinded, placebo-controlled trials of investigational medicinal products in pregnancy.
5. Previous or current diagnosis of cardiac disease

3.5. Ineligible patients

If a woman is screened but is not eligible for the TABLET trial or consent for randomisation is not given, a record of the case will be kept in the screening log (Appendix E). The log will collect hospital number, mother initials, date of birth, age, ethnic group, BMI, thyroid function test results, TPO status and reason not eligible for the trial. The log should be kept in the centre's site file and a copy (in an anonymised format – removing initials and hospital number) sent to BCTU. This will inform recruitment targets. The data collected on the screening log will also be used for assessment of thyroid function in the overall population being studied and all patients who have consented for screening will be made aware that their screening data will form part of the trial dataset. No further information will be collected on ineligible patients or those that have not given consent for randomisation.

4. RANDOMISATION

4.1. Randomisation

Immediately after consent has been obtained, all eligibility criteria have been confirmed and all baseline prognostic factors gathered, the woman should be randomised into the trial. Patients are committed and randomised into the trial by a secure online randomisation which is available at https://www.trials.bham.ac.uk/TABLET. Each centre and each randomiser will be provided with a unique log-in username and password to do this. Online randomisation is available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance. As a back-up, the randomiser can make one telephone call to the toll-free randomisation service 0800 953 0274. Telephone randomisations are available Monday-Friday, 09:00-17:00.

Randomisation notepads (Appendix F) will be provided to investigators and may be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation notepad will need to be answered and entered onto the e-crf before a trial number and bottle number can be given. If some data items are missing, randomisation will be suspended but can be resumed once the information is available. Only when all eligibility criteria and baseline data items have been entered onto the e-crf, will the trial and bottle numbers be given and a confirmatory email sent to the randomising investigator, the local PI and the research midwife. The trial number will be linked to a drug bottle number available in the hospital pharmacy, who will also receive notification of the randomisation by email.

4.2. Randomisation method and stratification variables

Participants will be randomised individually **into** the TABLET Trial in an equal ratio of levothyroxine to placebo. A 'minimisation' procedure using a computer-based algorithm will be used to avoid chance imbalances in important stratification variables. Strata used in the minimisation will be:

- maternal age (<35, >/=35)
- number of previous miscarriages (0, 1-2, ≥3)
- initial TSH concentration (</=2.5mU/L, >2.5mU/L)
- Women who are having infertility treatment (yes/no)

For logistical reasons the randomisation will be minimised by centre.

4.2.1 Informing the participant's GP

The patient's GP will be notified, with the patient's consent, and a specimen "Letter to GP" is supplied (Appendix G).

5. TREATMENT ALLOCATIONS

5.1. Trial treatment

5.1.1 Trial interventions levothyroxine and placebo

The investigational medicinal product (IMP) is levothyroxine, as 50µg levothyroxine sodium as an encapsulated tablet. The up-to-date Summary of Product Characteristics for levothyroxine can be found in appendix I.

The placebo will be a placebo tablet, encapsulated in the same format as the IMP to be identical in colour, shape and weight.

5.1.2 Dose and route of administration

Levothyroxine oral tablets 50µg or placebo once daily will be initiated after randomisation and pre-conceptually, and continued to the end of any pregnancy or until 12 months post-randomisation if pregnancy does not occur.

The choice 50µg/day was made after a careful review of the existing literature (7;8), an extensive survey of endocrinologists as well as obstetricians with an interest in maternal medicine, a review of the host organisation's obstetric-endocrine practice database and a review of other related evidence.

5.1.3 Packaging, Formulation, Storage and Supply of Levothyroxine and Placebo

The trial drug will be supplied by Sharp Clinical Services (formerly Bilcare (UK) Ltd.) Sharp Clinical Services will procure the trial drug and manufacture the placebo tablet, inspecting the certification of the IMP (levothyroxine 50mcg tablets, marketing authorisation no. P10972/0031 supplied by the manufacturer Mercury Pharma Group and retains one original blister pack per batch as reference. Sharp Clinical Services will overencapsulate the IMP and placebo and dispense into containers accordingly.

At study initiation, BCTU will arrange an initial supply of levothyroxine and placebo to be automatically shipped by Sharp Clinical Services (formerly Bilcare (UK) Ltd) and to be stored in the local pharmacy. The pharmacist will check the amount and condition of the drug and will confirm these details in a Condition of IMP receipt form.

All details of trial drug supply, labeling, storage and preparation are as per the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004 and are detailed in the TABLET Pharmacy Manual. This manual is supplied to pharmacy at the time of site approval.

Sharp Clinical Services will provide the QP batch release service under the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004.

5.1.4 Dispensing and accountability

At randomisation, the first bottle number is provided and this will correspond to a trial treatment bottle available in the hospital pharmacy. The pharmacist will receive notification of the name and trial number of the randomised woman and will prepare the trial treatment bottle for dispensing. The trial treatment bottle will contain 13 weeks' supply of 91 capsules for use by one participant.

A single capsule must be taken orally once daily before breakfast and ingested with water (milk, iron supplements, calcium supplements and antacids can impair the absorption of levothyroxine and should not be taken at the same time.) The first dose should be taken the morning following randomisation and subsequently every morning before breakfast. Treatment should continue daily for 12 months, or once pregnant, until the pregnancy is ended. A sheet giving instructions on how to take the capsules, and what to do if a capsule is missed, will be given to the participant at the randomisation appointment.

The pharmacist should keep accurate records of trial drugs dispensed using a pharmacy log provided by the TABLET Trial Office. Trial drugs must be kept in the packaging supplied and under no circumstances used for other participants or non-participants.

5.2. Further supply of Trial Drug to Participants

Trial participants will return to the randomising hospital at two further intervals whilst trying to conceive and for routine ante-natal appointments. At each visit, a blood sample will be taken for TSH monitoring

The clinician or research midwife will record the taking of the blood sample and any adverse events on the TABLET trial database, which will then allocate another bottle number from the available stock at the centre's pharmacy. An allocation of capsules will be also be made at 9 months following randomisation. The pharmacist will receive notification of the participant's name and trial number and will prepare another trial treatment bottle for dispensing. Each subsequent trial treatment bottle will contain a further 13 weeks' supply of 91 capsules.

5.2.1 Treatment Duration

It is assumed that for the majority of participants, pregnancy will occur within 1 year of randomisation and that the pregnancy is continued to term at 42 weeks. Thus the treatment period will range from 42-44 weeks to 94 weeks for term pregnancies. If miscarriages and premature deliveries occur, treatment duration will be shorter. In those women who do not get pregnant within 12 months of randomisation, trial treatment will cease at 12 months. Treatment will also cease after a pregnancy loss, e.g. miscarriage, termination or biochemical pregnancy or still birth. If conception has not taken place by the end of the 12th month, the woman will be asked to perform a pregnancy test and ensure it is negative prior to stopping trial medication.

5.2.2 Resupply of Trial Drug to Centres

The computer program underpinning the randomisation process will automatically notify Sharp Clinical Services when centre supply is low to enable Sharp Clinical Services to issue another batch of trial drugs to the centre's pharmacy. However, if the site notices that supplies are getting low and additional drug supplies are needed, the site should contact the TABLET Trials Office who will be able to initiate an additional supply.

5.3. Compliance monitoring

The dispensing of the trial drug will be recorded on the pharmacy drug accountability log. The Trial Coordinator will periodically monitor the trial drug chart to verify that the dispensing system is being followed and note any deviations from the 3-monthly schedule, and will notify the local PI of any problems or deviations.

We will evaluate compliance by two methods, "pill-counting" and direct questioning. Women will be asked to bring completed, partially used and unused treatment bottles to the trial centres at follow up visits. The research nurse will receive the empty/partially used/unused treatment bottles at the local centres, and will document this in the database for each trial participant. In an effort to improve compliance, women who fail to return the treatment bottles, whether empty or not, will be contacted by telephone or email by the research nurse for advice and support. Furthermore there will be a routine question at each follow up and after completion asking' number of capsules remaining in current bottle' and 'Since their last appointment how often does the participant feel they took their pill equating to a range of percentages (Never (0%), Hardly any (1-24%), Some (25-49%), Most (50-74%), almost always (75-99%) and every day (100%). Participants will be encouraged to be honest with their answers. Non-compliance is defined as less than 75% usage of trial medicines.

5.4. Excluded medications or interactions

There are drugs which can independently affect thyroid function and women taking these drugs at the time of selection for screening should not have been recruited into the trial. The use of Amiodarone and Lithium are relatively contraindicated in pregnancy so it will only be used rarely in women where no other treatment option is available for their condition. If women are not aware of

this, they should be receiving pre-pregnancy counselling by relevant healthcare professionals before embarking on a pregnancy.

Women should be advised to withdraw from taking the TABLET study treatment if the following drugs are indicated:

1. Amiodarone
2. Lithium

Patients will be advised to inform their GP or any other clinician caring for them that they are participating in the TABLET trial, and may be taking levothyroxine. Participants will be given a small information card to carry with them (Appendix G), with TABLET trial contact information, to direct clinicians to information regarding potential drug interactions. Concurrent drug use other than Amiodarone or Lithium does not necessitate withdrawal from TABLET trial treatment.

Withdrawal from trial treatment does not necessitate withdrawal from the TABLET study – see Section 5.5

5.5. Withdrawal of treatment or protocol violation

A participant can be withdrawn from the trial treatment if, in the opinion of the investigator or the care providing clinician or clinical team, it is medically necessary to do so. With premature cessation of trial treatment, the study personnel will make every effort to obtain, and record, information about the reasons for discontinuation, any adverse events and to follow-up the women for all safety and efficacy outcomes, as appropriate. The details of withdrawal (date, reason and type withdrawal) should be clearly documented in the source data.

A participant may voluntarily withdraw participation in this study at any time. If a participant does not return for a scheduled visit, attempts will be made to contact her and where possible, review compliance and adverse events. If a woman decides, after randomisation, she does not wish to conceive or her circumstances have changed, she may withdraw herself from the trial. Oral contraceptives may alter the pharmacodynamics of thyroxine, so women should be advised to stop trial treatment in these circumstances. We will aim to document the reason for self-withdrawal.

Clear distinction will be made as to whether the patient is withdrawing from trial treatments whilst allowing further follow-up, or whether the patient refuses any follow-up. If a patient explicitly withdraws consent to have any further data recorded their decision will be respected and recorded on the electronic data capture system. All communication surrounding the withdrawal will be noted in the patient's records and no further data will be collected for that patient.

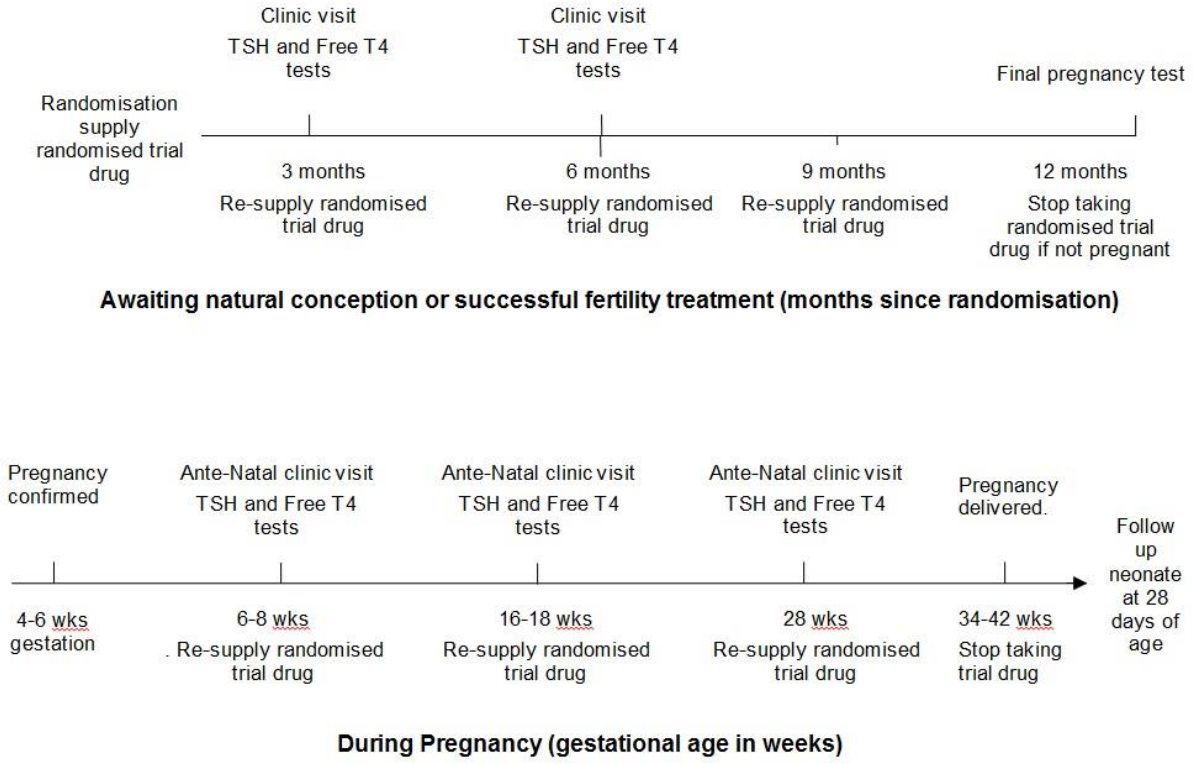
5.5.1 Thyroid hormone monitoring and criteria for stopping trial treatment

Following randomisation, and either pre-pregnancy or during pregnancy, in the event that a woman develops overt or subclinical hypothyroidism with TSH concentrations above the decision limit of for the specified analyser, or overt hyperthyroidism with a free T4 above the decision limit for the specified analyser, she will discontinue trial medication and will be treated, according to standard clinical guidelines. Analyser specific monitoring ranges will be set by the TMG, and a document describing management options to advise clinicians will be provided in the site file.

5.5.2 Drug Supply to Patient

In order to avoid participants having to return to the randomising centre on repeated occasions, the participant will be dispensed the next trial drug bottle at the clinic visit when the blood sample is taken for the thyroid function test, or at 9 months post randomisation, when a test will not be performed (see figure 6). The test results will usually be available within 7 days. The coordinating midwife/nurse will be responsible for recording the TSH and free T4 levels in the trial database, which will alert if discussion with the TMG is required. If withdrawal from trial drug is indicated following discussion between the TMG and the local PI the latter will take over management of the woman and recall her to the clinic, or refer to GP as appropriate. Otherwise the woman should be told to continue taking the trial drug.

Figure 6 Thyroid drug supply and monitoring timelines



5.5.3 Unblinding

Participants, investigators, research midwives/nurses and other attending clinicians will remain blind to the trial drug allocation for the duration of the trial and will not have access to the trial number-treatment allocation code for the duration of the interventional phase of the trial.

Should a serious, adverse event occur, management and care of the women will be initiated as though the woman **was** taking levothyroxine. Cases that are considered serious, unexpected and possibly, probably or definitely related (i.e. possible SUSARs see Section 6) will be unblinded only at the Trial Office by the TABLET Trial Coordinator. The attending clinician and local PI will not be made aware of drug allocation the actual trial drug.

In all other circumstances, investigators and research midwives will remain blind to drug allocation whilst the participant remains in the trial. However, if a participant is withdrawn from the trial due to abnormal thyroid function tests (see Section 5.5.1) and only if the drug allocation is required for the continued medical management of the withdrawn participant, clinicians should contact the TABLET Trial Office or use the online TABLET code-break system. This service will be available 24 hours a day, 7 days a week.

6. SAFETY MONITORING PROCEDURES

The safety of levothyroxine treatment during pregnancy is not known, although a literature review shows no clear or consistent evidence of serious adverse effects on the mother or the baby of levothyroxine in hypothyroid pregnant women (see Section 1.4.1). The unknown risk of foetal abnormalities should be weighed against the risk of miscarriage.

There may yet be unexpected serious adverse reactions associated with levothyroxine when used in pregnant women. Levothyroxine has been used to prevent miscarriages in two previous trials (7;8). The Summary of Product Characteristics (SmPC) lists some rare but serious adverse reactions (see Appendix I).

The Medicines for Human Use (Clinical Trials) Regulations 2004 define categories of adverse events, the responsibilities of the investigators to notify adverse events to the sponsor and for the sponsor to report to the regulatory authority and ethics committee. It is therefore imperative that all investigators have a thorough understanding of anticipated adverse events and the reporting process of these events. The Investigator will assess the seriousness and causality (relatedness) of all AEs experienced by the participant.

6.1. General Definitions

6.1.1 Adverse Events (AEs)

An AE is:

- any unintentional, unfavourable clinical sign or symptom in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. This will include complications of miscarriages.
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests

The following are not AEs:

A pre-existing condition (unless it worsens significantly during treatment).

Diagnostic and therapeutic procedures, such as surgery (although the medical condition for which the procedure was performed must be reported if new).

6.1.2 Adverse Reactions (ARs)

An AR is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

6.1.3 Serious Adverse Events (SAEs)

An SAE is an untoward event which:

- Results in death
- Immediately threatens the life of participant*
- Results in hospitalisation or a longer than anticipated stay in hospital
- Results in a persistent or significant disability or incapacity
- Results in any congenital anomaly or birth defect in any pregnancy

*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 the event. It does not refer to an event which hypothetically might have caused death if it were more severe. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Events NOT considered to be SAEs are hospitalisations for the following events, as these are expected. These events will be recorded on the electronic Case Report Form (e-CRF), patient's medical notes and reported to the DMC as part of the safety review.

- routine treatment or monitoring of miscarriage or threatened preterm birth, not associated with any deterioration in condition including :
    - PROM or suspected PROM
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study, and did not worsen including:
    - Elective Caesarean Section,
- admission to a hospital or other institution for general care, not associated with any deterioration in condition including:
    - Hospitalisation for rest
    - Hospitalisation for observation or monitoring of pregnancy
    - Hospitalisation for Maternal Discomfort

- Hyperemesis which is quickly resolved.

- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

6.1.4 Expected SAEs

Expected SAEs are those listed in section 4.8 of the current SmPC for levothyroxine. The BCTU team will ensure that any SmPC updates are circulated to all investigators.

6.1.5 Suspected unexpected serious adverse reactions (SUSARs)

A SUSAR is an SAE suspected to be related to a product, which is of a **type or severity** which is NOT consistent with the approved version RSI for levothyroxine.

6.2. Reporting AEs

All adverse events, from the first administration of trial treatment until the end of the pregnancy or 12 months of trial participation without pregnancy (whichever is later), whether observed directly or reported by the patient, will be collected and recorded. Non-serious adverse reactions or events are not required to be reported in an expedited manner, but will be recorded on the data collection forms and in the patients' medical notes. Trial participants will be asked about the occurrence of AEs and SAEs at each study visit. AE and SAEs may also be identified via information from support department's e.g. laboratories.

6.3. Reporting SAEs

All SAEs must be recorded on the SAE Form and faxed to the BCTU on 0121 415 9136 within 24 hours of the research staff becoming aware of the event. The local Principal Investigator (or other nominated clinician) has to assign seriousness, severity, causality and expectedness to the SAE before reporting. All SAEs should be assessed for seriousness, causality and expectedness as though participant were prescribed levothyroxine. The assessment for causality will be made against the Reference Safety Information (RSI) in section 4.8 in the appended SmPC.

For each SAE, the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome
- causality, in the opinion of the investigator
- whether the event would be considered expected or unexpected (refer to the most recent and relevant SmPC)

Assessment of causality and expectedness must be made by a doctor. If a doctor is unavailable, initial reports without causality and expectedness assessment should be submitted to the BCTU by a healthcare professional within 24 hours, but must be followed up by medical assessment as soon as possible thereafter, ideally within the following 24 hours. An SAE which is assessed as possibly, probably or definitely related to trial treatment is classified as a Serious Adverse Reaction (SAR)

The local investigator and others responsible for patient care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors and provide further follow-up information as soon as available. If a participant dies, any post-mortem findings must be provided to the BCTU.

SAEs still present at the end of the trial must be followed up at least until the final outcome is determined, even if it implies that the follow-up continues after the patient finishes the trial treatment and or the pregnancy has ended.

The BCTU will report all SAEs to the DMC approximately 6-monthly. The DMC will view data blinded to treatment but will be able to review unblinded data if necessary. BCTU will also report all SAEs to the main REC and MHRA annually, and to the Trial Steering Committee 6-monthly. The main REC, MHRA and TSC will only view data blinded to trial treatment. Local Investigators are

responsible for reporting SAEs to their host institution, according to local regulations, but they do not need to inform MHRA or main REC as this will be done by the BCTU as detailed above.

6.4. Reporting SUSARs

SAEs categorised by the local investigator as **both** suspected to be related to the trial drug **and** unexpected are SUSARs, and are subject to expedited reporting. For the purposes of this trial, irrespective of trial arm (levothyroxine or placebo), all these events will be considered to be SUSARs and will be subject to expedited reporting.

All SUSARs must be recorded on the SAE Form and faxed to the BCTU on 0121 4159136 immediately or within 24 hours of the research staff becoming aware of the event. The Chief Investigator (CI) or nominated individual will undertake urgent review of SUSARs within 24 hours of reporting and may request further information immediately from the patient's clinical team. The CI will not overrule the causality, expectedness or seriousness assessment given by the local investigator. If the CI disagrees with the local investigator's assessment, further clarification and discussion should take place to reach a consensus. If a consensus cannot be reached, both the opinion of the local investigator and the CI should be provided in the report to the Medicines and Healthcare and Regulatory Agency (MHRA) and the MREC.

The BCTU will report all SUSARs to the MHRA and the MREC. These will be blinded to treatment. If the SUSAR resulted in death or was life-threatening this will be done within 7 days of the initial report being received or within 15 days for any other SUSAR.

If information is incomplete at the time of initial reporting, or the event is ongoing, the BCTU will request follow-up information, including information for categorisation of causality, from the local investigator and will send the follow-up information to the MHRA and MREC within an additional 8 days for fatal or life-threatening SUSARs and as soon as possible for any other events.

6.4.1 Notification of deaths

All deaths will be reported to the BCTU on the SAE Form irrespective of whether the death is related to the trial drug, or an unrelated event. If a participant dies, any post-mortem findings must be provided to the BCTU with the SAE form. The BCTU will report all deaths to the DMC for continuous safety review.

6.5. Pharmacovigilance responsibilities

6.5.1 Local Principal Investigator (or nominated individual in PI's absence):

- To record **all** AE/ARs occurring in the subjects taking part in the trial. This includes non-serious, serious, expected or unexpected adverse events or reactions.
- Medical judgement in assigning seriousness, expectedness and causality to AEs.
- To fax SAE forms to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available.
- To report SAEs to local committees if required, in line with local arrangements.
- To sign an Investigator's Agreement accepting these responsibilities.

6.5.2 Chief Investigator (or nominated individual in CI's absence):

- To assign causality and expected nature of SAEs where it has not been possible to obtain local assessment
- To review all events assessed as SAEs in the opinion of the local investigator
- To review all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and CI with regards to SUSAR status, local assessment will not be over-ruled, but the CI may add comments prior to reporting to MHRA.

6.5.3 Birmingham Clinical Trials Unit:

- To report SUSARs, blinded to treatment, to MHRA and MREC within required timelines as detailed above
- To prepare annual safety reports, blinded to treatment, to MHRA, MREC and TSC.

- To prepare SAE safety reports for the DMC at 6-monthly intervals. Data will be presented blinded to treatment, but the DMC will be able to review unblinded data if necessary.
- To report all fatal SAEs to the DMC for continuous safety review
- To notify Investigators of SUSARs which compromise patient safety

6.5.4 Trial Steering Committee (TSC):

- To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies.
- To review data, patient compliance, completion rates, adverse events (during treatment and up to end of follow-up).
- To receive and consider any recommendations from the DMC on protocol modifications.

6.5.5 Data Monitoring and Ethics Committee (DMC):

- To review (initially at approx. 6-monthly intervals) overall safety and morbidity data to identify safety issues which may not be apparent on an individual case basis
- To recommend to the TSC whether the trial should continue unchanged, continue with protocol modifications, or stop.

7. FOLLOW-UP AND OUTCOME MEASURES

7.1. Primary outcome measures

The primary outcome is the proportion of women with a live birth at or beyond 34 completed weeks. This proportion will be calculated with the denominator totalling all women randomised, and the numerator (i.e., treatment successes) totalling women who conceive within one year of randomisation and go on to give live birth at or beyond 34 weeks gestation. Women who fail to conceive within a year, or who become pregnant but either miscarry, give birth before 34 weeks or experience a still birth will thus be included in the denominator but not the numerator.

7.2. Secondary outcome measures

Secondary outcomes are as follows:

- Clinical pregnancy at 7 weeks
- On-going pregnancy at 12 weeks
- Miscarriage <24 weeks
- Stillbirth (inter-uterine death ≥24 weeks)
- Ectopic pregnancy
- Termination (and reasons)
- Live birth<34 weeks
- Time from conception to pregnancy end (any reason)
- Mode of initiation of labour (spontaneous/induced)
- Mode of delivery (vaginal/operative vaginal/caesarean)
- Gestation at delivery, weeks
- Time from conception to live birth
- Gestation at delivery <28 weeks/<34 weeks/<37 weeks
- Birth weight, grams
- Birth weight adjusted for gestational age and sex, centiles
- Birth weight adjusted for gestational age, sex, parity, maternal BMI and ethnicity, centiles
- Small for gestational age and sex (proportion<10th centile)

- Small for gestational age, sex, parity, maternal BMI and ethnicity (birth weight proportion<10th centile)
- Large for gestational age and sex (proportion>=90th centile)
- Large for gestational age, sex, parity, maternal BMI and ethnicity (birth weight proportion>=90th centile)
- APGAR score at 1 minute/5 minutes
- Serum TSH concentration (mu/l; log transformed) at each assessment time
- Serum Free T4 level (pmol/L) at each assessment time
- Subclinical/overt hypothyroidism
- Subclinical/overt hyperthyroidism
- Maternal antenatal complications (Hyperemesis gravidarum/gestational diabetes /pre-eclampsia or eclampsia/obstetric cholestasis/pre-term pre labour rupture of membranes (PPROM)/intrauterine growth restriction (IUGR)/others)
- Intrapartum complications (shoulder dystocia/others)
- Maternal postnatal complications (admission to HDU or ITU/Abnormal thyroid test within four weeks/Referred to psychiatrist or started on antidepressants/others)
- Neonatal complications (Early neonatal death defined as death within 7 days after delivery/late neonatal death defined as death beyond 7 days and before 28 days post-delivery/admission to NNU/SCBU/active resuscitation within first 28 days/surfactant use/mechanical ventilation/intermittent positive pressure ventilation/continuous positive airway pressure/oxygen use/congenital abnormalities/hypoxic ischaemic encephalopathy/retinopathy of prematurity/respiratory distress syndrome/pneumothorax/intraventricular haemorrhage (grade 3 or 4)/necrotizing enterocolitis/early infection/others)
- Reported symptoms that participant is concerned about at each assessment time
- Serious Adverse Events

7.3. Outcomes for future studies

Women will be asked to consent for future evaluation of themselves, the child and the health records of both, and babies will be flagged with the Office of National Statistics (ONS) or equivalent. Although long-term follow up is outside the scope of this trial we plan to conduct further studies on outcomes such as the composite endpoint of death or neurodevelopmental impairment at two years of age, the Bailey III cognitive scale cognitive scale standardised score at two years of chronological age, and disability classified into domains according to professional consensus. Hospital number and NHS numbers for each baby will be recorded to facilitate future follow up studies.

7.4. Follow-up assessments

7.4.1 Format

Relevant trial data will be transcribed directly into the web-based database. Source data will comprise of the research clinic notes, hospital notes, hand-held pregnancy notes and laboratory results.

Women will be encouraged to report pregnancies, miscarriages or other pregnancy losses, deliveries and adverse events occurring between clinic visits or presenting at non-participating hospitals to the research midwife. Self-reports will be verified against clinical notes.

7.4.2 Frequency

Participants will be invited back to a clinic appointment 3 and 6 months after randomisation if they are not pregnant for thyroid function tests and to receive further supplies of trial treatment bottles. If the participant has not conceived after 9 months, the patient will be asked to return for a further 3 months drug supply.

Once pregnant, thyroid function tests will follow the normal ante-natal care visits at 6-8 weeks (booking visit), 16-18 weeks and 28 weeks.

Neonatal survival will be collected by flagging all babies with the NHS Information Centre to receive death certificates. Consent will also be obtained for use of NHS records to trace babies for future long term follow-up studies. These will be conducted under a separate protocol.

Table 1 Outcome assessment details

Outcome assessed	When?	How?	By whom?
Biochemical pregnancy	Approximately 4 weeks of gestation	Urinary pregnancy test	Study participant
Clinical pregnancy	6 – 8 weeks	Ultrasound	Ultrasonographer
Ongoing pregnancy	11 – 13 weeks	Ultrasound	Ultrasonographer
Antenatal outcomes	Anytime in the antenatal period or afterwards	From: ❖ Clinical records ❖ Telephonic or face-to-face interview with the participant	Research nurse or doctor
Final pregnancy outcomes, including: ❖ Miscarriage ❖ Live birth ❖ Gestation at Delivery ❖ Birth weight	At or after the end of pregnancy	From: ❖ Outcome 'post cards' ❖ Clinical records ❖ Telephonic or face-to-face interview with the participant	Research nurse or doctor
Neonatal outcomes	Up to 28 days of neonatal life	From: ❖ Neonatal records ❖ Interview with participants	Research nurse or doctor
Thyroid function tests	❖ At 3 and 6 months in the year awaiting spontaneous pregnancy ❖ Once pregnant, at: o 6-8 weeks o 16-18 weeks o 28 weeks	Venous blood sample	Nurse or phlebotomist

7.5. Data management and validation

7.5.1 Confidentiality of personal data

Personal data and sensitive information required for the TABLET Trial will be collected directly from trial participants and hospital notes. Participants will be informed about the transfer of this information to the TABLET trial office at the BCTU and asked for their consent. The data will be entered onto a secure computer database, directly via the internet using secure socket layer encryption technology or indirectly from paper Serious Adverse Event Report forms by BCTU staff.

All personal information received in paper format for the trial will be held securely and treated as strictly confidential according to BCTU policies. All staff involved in the TABLET Trial (clinical, academic, BCTU) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be stored on a secure server at BCTU under the provisions of the Data Protection Act and/or applicable laws and regulations.

7.6. Withdrawal from treatment follow-up

Withdrawal from follow-up is the decision of the participant (see Section 5.5). However, withdrawn patients can bias clinical trial results and reduce the power of the trial to detect important differences, so women should be encouraged to allow data collection to continue even if trial treatment ceases. If a participant wishes to withdraw from treatment and/or follow-up, there will be a checklist to guide investigators as to what to do with data, drug treatment packs and samples. To reduce loss to follow-up, we shall record mother's NHS number, which will allow us to trace participants via their GP practice.

7.7. Long-term follow-up

The developmental function of the infants born to participants in the TABLET Trial is of interest but outside the scope and time-frame for the trial as it currently stands. Should further funding become available, a new observational protocol will be developed, approval gained and participants traced through the randomising centre and the mother's and baby's NHS numbers.

7.8. Definition of the End of Trial

The interventional phase of the trial will end when the last participant has delivered her baby, suffered a pregnancy loss, or has completed 12 months of treatment without becoming pregnant. The observational phase of the trial will cease when the 28 day follow-up has been completed for the baby of the last participant recruited who became pregnant

8. ACCRUAL AND ANALYSIS

8.1. Sample size

We plan to randomise 900 women (450 in each arm). To detect a minimally important difference of 10% in live birth at or beyond 34 weeks (from 55% to 65%), at p=0.05 and power of 80%, 380 women will need to be randomised to the levothyroxine arm, and 380 women to the placebo arm (760 in total). However, assuming and adjusting for a worst case scenario of 15% attrition in terms of study withdrawal and lost to follow-up, the total number of participants required will be 900.

The minimally important difference of 10% was defined following consultations amongst health care practitioners, patients and representatives of patient bodies for the PROMISE Trial of progesterone for prevention of miscarriage (ISRCTN92644181). However, it should be noted this difference is smaller than what could be expected from the existing literature, which has shown that the risk of miscarriage alone is halved with levothyroxine therapy (RR 0.48, 95% CI: 0.25, 0.92). Hence, assuming an expected absolute difference of 15% in live births at or beyond 34 weeks, 900 participants (after accounting for 15% attrition) will provide a power of 99%.

The 55% baseline live birth rate in the control group is based on the assumption that 10% of women will fail to conceive within a year(24), and a further 35% will either miscarry or have a preterm birth.

8.2. Projected accrual and attrition rates

If the prevalence of TPO antibodies averages 20%, 4500 women will need to be approached for consent for screening. This equates to each centres *screening* an average of 17 women per month over the 18 month recruitment period.

8.3. Statistical Analysis

Participants will be analysed in the treatment group to which they were randomised in the first instance, irrespective of compliance with the treatment protocol. Every attempt will be made to gather data on all women randomised. Estimates of differences between groups will be presented with 95%, two-sided, confidence intervals. P-values from two-sided tests at the 5% significance level will be generated. A comprehensive Statistical Analysis Plan will be drawn up prior to any analysis and provided to the independent Data Monitoring and Trial Steering Committees for review.

8.3.1 Interim Analyses

Interim analyses will be conducted on behalf of an independent Data Monitoring Committee (DMC – see Section 6.5.5). These will be considered together with a report of the Serious Adverse Events. The DMC will meet before recruitment commences, and thereafter at least at annual intervals. Effectiveness and futility criteria will be defined by the DMC. The DAMOCLES charter will be adopted for the DMC and will include a specific remit for reviewing emerging data from other trials.

8.3.2 Primary endpoint analyses

A log-binomial model will be used to generate relative risks along with 95% confidence intervals, adjusting for the minimisation parameters. Statistical significance of the treatment group parameter will be determined (p-value generated) through examination of the associated chi-squared statistic. To determine gestational age at birth in this analysis we will in the first instance use measurement of crown rump length (CRL) determined at the participants dating scan (via ultrasound at approximately 9-14 weeks or 6-8 weeks if not available). If CRL measurements are not available for any reason then we will revert to date of last menstrual period (LMP) as estimated by the participant.

8.3.3 Secondary endpoint analysis

Analysis will be performed as per the primary outcome for the other binary outcomes. For maternal pregnancy outcomes (such as miscarriage and stillbirth) the analysis population will be women who went on to achieve confirmed pregnancy. For secondary maternal and neonatal outcomes the analysis population will be in live births ≥24 weeks. For neonatal outcomes and complication rates, twin babies – in the first instance – will both be counted in the analysis population. The effect of this will be explored through sensitivity analysis. In the event of twin babies having different pregnancy outcomes, for example one live birth and one miscarriage, both the events will be counted in the separate categories, i.e. they will contribute to both a live birth event and a miscarriage event.

For time from conception to pregnancy end (any reason) and time from conception to birth a Cox Proportional Hazard model will be employed adjusting for the minimisation variables (see section 9.11); a chi-squared test will be used to test the statistical significance of the treatment group parameter. For continuous outcomes (e.g. birth weight or birthweight centiles), a linear regression model will be used to generate difference between group means and confidence intervals, adjusting for the minimisation parameters. The same method will be applied to TSH (following a log transformation) and Free T4 values, in this instance also adjusting for baseline score. An F-test will be used to test the statistical significance of the estimated treatment group parameter generated from the restricted maximum likelihood estimates.

8.3.4 Handling missing data

Every attempt will be made to collect full follow up data on all women; in particular participants will continue to be followed up even after protocol treatment violation. It is thus anticipated that missing data will be minimal. Patients with missing primary outcome data will not be included in the primary analysis. This presents a risk of bias, and secondary sensitivity analyses will be undertaken to assess the possible impact of this; this will include the assumption that all patients lost to follow up were treatment failures.

8.3.5 Sub-group analysis

The planed subgroup analyses (limited to the primary outcome measure and miscarriage rate) are as follows: a) maternal age: (<35, >/=35); b) number of previous miscarriages (0, 1-2, ≥3); c) initial TSH concentration (</=2.5mU/L, >2.5mU/L); d) women undergoing infertility treatment (yes, no); e) ethnicity (Black, White, Chinese, South Asian, other); f) TPO baseline level ('very high' taken as >=50th percentile, and 'high' taken as <50th percentile); and g) BMI (<25 kg/m^2, >=25 kg/m^2). The effects of these subgroups will be examined by adding the subgroup by treatment group interaction parameters to the log-binomial model. Results of sub-group analyses will be treated with caution, and used for the purposes of hypothesis generation only.

9. DATA ACCESS AND QUALITY ASSURANCE

9.1. Confidentiality of personal data

Personal data and sensitive information required for the TABLET Trial will be collected directly from trial participants and hospital notes. Participants will be informed about the transfer of this information to the TABLET trial office at the BCTU and asked for their consent. The data will be entered onto a secure computer database, either directly via the internet using secure socket layer encryption technology or indirectly from paper by BCTU staff.

All personal information received in paper format for the trial will be held securely and treated as strictly confidential according to BCTU policies. All staff involved in the TABLET Trial (clinical, academic, BCTU) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be stored on a secure server at BCTU under the provisions of the Data Protection Act and/or applicable laws and regulations.

9.2. In-house Data Quality Assurance

The trial will adopt a centralised approach to monitoring data quality and compliance. The database will be interrogated on a regular basis for missing and inconsistent data.

9.2.1 Monitoring and Audit

Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place, providing direct access to source data and documents as requested. Trusts may also be subject to inspection by the MHRA and/ or by the Research and Development Manager of their own Trust and should do everything requested by the CI in order to prepare and contribute to any inspection or audit. Trial participants will be made aware of the possibility of external audit of data they provide in the participant information sheet.

9.2.2 Trial drug quality assurance

To verify the integrity of the randomisation list and labelling process, a sample of capsules will be destruction tested from each batch of treatment bottles produced.

9.2.3 Statistical monitoring throughout the trial

The trial will also adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the trial data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry will be periodically

undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables.

9.3. Independent Trial Steering Committee

The TSC provides independent supervision for the trial, providing advice to the Chief and Co-Investigators and the Sponsor on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Trial Office to the chairman of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

9.4. Data Monitoring and Ethics Committee: determining when clear answers have emerged

The DMC will adopt the DAMOCLES charter to define its terms of reference and operation in relation to oversight of the TABLET trial. If levothyroxine really is substantially better or worse than placebo with respect to reduction of risk of miscarriage and/ or preterm birth, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that levothyroxine is definitely more, or less, effective than placebo. To protect against this, during the period of recruitment to the study, interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMC) along with updates on results of other related studies, and any other analyses that the DMC may request.

The DMC will advise the chair of the Trial Steering Committee if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt” that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the primary outcome, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference equating to at least $p<0.001$ in an interim analysis of the primary outcome may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

9.5. Long-term storage of data

After the end of the trial, the site files from each centre will be archived at the site.

In line with the Medicines for Human Use (Clinical Trials) Regulations, once data collection is complete on all participants, all data will be stored for at least 5 years (but ideally not less than 25 years). This will allow adequate time for review and reappraisal, and in particular with the TABLET trial, form the basis for further follow-up research. Any queries or concerns about the data, conduct or conclusions of the trial can also be resolved in this time. Limited data on the participants and records of any adverse events may be kept for longer if recommended by an independent advisory board.

Trial data will be stored within the BCTU under controlled conditions for at least 3 years after closure. Long-term offsite data archiving facilities will be considered for storage after this time. The BCTU has standard processes for both hard copy and computer database legacy archiving.

9.5.1 Data Sharing

Anonymous data will be made available to other researchers, for example for individual patient data meta-analysis, if the aim is to answer further resolved questions in a scientifically rigorous study design.

10. ORGANISATION AND RESPONSIBILITIES

To ensure the smooth running of the trial and to minimise the overall procedural workload, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the trial.

All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, adverse drug reactions and other events or suspected misconduct through the appropriate systems.

10.1. Centre eligibility

Participating centres will be NHS hospitals, with at least one of the following:

- a dedicated EPAU where suspected miscarriages are managed
- another miscarriage clinic
- an infertility clinic

The centre must use, or have access to for the purpose of the trial, an appropriate analyser that has been recommended by the TMG. The centre must also be able to provide appointments in a dedicated clinic in which to see participants, and have pharmacy on site to dispense medication to participants.

10.2. Local Co-ordinator at each centre

Each Centre will have a local Principal Investigator who will be responsible for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. Close collaboration between all clinical teams is particularly important in TABLET in order that patients for whom TABLET is an option can be identified sufficiently early for entry. The responsibilities of the local Principal Investigator will be to ensure that all medical, nursing and midwifery staff involved in the care of miscarriages and infertility services are well informed about the study and trained in trial procedures, including obtaining informed consent and conduct of the trial according to good clinical practice. The local Principal Investigator will liaise with the Trial Coordinator on logistic and administrative matters connected with the trial.

10.3. Nursing or Midwifery Co-ordinator at each centre

Each participating centre should also designate one nurse or midwife as local Nursing/Midwifery Coordinator. This person would be responsible for ensuring that all eligible patients are considered for the study, that patients are provided with study information sheets, and have an opportunity to discuss the study if required. The nurse may be responsible for collecting the baseline and randomisation data and for coordinating the follow-up evaluations. Again, this person would be sent updates and newsletters, and would be invited to training and progress meetings.

10.4. The TABLET Trial Office

The Trial Office at the University of Birmingham, BCTU is responsible for providing all trial materials, including the trial folders containing printed materials and the promotional materials. These will be supplied to each collaborating centre, after relevant ethics committee approval has been obtained. Additional supplies of any printed material can be obtained on request. The Trial Office also provides the central randomisation service and is responsible for collection and checking of data (including reports of serious adverse events thought to be due to trial treatment), for reporting of serious and unexpected adverse events to the sponsor and/ or regulatory

authorities and for analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

10.5. Research Governance

The conduct of the trial will be according to the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the principles of the International Committee on Harmonisation Good Clinical Practice Guidelines.

All centres will be required to sign an Investigator's Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the TSC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.

The Trial Office will ensure researchers not employed by an NHS organisation that will be in position to impact on the care of patients, or require access to patient notes, hold an NHS research passport or letter of access as appropriate.

10.6. Regulatory and Ethical Approval

10.6.1 Ethical and Trust Management Approval

The Trial has a favourable ethical opinion from South West 3 Multi-centre Research Ethics Committee (MREC) approval, determining that the trial design respects the rights, safety and wellbeing of the participants.

The Local Comprehensive Research Network will conduct governance checks and assess the facilities and resources needed to run the trial, in order to give host site permission. The Trial Office is able to help the local Principal Investigator in the process of the Trust research governance approval by completing much of Site Specific Information section of the standard IRAS form as possible. The local Principal Investigator will be responsible for liaison with the Trust management with respect to locality issues and obtaining the necessary signatures at their Trust.

As soon as Trust approval has been obtained, the Trial Office will send a folder containing all trial materials to the local Principal Investigator. Potential trial participants can then start to be approached

10.6.2 Clinical Trial Authorisation

The Trial Office has obtained Clinical Trials Authorisation from the Medicines and Healthcare Regulatory Authority and has obtained a unique EudraCT number for the trial.

10.7. Funding and Cost implications

The research costs of the trial are funded by a grant from the NIHR Efficacy and Mechanistic Evaluation programme awarded to the University of Birmingham.

The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs service support costs associated with the trial, e.g. gaining consent, pre-pregnancy clinic visits etc., are estimated in the Site Specific Information section of the standard IRAS form. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

10.8. Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. The study is not an industry-sponsored trial and so ABPI/ABHI guidelines on indemnity do not apply. The normal NHS indemnity liability arrangements for research detailed in HSG96(48) will operate in this case.

However, it should be stressed that in terms of negligent liability, NHS Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical trial. Apart from defective products, legal liability does not arise where there is non-negligent harm. NHS Trusts may not offer advance indemnities or take out commercial insurance for non-negligent harm.

10.9. Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Centres may be permitted to publish data obtained from participants in the TABLET Trial that use trial outcome measures but do not relate to the trial randomised evaluation and hypothesis, provided they inform the TMG of their intentions.

10.10. Ancillary studies

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some patients (e.g. special investigations in selected hospitals) be referred to the TMG for consideration. In general, it would be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.

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APPENDIX A: SCREENING INFORMATION SHEET

Thyroid **A**nti**B**odies and **LE**vo**T**hyroxine Study

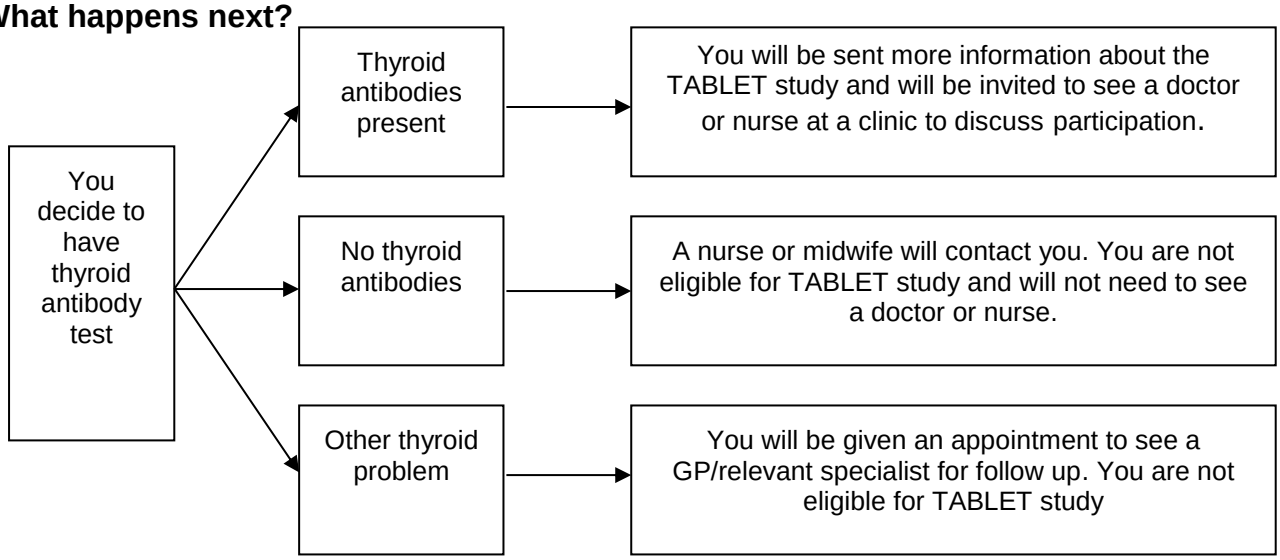
Patient Screening Information

Summary of testing stage

- There is evidence that thyroid antibodies can influence important clinical outcomes such as the chance of completing a successful pregnancy.
- We would like to invite you to have a blood test to find out if you have thyroid antibodies. The blood test will also measure your thyroid hormone levels.
- It is believed that taking *thyroid hormone tablets* may counteract the influence of thyroid antibodies.
- If the results of the blood tests show you *do* have thyroid antibodies, you will be invited to take part in a study of a thyroid hormone supplement – levothyroxine - that might reduce the risk of miscarriage. The study is called TABLET.
- The results of the blood tests may show you have unusual thyroid hormone levels, but this is rare. If this is the case, you will be given an appointment to see a doctor to discuss treatment. You will not be eligible for the TABLET study.
- You will not be asked to decide whether you want take part in the study until the test results are available. We expect less than 1 in 5 women to have thyroid antibodies.
- Your anonymised test results and other basic information e.g. age may be used by researchers to look at thyroid hormone levels in pregnant women in general. This information will be anonymised and you will not be identified to the researchers
- Please take as much time as you feel you need to make the decision whether or not to have this test.
- Taking the blood sample may be a little painful and may result in short-lived bruising.

If you think you might be interested in the study, you will need to have the thyroid antibody test. If you decide not to have the test, you may be able to have it at a later date. Your care will not be affected by your decision.

What happens next?



For further information about the blood test or the study please contact:

Name:- Tel:-

APPENDIX B: SCREENING CONSENT FORM

TO BE INSERTED ON LOCAL HOSPITAL PAPER

Thyroid **A**nti**B**odies and **LE**vo**T**hyroxine Study

Please initial boxes

Blood Screening Consent Form

I confirm that I have read and understand the participant screening information sheet dated 15/02/2015 version 5.0 for the above study. I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily.	
I agree to provide a blood sample for thyroid antibody and thyroid function testing.	
I understand that the thyroid test results and data collected at screening will be anonymised, and looked at by researchers at The University of Birmingham, and I give my permission for these individuals to have access to my anonymised information.	
I understand that sections of any of my medical notes may be looked at by responsible individuals *from the research team, regulatory authorities or from the NHS Trust* where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
I understand that my participation is voluntary and that I am not obliged to take part in the subsequent trial, and that my medical care or legal rights will not be affected.	

.....	_____	_____
Name of Patient	Date	Signature
.....	_____	_____
Name of Researcher	Date	Signature

Copies of Consent Forms: 1 copy for patient, 1 copy for site file, 1 copy to be kept in patient's hospital notes

APPENDIX C: STUDY PARTICIPANT INFORMATION SHEET

The participant information sheet will be printed on Trust headed paper, with the name and contact details for the local principal investigator and coordinating midwife/ nurse for the centre and also for the Trusts' patient advocacy and liaison service.

Thyroid **A**nti**B**odies and **LE**vo**T**hyroxine Study

Participant Information Sheet

Invitation to participate in the TABLET study

You are invited to take part in a research study to find out whether thyroid hormone supplements can help prevent miscarriage. This study is called TABLET (**T**hyroid **A**nti**B**odies and **LE**vo**T**hyroxine Trial) and compares a type of thyroid hormone (levothyroxine) with a dummy treatment (placebo). The study is entirely voluntary – you do not have to take part, nor do you have to give a reason if you decide not to participate. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take your time to read this information sheet carefully and talk to others about the study if you wish. If there is anything that is not clear, or if you would like more information, you should ask your obstetrician/gynaecologist or the research nurse/midwife for further advice.

PART ONE of this leaflet tells you about the purpose of the TABLET study and what will happen if you take part.

PART TWO gives you more detailed information about the conduct of the study.

PART ONE

What is the purpose of the study?

Recent scientific research has shown that thyroid antibodies are associated with miscarriage. About 1 in 4 or 5 pregnancies result in miscarriage but, the risk approximately doubles if a woman has thyroid antibodies in her blood. Thyroid antibodies are also associated with premature births. Why thyroid antibodies increase the risk is unclear. The TABLET study aims to find out if treatment with levothyroxine (a thyroid hormone tablet) can reduce miscarriage and premature births in women with thyroid antibodies.

Why have I been asked to take part?

You have been asked to take part because the blood test that you had showed that you have thyroid antibodies.

Your **thyroid hormone** tests were normal – this means that you **do not** have a thyroid illness that requires treatment.

We understand that this might be a difficult time for you and your partner. As you wish to try for a baby within the next year, we would like to invite you to take part in this trial. The TABLET trial is looking at the effect of thyroid hormone supplements in pregnancy, so we need to work with couples who will shortly be trying to conceive again.

We aim to recruit 900 women with thyroid antibodies from throughout the country to this study.

Do I have to take part?

You do not have to take part. It is entirely up to you to decide. If you do not wish to take part, you do not have to give a reason and your decision will not affect the care you will receive. Similarly, if you do decide to take part, you are entitled to withdraw from the study at any time, without having to give a reason, and this will not affect your medical care in any way. Whether you take part or not, you will have the same access to support.

If I take part will I have levothyroxine or the placebo treatment?

Neither you nor a doctor can choose which treatment you receive. The decision is made randomly by computer at the TABLET study office. This is essential so that a fair comparison can be made between the two treatment groups. Dividing people into groups in this way is called a **'randomised clinical trial'** and it is the standard and most reliable way of comparing different treatments. There is an equal chance of being allocated to the levothyroxine group or the dummy drug (placebo) group. In addition, neither you nor your gynaecologist/obstetrician or nurse/midwife or GP will know which of the groups you will be in. This is called a **'double blind randomised controlled trial'**.

What will happen to me if I take part?

You will be asked to take one capsule every morning whilst you are trying to get pregnant. If and when you get pregnant, you will be asked to keep taking one capsule every morning until the end of the pregnancy. This is in addition to any other drugs that the doctors looking after you think is appropriate for you during the time you are trying for a baby and during pregnancy.

Will the thyroid hormone supplements help me get pregnant again?

No, there is no evidence to suggest that thyroid hormone supplements will help you conceive.

What happens if I don't get pregnant?

We don't want you to feel pressurised to get pregnant and to know that at any time, you may decide to wait before trying again. We will ask you take the tablets for up to one year. We have chosen to approach more women than is needed to answer the question about miscarriage because we know some will not get pregnant.

What will I have to do?

Pre pregnancy You will be asked to take 1 capsule daily, and give a blood sample at each clinic visit. You will be given a 13 week supply of capsules to begin with. You will be asked to return to the clinic about 3 and 6 months after you start the capsules to have a blood test and to receive another 13 weeks supply. You will have another clinic visit about 9 months after the start and you will receive a final 13 weeks supply of capsules.

During Pregnancy If you become pregnant at any point, you will need to inform your research nurse/midwife and the clinic timetable may then change to fit in around the routine ante-natal clinic visits. You will come for three clinic visits: when you are 6-8 weeks, 16-18 weeks and about 28 weeks' of pregnancy. Wherever possible we will try to fit in with your ante-natal clinic appointments. You will be given further supplies of capsules at each visit.

You may also be asked if some of the blood taken could be used for quality control purposes, and possible future research. Any blood used in this way would be anonymised (so your name is not registered with it). Again it is entirely up to you to decide if you want to allow this or not.

Follow-up We will collect information about the outcome of your pregnancy, the number of weeks of pregnancy, and details about you and your baby up until he or she is 4 weeks old. We will not take blood from your baby for the study at any time. We may need to contact you by letter, telephone or e-mail after the baby is born, with your permission.

What are the side effects of treatment received when taking part?

Levothyroxine is taken by millions of pregnant and non-pregnant people worldwide without many side effects. We do not expect any particular side-effects for people who take part in the study but we will look out for any problems in case this might happen.

The blood samples given at clinic visits will test if your thyroid hormone levels have become too high or too low. If this happens, you may be told to stop the study treatment and you will be treated appropriately. If you do feel ill in any way at all, you must tell your doctor or the midwife/nurse, who will check to see whether you are having a side effect of the drug.

Are there any benefits for me from taking part in the study?

You might not gain any personal benefit. Firstly, we don't know whether you will be taking the thyroid hormone supplement, or the dummy drug. Secondly we hope levothyroxine will help reduce the risk of miscarriage and premature birth, but we cannot be sure in advance whether this is the case – that is the reason for doing this study. The main benefit from the TABLET study will be that information gained from the study will help improve the options available in the future for women in similar circumstances.

What are the possible risks and disadvantages of taking part?

Levothyroxine is safely used by many millions of people who have low thyroid hormone levels, mainly older people. The risk of too low or too high thyroid hormone levels in women of reproductive age is very low and the very first blood test would have detected the tiny minority of women with non-normal levels. The regular blood tests will monitor the level throughout the study and appropriate care offered if necessary.

There are some classes of drugs that interact with levothyroxine. Please tell your obstetrician if you are, or start taking, any prescription drugs. You will be given a leaflet about interactions, potential side effects and how to take your capsules when you receive each batch. Taking the blood samples may be a little painful and may result in short-lived bruising.

If you are interested in the TABLET study, the next section provides more information.

PART TWO

What if new information becomes available?

To protect patients' safety, an independent committee of experts will review the results of the TABLET study on an ongoing basis, as well as information from other relevant trials. If thyroid hormone supplements unexpectedly turn out to increase the risk of miscarriage, or cause other problems, that would be detected as soon as possible and the study stopped.

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it and discuss with you what to do next. If you decide to withdraw, you and your doctor will decide your future care. If you decide to continue in the study you will be asked to sign an updated consent form.

What will happen if I don't want to carry on with the study?

If you do decide to take part, you can withdraw from the study at any time and stop taking the study treatment, without having to give a reason, and this will not affect the standard of your medical care in any way. However if you do withdraw, we would still like to follow up your progress. All information will be kept confidential (see section below). The reason for the follow-up is that an important aim of the study is to find out how many women complete their treatment and how women get on if they withdraw from treatment. For this reason, we would like to keep all data and samples collected up to the point of stopping treatment and we would like to continue to collect a few important details such as if you get pregnant or when the baby is born. In the unlikely event of you losing the ability to give continued consent during the study, with your permission we would also like to keep data that we have already collected about you for research purposes.

What if there is a problem?

Whether or not you take part in this project, you would retain the same legal rights as any other patient treated in the National Health Service. If you are harmed by taking part in this research project, there are no special compensation arrangements. But if you are harmed due to someone's negligence, then you have grounds for a legal action, though may have to pay for it. If you are not satisfied with any aspect of the way you have been approached or treated during the course of this study, you should first speak to the researchers (contact details are on the front cover of this information sheet) who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can use the normal National Health Service complaints process: ask to speak to the complaints manager for the hospital.

Will information about me be kept confidential?

Yes, all information collected in the study will be kept strictly confidential in the same way as your other medical records. If you agree to take part, your doctor will send basic information about you and your condition to the TABLET Trial Office at the University of Birmingham Clinical Trials Unit (BCTU), on paper and electronically, where it will be securely stored under the provisions of the 1998 Data Protection Act and/ or applicable laws and regulations. Information held by the NHS may be used to follow your progress. Your GP, and other doctors involved in your clinical care, will be kept informed, but otherwise all information about you and your treatment will be kept confidential.

If you take part in the study, your relevant medical records may be inspected by authorised individuals from the BCTU. They may also be looked at by regulatory authorities. The purpose of this is to check the study is being carried out correctly.

In line with Good Clinical Practice Regulations, at the end of the study, the data will need to be securely stored for at least 5 years (but ideally not less than 25 years). Arrangements for confidential destruction will then be made.

We aim to conduct a follow-up study, looking at the development of babies born to mothers in the TABLET study. We wish to contact you via your GP when your baby is two years old to ask for your consent to the follow-up study.

What will happen to the results of the research study?

When the results of the TABLET study are known they will be published in medical journals and the results circulated to medical staff and participants. No individuals will be identified.

Involvement of the General Practitioner/Family doctor

With your consent we will inform your GP of your participation in the TABLET Study.

Who has organised, reviewed and funded the research?

The TABLET Study is funded by the National Institute for Health Research. The Clinical Trials Unit at the University of Birmingham will collect and analyse the data. The study is sponsored by the University of Birmingham. The research has been reviewed by all these organisations and a Multicentre Research Ethics Committee. The Medicines and Healthcare Products Regulatory Authority have approved the use of levothyroxine in pregnant women and women trying to get pregnant in this study.

The doctors involved are not being paid for recruiting women into the study. Women are not paid to take part either, but their help in finding out more about how best to prevent miscarriage is much appreciated.

Do you have any further questions?

Having read this leaflet, it is hoped that you will choose to take part in the TABLET study. Please keep this copy of the TABLET Study Participant Information Sheet. You will also be given a copy of your signed consent form to keep if you decide to participate in the TABLET study.

If you have any questions about the study now or later feel free to ask your specialist or the research midwife or nurse.

Other Useful Contacts

Miscarriage Association; email info@miscarriageassociation.org.uk or telephone helpline 01924 200799 (Mon-Fri, 9am - 4pm)

Website: www.miscarriageassociation.org.uk

Infertility Network UKCharter House
43 St Leonards Road
Bexhill on Sea
East Sussex TN40 1JA
Tel: 0800 008 7464
Fax: +44 (0) 1424 731858
Email: admin@infertilitynetworkuk.com www.infertilitynetworkuk.com

Thank you for taking the time to read this Participant Information Sheet about the TABLET study.

APPENDIX D: PATIENT STUDY CONSENT FORM

TO BE INSERTED ON LOCAL HOSPITAL PAPER

Thyroid **A**nti**B**odies and **LE**vo**T**hyroxine Study

Patient Consent Form

	Please initial boxes
I confirm that I have read and understand the information sheet dated 26/3/2012 version 4.0 for the above study. I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, and without my medical care or legal rights being affected.	
I understand that my doctors will provide a copy of my consent form and personal information about my progress, in confidence, to the central organisers at Birmingham Clinical Trials Unit (BCTU) for use in the TABLET trial. I understand that the information held by the NHS may be used to keep in touch with me and follow up my pregnancy status.	
I understand that the information collected will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Birmingham, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I understand that researchers based at my hospital or at the BCTU may contact me by telephone, mobile telephone, post or e-mail to request information.	
I understand that researchers may want information about my baby's development in the future. I understand I may be contacted in the future to give my consent for future studies, and that I may be traced through the NHS databases and GP records.	
I agree to my GP being informed of my participation in the TABLET study.	
I agree to provide blood samples as part of the TABLET Trial.	
I agree to my anonymised serum samples being stored and analysed for research both within this study and in future related studies. Any such study on these samples would require Research Ethics Committee approval. *(BWH, Birmingham Heartlands, City and Sandwell, Coventry and Warwick Hosp. only).*	
I understand what is involved in the TABLET Trial and agree to participate.	

---------- _____ _____

Name of Patient Date Signature

---------- _____ _____

Name of Researcher Date Signature

Patient Study Number: | | | | | | (Please complete when patient is randomised)

Original copy to be kept in site file, 1 copy for patient, 1 copy to be kept in patient's hospital note**s and 1 copy to be sent to TABLET Trial Office,** FREEPOST RRKR-JUZR-HZHG, Birmingham Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT

APPENDIX E: SCREENING LOG

Patient Screening Log

Pincipal Investigator:<enter name>
MREC trial Number: 11/SW/0036
Date Completed ___/___/___

Site: <Enter Site Name>

ISRCT Number: <enter ISRCT umber>

Study ID	Patient Initials (FML)	Patient DOB (do not store)	Age (auto calc)	Ethnic Group *	Height (cm)	Weight (Kilos)	BMI (kg/m²) (auto calc)	Date of Miscarriage *(Complete only if patient identifiedfrom miscarriage clinic)*	Consent for screening taken?	Consent version	Blood Sample taken?
☐☐☐☐☐	☐☐☐	dd/mmm/yyyy	☐☐	☐☐☐	☐☐☐	☐☐☐.☐	☐☐.☐	dd/mmm/20yy	Y / N	☐☐.☐	TPO Y / N dd/mmm/yyyy TFT Y / N dd/mmm/yyyy

*Ethnic Group Codes (Source NIHR CC)

249	White
250	Mixed - white and black Caribbean
251	Mixed - white and black African
252	Mixed - white and Asian
253	Other mixed background
254	All mixed groups
255	Asian - Indian
256	Asian - Pakistani
257	Asian - Bangladeshi
258	Other Asian background
259	All Asian groups
260	Black - Caribbean
261	Black - African
262	Other Black background
263	All Black groups
264	Chinese
265	Other ethnic group
266	Not stated

- **Remember to check patients telephone number to call when test results are available**

APPENDIX F: RANDOMISATION NOTEPAD

TABLET Trial Randomisation Form

FOR RANDOMISATIONS TELEPHONE: 0800 953 0274 (Mon to Friday 9am to 5pm)
Website: https://www.trials.bham.ac.uk/tablet

PART A: CONSENT

Has written consent been obtained from the participant Yes ☐ No ☐ Consent version: ___.___ Dated: DD /MMM /YYYY

If No please give reason : ☐ 1 = DNA, 2 = Did not meet eligibility criteria, 3 = Patient changed mind, 4 = No reason given

PART B: IDENTIFICATION DETAILS Randomising Researcher: _____Hospital: _____

Patient's Surname: _____

Patient's Forenames: _____

Patient's title: Mrs Ms Dr Other: _____

Date of birth: DD /MMM /YYYY

Patient's NHS No: _____

Patient's Hospital No.:_____

Patient's Address (if randomised)

_____

_____

Patient's tel. no. (If randomised)_____

Patient's e-mail address (if randomised):

_____

A tick in a shaded box means that the patient is NOT eligible for TABLET

PART C: ELIGIBILITY

	Yes	No
Test positive for TPO?	☐	■
TSH between 0.44 and 3.63 mU/L?	☐	■
T4 between 10.0 and 21.0 pmol/L?	☐	■
Aim to conceive in next 12 months?	☐	■
Taking amiodaroneor lithium?	■	☐
Taking part in other double blind placebo trials in pregnancy?	■	☐
Current or past treatment for thyroid condition, reported by patient and confirmed by investigator?	■	☐
Aged between 16 and 40 yrs + 364 days at randomisation?	☐	■
Current or previous diagnosis of heart disease?	■	☐

PART C: CLINICAL INFORMATION

TSH concentration _____ mU/L

Free T4 level _____ pmol/L

Date of last Miscarriage resolution Date: DD /MMM /YYYY
(complete only if patient has miscarried)

Number of previous miscarriages (not terminations) <24 wks _____

Treated for Infertility? Yes ☐ No ☐

Ethnic Group? White ☐ Black ☐ Asian ☐ Other ☐

PART D: RANDOMISATION – TREATMENT ALLOCATION

TABLET Trial Number: ☐☐☐☐☐ TABLET Treatment Bottle number: **T** ☐☐☐☐

Date of Randomisation: DD /MMM /YYYY

Please return this form within 1 week of entry into the trial to: TABLET Trial Office, FREEPOST RRKR-JUZR-HZHG, Birmingham Clinical Trials Unit, School of Cancer Sciences, University of Birmingham. Birmingham B15 2TT

Tel: 0121 415 9111; Fax: 0121 415 9136; Email: tablet-trial@trials.bham.ac.uk; Website: www.tablet.bham.ac.uk

APPENDIX G: GP LETTER

To be printed on local trust headed paper

LOCAL PRINCIPAL INVESTIGATOR NAME
LOCAL PRINCIPAL INVESTIGATOR CONTACT NUMBER
GP Name
Practice Name
GP Address 1
GP Address 2
GP Address 3
GP Postcode

Date

Dear Dr. *GP NAME*

Your Patient: .....

Date of Birth: ☐☐ ☐☐☐ ☐☐☐☐ TABLET Trial No.: ☐☐☐☐☐

Date Randomised: ☐☐ ☐☐☐ ☐☐☐☐ Hospital No.: .....

Has given written consent, and has agreed to participate in the TABLET trial.

On finding thyroid peroxidise autoantibodies but otherwise normal thyroid function, randomisation was between daily 50ug levothyroxine and placebo. The TABLET trial is double blind and treatment continues until the end of pregnancy or after 12 months of trying to conceive. Levothyroxine is a safe drug and is used during pregnancy for treatment of hypothyroidism, however if any adverse events occur that could potentially be related to treatment, please could you contact me immediately.

The Chief Investigator for TABLET is Professor Arri Coomarasamy, Consultant Obstetrician and Gynaecologist, Birmingham Women's Hospital, United Kingdom B15 2TG, Tel: 0121 623 6805. TABLET is coordinated by the University of Birmingham Clinical Trials Unit and funded by the NIHR Efficacy and Mechanistic Evaluation Programme. Please file this letter in the patient's notes. Please contact the TABLET Trial Office Tel: 0121 415 9111 if there are any errors in the details above or if she is no longer one of your patients.

I have enclosed a trial exit leaflet explaining post-partum thyroiditis , which may occur post delivery or miscarriage. This will be given to your patient when she exits the trial, having given birth or miscarried. We recommend that you monitor thyroid function 6-8 weeks post -delivery.

Yours sincerely
Local Principal Investigator

APPENDIX H: PATIENT CARD

For information about the trial or in case of emergency, please contact:

Investigator Name:

Telephone

Address

Patient Name: _____

Is participating in a University of Birmingham sponsored clinical study: **TABLET**

With treatment: Levothyroxine 50mcg **or** Placebo

Please keep this card with you at all times

Patient information card V 1.0

APPENDIX I – SUMMARY OF PRODUCT CHARACTERISTICS

Levothyroxine 50mcg tablets

Summary of Product Characteristics Updated 28-Apr-2017 | Concordia International - formerly AMCo

1. Name of the medicinal product

Eltroxin 50mcg tablets

Levothyroxine 50mcg tablets

2. Qualitative and quantitative composition

Each tablet contains 50 micrograms Levothyroxine sodium anhydrous.

Excipient with known effect

Lactose 48.86mg per tablet

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

White, uncoated, biconvex tablets engraved on one face with "LT" and 50 on the other.

4. Clinical particulars

4.1 Therapeutic indications

Recommended clinical indications: Control of hypothyroidism, congenital hypothyroidism *in infants*, acquired hypothyroidism in children and juvenile myxoedema.

4.2 Posology and method of administration

Posology

In younger patients, and in the absence of heart disease, a serum Levothyroxine (T4) level of 70 to 160 nanomols per litre, or a serum thyrotrophin level of less that 5 milli-units per litre should be targeted. A pre-therapy ECG is valuable because ECG changes due to hypothyroidism may be confused with ECG evidence of cardiac ischaemia. If too rapid an increase in metabolism is produced (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors, and sometimes anginal pain where there is latent cardiac ischaemia,) dosage must be reduced, or withheld, for a day or two, and then re-started at a lower dose level.

Adults: Initially 100 micrograms daily, preferably taken before breakfast or the first meal of the day. Adjust at three to four week intervals by 50 micrograms until normal metabolism is steadily maintained. The final daily dose may be up to 100 to 200 micrograms.

Elderly: As for patients aged over 50 years.

For patients over 50 years, initially, it is not advisable to exceed 50 micrograms daily. In this condition, the daily dose may be increased by 50 micrograms at intervals of every 3-4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 to 200 micrograms.

Patients over 50 years with cardiac disease:

Where there is cardiac disease, 25 micrograms daily or 50 micrograms on alternate days is more suitable. In this conditions, the daily dose may be increased by 25 micrograms at intervals of every 4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 to 200 micrograms.

For patients aged over 50 years, with or without cardiac disease, clinical response is probably a more acceptable criteria of dosage rather that serum levels.

Paediatric population:

The maintenance dose is generally 100 to 150 micrograms per m^2 body surface area. The dose for children depends on their age, weight and the condition being treated. Regular monitoring using serum TSH levels, as in adults, is required to make sure he/she gets the right dose. Infants should be given the total daily dose at least half an hour before the first meal of the day.

Congenital hypothyroidism in infants:

For neonates and infants with congenital hypothyroidism, where rapid replacement is important, the initial recommended dosage is 10 to 15 micrograms per kg BW per day for the first 3 months. Thereafter, the dose should be adjusted individually according to the clinical findings and thyroid hormone and TSH values.

Acquired hypothyroidism in children:

For children with acquired hypothyroidism, the initial recommended dosage is 12.5-50 micrograms per day. The dose should be increased gradually every 2 to 4 weeks according to the clinical findings and thyroid hormone and TSH values until the full replacement dose is reached.

Juvenile myxoedema in children:

The initial recommended dosage is 25 micrograms daily. In such conditions, the daily dose may be increased by 25 micrograms at intervals of every 2 - 4 weeks, until mild symptoms of hyperthyroidism is seen. The dose will then be reduced slightly.

In children under 5 years of age, the administration of whole tablets is not recommended. It is also not recommended that tablets are crushed and dispersed in water or other liquids, owing to limited solubility which could lead to dosing inaccuracy. In this age group it is preferable to administer an approved oral solution of levothyroxine.

Method of administration

Oral

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

- Thyrotoxicosis
- Adrenal gland disorder or adrenal insufficiency

4.4 Special warnings and precautions for use

Levothyroxine should be introduced very gradually in patients aged over 50 years (see section 4.2) and those with long standing hypothyroidism to avoid any sudden increase in metabolic demands.

Patients with panhypopituitarism or other causes predisposing to adrenal insufficiency may react to levothyroxine treatment, and it is advisable to start corticosteroid therapy before giving levothyroxine to such patients.

Levothyroxine sodium should be used with caution in patients with cardiovascular disorders, including angina, coronary artery disease, hypertension, and in the elderly who have a greater likelihood of occult cardiac disease.

To minimise the risk of adverse effects of undetected overtreatment, such as atrial fibrillation and fractures associated with low serum levels of thyroid stimulating hormone (TSH) in older patients, it is important to monitor serum TSH and adjust the dose accordingly during long term use

In individuals suspected to have cardiovascular disease or to be at high risk, it is important to perform an ECG prior to commencement of levothyroxine treatment in order to detect changes consistent with ischaemia in which case, levothyroxine should be initiated at a low dose, followed by cautious dose escalation to avoid worsening of ischaemia or precipitation of an infarct.

Thyroid replacement therapy may cause an increase in dosage requirements of insulin or other anti-diabetic therapy (such as metformin). Care is needed for patients with diabetes mellitus, and diabetes insipidus.

See note above regarding withdrawal of treatment.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Subclinical hyperthyroidism may be associated with bone loss. To minimise the risk of osteoporosis, dosage of levothyroxine sodium should be titrated to the lowest possible effective level.

Parents of children receiving thyroid agent should be advised that partial loss of hair may occur during the first few months of therapy, but this effect is usually transient and subsequent regrowth usually occurs.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions affecting other drugs:

Levothyroxine increases the effect of anticoagulants (Warfarin) and it may be necessary to reduce the anticoagulation dosage if excessive, hypoprothrombinaemia and bleeding are to be avoided.

Blood sugar levels are raised and dosage of anti-diabetic agents may require adjustment.

Tricyclic anti-depressants (e.g. amitriptyline, imipramine, dosulepin) response may be accelerated because levothyroxine increases sensitivity to catecholamines; concomitant use may precipitate cardiac arrhythmias.

The effects of sympathomimetic agents (e.g. adrenaline or phenylephrine) are also enhanced

If levothyroxine therapy is initiated in digitalised patients, the dose of digitalis may require adjustment. Hyperthyroid patients may need their digoxin dosage gradually increased as treatment proceeds because initially patients are relatively sensitive to digoxin.

False low plasma concentrations have been observed with concurrent anti-inflammatory treatment such as phenylbutazone or acetylsalicylic acid and levothyroxine therapy.

Beta Blockers: levothyroxine (thyroxine) accelerates metabolism of propranolol, atenolol and sotalol.

Isolated reports of marked hypertension and tachycardia have been reported with concurrent ketamine administration.

Interactions affecting Levothyroxine:

Amiodarone may inhibit the de iodination of thyroxine to tri iodothyronine resulting in a decreased concentration of tri iodothyronine, thereby reducing the effects of thyroid hormones.

Anti-convulsants, such as carbamazepine and phenytoin, enhance the metabolism of thyroid hormones and may displace them from plasma proteins.

Initiation or discontinuation of anti-convulsant therapy may alter levothyroxine dosage requirements.

Effects of Levothyroxine may be decreased by concomitant sertraline.

Absorption of levothyroxine (thyroxine) possibly reduced by antacids, proton pump inhibitors, calcium salts, cimetidine, oral iron, sucralfate, colestipol, polystyrene sulphonate resin and cholestyramine (administration should be separated by 4-5 hours).

Metabolism of levothyroxine (thyroxine) accelerated by rifampicin, barbituarates, and primidone. (may increase requirements for levothyroxine (thyroxine) in hypothyroidism)

Imatinib: plasma concentration of levothyroxine (thyroxine) possibly reduced by imatinib.

Beta blockers may decrease the peripheral conversion of levothyroxine to triiodothyronine. Oestrogen, oestrogen containing product (including hormone replacement therapy)and oral contraceptives may increase the requirement of thyroid therapy dosage. Conversely, androgens and corticosteroids may decrease serum concentrations of Levothyroxine-binding globulins.

Anti-obesity drugs such as orlistat may decrease levothyroxine absorption which may result in hypothyroidism (monitor for changes in thyroid function).

A number of drugs may affect thyroid function tests and this should be borne in mind when monitoring a patient on levothyroxine therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Levothyroxine treatment during pregnancy is not known, but any possible risk of foetal abnormalities should be weighed against the risk to the foetus of untreated hypothyroidism.

Breast-feeding

Levothyroxine is excreted in breast milk in low concentrations, and it is contentious whether this can interfere with neonatal screening.

4.7 Effects on ability to drive and use machines

Levothyroxine has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Side-effects are usually indicative of excessive dosage and usually disappear on reduction of dosage or withdrawal of treatment for a few days. Adverse reactions listed below have been observed during clinical studies and/or during marketed use and are based on clinical trial data and classified according to MedDRA System Organ Class. Frequency categories are defined according to the following convention:

Not known (cannot be estimated from the available data)

System organ class	Frequency	Undesirable effects
Immune system disorders	Not known	Hypersensitivity reaction,
Endocrine disorders	Not known	Thyrotoxic crisis[1]
Psychiatric disorders	Not known	Restlessness, agitation, insomnia
Nervous system disorders	Not known	Tremor,
Cardiac disorders	Not known	Angina pectoris, arrhythmia, palpitations, tachycardia
Vascular disorders	Not known	Flushing,
Respiratory, thoracic and mediastinal disorders	Not known	Dyspnoea
Gastrointestinal disorders	Not known	Diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Not known	Hyperhidrosis, rash, pruritus

Musculoskeletal and connective tissue disorder	Not known	Arthralgia, muscle spasm, muscular weakness,
Reproductive system disorders	Not known	Menstruation irregular
General disorders and administration site conditions	Not known	Headache, pyrexia, malaise, oedema
Investigations	Not known	Weight decreased

[1]Some patients may experience a severe reaction to high levels of thyroid hormone. This is called a "thyroid crisis" with any of the following symptoms: Hyperpyrexia, tachycardia, arrhythmia, hypotension, cardiac failure, jaundice, confusion, seizure and coma

Paediatric population

Heat intolerance, transient hair loss, benign intracranial hypertension, craniostenosis in infants and premature closure of epiphysis in children.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

In most cases there will be no features. Signs of an overdose may include: fever, chest pain (angina), racing or irregular heartbeat, muscle cramps, headache, restlessness, flushing, sweating, diarrhoea, tremor, insomnia and hyperpyrexia. These signs can take up to 5 days to appear. Atrial fibrillation may develop. Convulsions occurred in one child. There may be increased toxicity in those with pre-existing heart disease.

Management:

Give oral activated charcoal if more than 10mg has been ingested by an adult or more than 5mg by a child, within 1 hour. If more than 10mg has been ingested by an adult or more than 5mg by a child, take blood 6-12 hours after ingestion for measurement of the free thyroxine concentration. The analysis does not need to be done urgently but can wait until the first working day after the incident. Patients with normal free thyroxine concentrations do not require follow up. Those with high concentrations should have outpatient review 3-6 days after ingestion to detect delayed onset hyperthyroidism. Features of clinical hyperthyroidism should be controlled with beta-blockers, e.g. propranolol.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thyroid hormones

ATC Code: H03AA01

Eltroxin is a tablet containing the hydrated form of Levothyroxine sodium which is used for the treatment of hypothyroidism. The thyroid gland is dependant upon 2 active principles for it's main hormone activity these are Levothyroxine (tetraiodothyronine) and Tri-iodothyronine (see Goodman and Gilman, 1985). These closely related iodine containing amino acids are incorporated into the glycoprotein thyroglobulin. The chief action of these hormones is to increase the rate of cell metabolism. Levothyroxine is deiodinated in peripheral tissues to form Tri-iodothyronine which is thought to be the active tissue form of thyroid hormone. Tri-iodothyronine is certainly more rapid acting and has a shorter duration of action than Levothyroxine.

5.2 Pharmacokinetic properties

Levothyroxine sodium is incompletely and variably absorbed from the gastrointestinal tract. It is almost completely bound to plasma proteins and has a half-life in the circulation of about a week in healthy subjects, but longer during pregnancy in patients with myxoedema. A large portion of the Levothyroxine leaving the circulation is taken up by the liver. Part of a dose of Levothyroxine is metabolised to triiodothyronine. Levothyroxine is excreted in the urine as free drug, deiodinated metabolites and conjugates. Some Levothyroxine is excreted in the faeces. There is limited placental transfer of Levothyroxine.

5.3 Preclinical safety data

No further data of relevance.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Citrate BP

Lactose BP

Maize starch BP

Powdered acacia BP

Magnesium Stearate BP

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months for polypropylene containers.

24 months for blister packs.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Polypropylene container with tamper-evident low density polyethylene lid, containing 28, 56, 100, 112, or 1000 Eltroxin 50mcg tablets.

Blister packaging PVC/PVDC film (heat treated foil/heat seal lacquer) containing 28, 56 and 112 Eltroxin 50mcg tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7. Marketing authorisation holder

Mercury Pharma Group Ltd

Capital House, 85 King William Street,

London EC4N 7BL, UK

8. Marketing authorisation number(s)

PL 10972/0031

9. Date of first authorisation/renewal of the authorisation

28/04/2010

10. Date of revision of the text

21/12/2016

Company Contact Details

Concordia International - formerly AMCo
http://www.concordiarx.com

Address
Capital House, 1st Floor, 85 King William Street, London, EC4N 7BL, UK

Fax
+44 (0)208 588 9200

Medical Information e-mail
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Medical Information Fax
+44 (0)20 8588 9200

Telephone
+44 (0)208 588 9131

Medical Information Direct Line
08700 70 30 33

Customer Care direct line
+44 (0)208 588 9273

APPENDIX J: TABLET TRIAL SCHEMA