Protocol Registration Receipt
08/10/2012

Thyroid Hormone Replacement for Subclinical Hypothyroidism (TRUST)

This study is not yet open for participant recruitment.

Verified by Professor David J Stott, University of Glasgow, August 2012

Sponsor:	NHS Greater Glasgow and Clyde
Collaborators:	University of Glasgow University College Cork University of Bern Leiden University Medical Center
Information provided by (Responsible Party):	Professor David J Stott, University of Glasgow
ClinicalTrials.gov Identifier:	NCT01660126

Purpose

Subclinical hypothyroidism (SCH) is a common condition (818%)among older men and women. Although by definition SCH comprises biochemically mild thyroid hormone deficiency without overt symptoms, it is a possible contributor to multiple problems in older age. Thyroid hormone has effects on numerous physiological systems, including the vascular tree, heart, skeletal muscle and brain. Therefore, thyroxine substitution to overcome thyroid hormone deficiency has the potential to give multisystem benefits to older people with SCH.

Small studies have reported reduced atherosclerosis and improved heart function with thyroxine replacement, but no large clinical trials have been performed. Therefore the available evidence is limited, leading to major variations in guidelines and clinical practice, with uncertainty regarding the indications for screening and treatment. The investigators propose a multicentre randomised placebo controlled trial to assess the impact of thyroxine replacement in 3,000 older adults with persisting SCH(excluding those in whom it is a temporary phenomenon who are unlikely to benefit). The investigators will include older men and women with a wide age range and of varying health status. Outcomes include cardiovascular events, health related quality of life, muscle strength and executive cognitive function over 3 years of follow up. Blood and urine samples will be stored in a biobank, to allow future research on causes of ill health in older people with SCH.

The investigators have the support of patient advocacy groups and a consortium with the wide range of expertise and experience required to conduct large scale multicentre clinical trials. The proposal explores the multisystem and quality of life benefits to older people of a tailored approach to management of SCH.

This clinical trial should definitively clarify whether thyroxine treatment for SCH provides benefits that are relevant for patients. This trial will provide strong evidence with the potential to improve clinical practice, reduce health care costs and promote healthy ageing of older adults.

Condition	Intervention	Phase
Subclinical Hypothyroidism	Drug: Levothyroxine Drug: Placebo	Phase 4

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized
Official Title: Multi-modal Effects of Thyroid Hormone Replacement for Untreated Older Adults With Subclinical Hypothyroidism; a Randomised Placebo-controlled Trial

Further study details as provided by Professor David J Stott, University of Glasgow:

Primary Outcome Measure:

- Fatal and non-fatal cardiovascular events [Time Frame: Up to a maximum of 4 years] [Designated as safety issue: No]
  This will include fatal and no fatal acute myocardial infarction and stroke; amputations for peripheral vascular disease; revascularisations for atherosclerotic vascular disease, including for acute coronary syndrome; heart failure hospitalisations.
- Thyroid-specific quality of life [Time Frame: Measured at baseline; 3 months; 12 months and close-out.] [Designated as safety issue: No]
  Change in symptom burden and thyroid-specific QOL (measured using the Thyroid-specific quality of life Patient Reported Outcome questionnaire - ThyPRO; symptom and fatigue domains only).

Secondary Outcome Measures:

- Health-related quality of life [Time Frame: measured at baseline; 3 month; 12 month and final follow up.] [Designated as safety issue: No]
  The EuroQol5D
- Handgrip strength [Time Frame: Measured at baseline; 12 months and final follow up.] [Designated as safety issue: No]
  Handgrip strength measured using the Jadaar hand dynamometer.
- Executive cognitive function [Time Frame: Measured at baseline and final follow-up.] [Designated as safety issue: No]
  Letter Digit Coding Test [LDCT).
- Total mortality [Time Frame: Up to final follow up (maximum 4 years)] [Designated as safety issue: No]
  Total mortality
- Basic Activities of Daily Living [Time Frame: Measured at baseline and final follow-up] [Designated as

safety issue: No]

Basic Activities of Daily Living (ADL) measured using the 20-point Barthel Index [BI].

- Extended activities of daily living [Time Frame: Measured at baseline and final follow-up] [Designated as safety issue: No]

  Extended activities of daily living measured using the older American resources and services [OARS]) questionnaire

- Haemoglobin [Time Frame: Measured at baseline and 1 year] [Designated as safety issue: No]

  Change in haemoglobin, measured on a full blood count

Estimated Enrollment: 3000
Study Start Date: November 2012
Estimated Study Completion Date: June 2016
Estimated Primary Completion Date: June 2016

Arms	Assigned Interventions
Active Comparator: Levothyroxine Oral Levothyroxine, starting dose 25 or 50 micrograms increased to a maximum of 150 micrograms once daily.	Drug: Levothyroxine The intervention will start with Levothyroxine 50 µg daily (reduced to 25 µg in subjects <50Kg body weight or if known coronary heart disease - previous myocardial infarction or symptoms of angina pectoris) versus matching placebo; at 3 months if the serum TSH level is <0.4 mU/L dose will be reduced by 25 µg; TSH >=0.4 and <4.6 mU/L, no change to dose; TSH >=4.6mUL, additional 25 µg. The process will be repeated at 12 months then annually. Mock titration will be performed in the placebo group. The maximum possible dose of Levothyroxine that will be prescribed is 150µg (after 4 increments of 25µg at 3 months, 1, 2 and 3 years; from the starting dose of 50µg). Other Names: Thyroxine
Placebo Comparator: Placebo Matched placebo	Drug: Placebo

Eligibility

Ages Eligible for Study: 65 Years and older
Genders Eligible for Study: Both

Inclusion Criteria:

- Community-dwelling patients aged >=65 years with Subclinical Hypothyroidism (SCH).

SCH is defined as elevated TSH levels (>=4.6, <=19.9 mU/L) and free thyroxine (fT4) in reference range measured on a minimum of two occasions at least 3 months apart.

Exclusion Criteria:

- Subjects currently on Levothyroxine or antithyroid drugs, amiodarone or lithium.
- Recent thyroid surgery or radio-iodine (within 12 months).
- Grade IV NYHA heart failure.
- Prior clinical diagnosis of dementia.
- Recent hospitalisation for major illness or elective surgery (within 4 weeks).
- Recent acute coronary syndrome, including myocardial infarction or unstable angina (within 4 weeks).
- Terminal illness.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
- Subjects who are participating in ongoing RCTs of therapeutic interventions (including CTIMPs)
- Plan to move out of the region in which the trial is being conducted within the next 2 years (proposed minimum follow-up period).

Contacts and Locations

Contacts

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Locations

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Investigators

Principal Investigator:	David J Stott, MBChB MD	University of Glasgow
Principal Investigator:	Jacobijn Gussekloo, MD	Leiden University Medical Center
Principal Investigator:	Rodondi N, MD	University of Bern
Principal Investigator:	Patricia Kearney, MD	University College Cork
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More Information

Responsible Party: Professor David J Stott, David Cargill Professor of Geriatric Medicine, University of Glasgow

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	2011-004554-26 [EudraCT Number]
Health Authority:	United Kingdom: National Health Service