Subclinical hypothyroidism in community-dwelling older people: consequences and treatment outcomes

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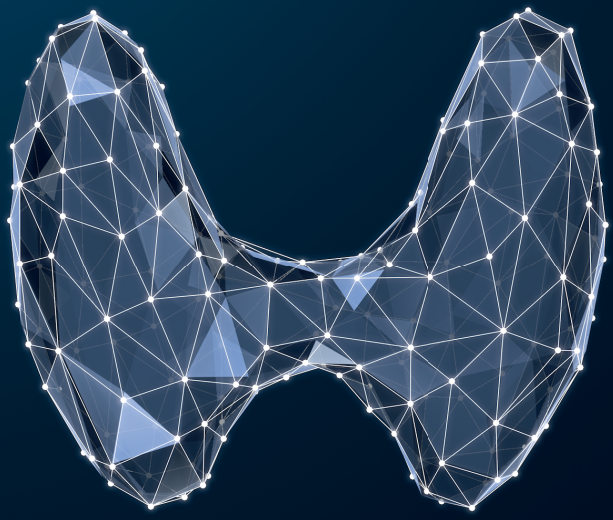

Chapter 6

Study protocol: a randomised controlled trial on the clinical effects of levothyroxine treatment for subclinical hypothyroidism in people aged 80 years and over

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BMC Endocrine Disorders, 2018;18(1):67

DOI: 10.1186/s12902-018-0285-8

ABSTRACT

Background

Subclinical hypothyroidism is common in older people and its contribution to health and disease needs to be elucidated further. Observational and clinical trial data on the clinical effects of subclinical hypothyroidism in persons aged 80 years and over is inconclusive, with some studies suggesting harm and some suggesting benefits, translating into equipoise whether levothyroxine therapy provides clinical benefits. This manuscript describes the study protocol for the Institute for Evidence-Based Medicine in Old Age (IEMO) 80-plus thyroid trial to generate the necessary evidence base.

Methods

The IEMO 80-plus thyroid trial was explicitly designed as an ancillary experiment to the Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism randomised placebo controlled Trial (TRUST) with a near identical protocol and shared research infrastructure. Outcomes will be presented separately for the IEMO and TRUST 80-plus groups, as well as a pre-planned combined analysis of the 145 participants included in the IEMO trial and the 146 participants from the TRUST thyroid trial aged 80 years and over.

The IEMO 80-plus thyroid trial is a multi-centre randomised double-blind placebo-controlled parallel group trial of levothyroxine treatment in community-dwelling participants aged 80 years and over with persistent subclinical hypothyroidism (TSH $\geq$ 4.6 and $\leq$ 19.9 mIU/L and fT4 within laboratory reference ranges). Participants are randomised to levothyroxine 25 or 50 micrograms daily or matching placebo with dose titrations according to TSH levels, for a minimum follow-up of one and a maximum of three years.

Primary study endpoints: hypothyroid physical symptoms and tiredness on the thyroid-related quality of life patient-reported outcome (ThyPRO) at one year. Secondary endpoints: generic quality of life, executive cognitive function, handgrip strength, functional ability, blood pressure, weight, body mass index, and mortality. Adverse events will be recorded with specific interest on cardiovascular endpoints such as atrial fibrillation and heart failure.

Discussion

The combined analysis of participants in the IEMO 80-plus thyroid trial with the participants aged over 80 in the TRUST trial will provide the largest experimental evidence base on multimodal effects of levothyroxine treatment in 80-plus persons to date.

Trial registration

Nederlands (Dutch) Trial Register: NTR3851 (12–02-2013), EudraCT: 2012–004160-22 (17–02-2013), ABR-41259.058.13 (12–02-2013).

BACKGROUND

Subclinical hypothyroidism (SCH) is a common aberrant biochemical finding defined as an elevated serum thyroid-stimulating hormone (TSH) and normal circulating thyroid hormone level.[1] SCH is associated with multiple health problems in old age ranging from mild non-specific symptoms such as tiredness and emotional susceptibility to coronary heart disease and decreased physical and cognitive functioning.[2]

As 8–18% of those over 65 years are affected and inference from both observational and experimental studies maintain the clinical equipoise whether the merits of levothyroxine treatment outweigh the risks,[3] the Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism randomised placebo controlled Trial (TRUST) [4] was designed to resolve this clinical uncertainty. The outcomes of the TRUST trial provided robust information that for community-dwelling persons of 65 years of age and older with SCH, levothyroxine treatment provides no apparent benefits.[4]

There are ample data to suggest that thyroid function is mediated by age and that the effects of SCH may be profoundly different in octogenarians and older.[3] Older persons generally require different dosages of levothyroxine to achieve euthyroidism than younger counterparts possibly due to changes in body weight, composition or hormonal status [5] and are at higher risk of adverse effects of overtreatment including cardiovascular events, arrhythmias and fractures.[6] In a large-scale, observational follow-up study among 599 community-dwelling participants aged 85 years and over, increasing levels of TSH were associated with prolonged life span.[7] This association, however, could not be confirmed in a later Individual Patient Data meta-analysis investigating mortality information in 4,344 participants with SCH aged 80 years and over.[8] In addition, members of families with exceptional longevity are characterised by slightly higher TSH and slightly lower circulating thyroid hormone levels when compared with the general population.[9]

To help resolve this clinical uncertainty of levothyroxine replacement treatment for SCH in older persons, we have performed an randomised controlled trial including participants over 80 years old in the presence of comorbid conditions; the Institute for Evidence-Based Medicine in Old Age (IEMO) 80-plus thyroid trial. The TRUST trial was not designed specifically to investigate the effects in 80-plus participants and was consequently inadequately powered for a subgroup analysis in participants aged 80 and over. The IEMO 80-plus thyroid trial was designed jointly with the TRUST trial as an ancillary trial using the same trial infrastructure and protocol to allow a pre-planned, joint analysis of all participants aged 80 and over. This combined endeavour will provide experimental evidence on potential multimodal effects of levothyroxine treatment from the largest sample of 80-plus persons with SCH to date.

Among the specific study objectives are:

1. Does levothyroxine treatment for SCH provide benefits for 80-plus persons with SCH?
2. Are benefits seen across a wide range of outcomes, including health-related quality of life, muscle function, cognition and prevention of cardiovascular disease?
3. Are benefits seen in specific subgroups of people with SCH, including women, and those with mild degrees of SCH (TSH 4.6–10 mIU/L)?
4. Are any benefits offset by adverse effects, such as atrial fibrillation or heart failure?

METHODS AND DESIGN

The IEMO 80-plus thyroid trial was designed as an ancillary randomised double-blind placebo-controlled parallel group trial of levothyroxine for persons over 80 years with subclinical hypothyroidism. From the outset the study was designed jointly and in parallel with the TRUST trial (details provided elsewhere [10]) and both trials share a near identical design and infrastructure including study protocols, standard operating procedures, independent data monitoring and endpoint committees, databases, statisticians and study nurses.

Initially, the IEMO 80-plus thyroid trial aimed to include 450 participants. Additionally, a preplanned combined analysis with the data from all 80-plus participants from the TRUST trial, resulting in a total of 900 participants in the final pooled analyses, was conceived to maximise statistical power. During the inclusion phase, it became apparent that the proposed target of 450 80-plus participants was unfeasible within the allotted study period (mirroring the experiences of the TRUST trial [10]) and revised power calculations were proposed with the new projected target of 145 IEMO 80-plus trial participants (see Sample size calculation).

Originally the trial was executed in 4 regions of the Netherlands (Leiden University Medical Center, Erasmus University Medical Center, University Medical Center Groningen and the University of Amsterdam). During the inclusion period, in an attempt to maximise the inclusion rate, organisational changes were accepted allowing for inclusion of participants from all locations within the Netherlands, coordinated by the Leiden University Medical Center. Additionally, because the trial infrastructure was already in place for the TRUST trial, additional participants were recruited from the University Hospital Bern in Switzerland.

Study population

One hundred forty-five community-dwelling participants ≥ 80 years with SCH are recruited. Similar to TRUST, participants are identified from clinical and primary care laboratory databases from all patients having biochemical features consistent with SCH. SCH is defined as persistently elevated TSH levels (≥ 4.6 and ≤ 19.9 mIU/L), measured on a minimum of two

occasions at least 3 months and no more than 3 years apart prior to enrolment and free thyroxine (fT4) within the laboratory reference range. All participants gave written individual informed consent to participate.

Exclusion criteria

- Participants currently on levothyroxine, antithyroid medication (including carbimazole, methimazole, propylthiouracil and potassium perchlorate), amiodarone or lithium.
- Recent thyroid surgery or radio-iodine therapy (within 12 months).
- Grade IV NYHA heart failure.
- Prior clinical diagnosis of dementia.
- Recent hospitalisation for major illness (within 4 weeks).
- Recent acute coronary syndrome, including myocardial infarction or unstable angina (within 4 weeks).
- Acute myocarditis or acute pancarditis
- Untreated adrenal insufficiency or adrenal disorder
- Terminal illness.
- Patients known to have rare hereditary problem of galactose intolerance.
- Participants who are participating in ongoing RCTs of therapeutic interventions (including clinical trials of investigational medicinal products [CTIMPs])
- Plan to move out of the region in which the trial is being conducted within the next 2 years.

Intervention

The investigational medicinal products are levothyroxine sodium (T4) as 25 or 50 microgram tablets for oral administration and a matching placebo. All tablets are white and round in shape with the strength imprinted, identically packaged in blisters and packed in plain cardboard cartons to maintain study blinding. Participants are advised to take the suggested dose of study medication once daily half an hour before breakfast.

The intervention group will start with levothyroxine 50 micrograms daily (25 micrograms in participants with < 50 kg body weight or with a history of coronary heart disease) and the control group with matching placebo for six to eight weeks.

After 6–8 weeks a venous blood sample is taken for TSH assessment. Based on the TSH results, the data centre advises the new dose of study medication or placebo to the clinical investigators.

- If TSH < 0.4 mIU/L: the treatment dose is reduced to 25 micrograms levothyroxine in those starting on 50 micrograms; reduced to 0 in those starting on 25 micrograms – effected by giving placebo matching the 25 micrograms dose. These participants will have a further

TSH check after 6–8 weeks. If TSH remains < 0.4 mIU/L participant will be withdrawn from randomised treatment and referred to usual care.
- If TSH ≥ 0.4 and < 4.6 mIU/L: no change to the treatment dose.
- If TSH remains elevated (≥ 4.6 mIU/L): 25 micrograms of levothyroxine will be added. Giving a total daily dose of 75 micrograms levothyroxine for those starting on 50 micrograms, or a total daily dose of 50 micrograms levothyroxine for those starting on 25 micrograms.

A maximum of two levothyroxine up-titrations at the start of the trial and one up-titration at 12- and 24-month (± 1 month) intervals with repeated TSH measurements after 6–8 weeks ensure adequate levothyroxine treatment while avoiding potential over-replacement. The maximum possible dose of levothyroxine is 150 micrograms.

A mock titration adopting an adaptive schedule is performed in the placebo group by the data centre. A similar proportion of placebo patients will have up and down titrations of study medication as the intervention group to ensure the number of tablets and assessments is similar in both groups.

Because all thyroid function measurements are available only to the data centre, the clinical investigators remain fully blinded to the treatment allocation process during the trial.

Accountability logs recording the quantities of study medication dispensed to and returned from study participants, batch numbers and expiry dates are available for all study drug movements.

Criteria for discontinuing or modifying allocated study medication:

- If overt biochemical hypothyroidism is identified (TSH > 20 mIU/L and/or fT4 below the reference range) a second TSH with fT4 within 2 weeks is requested. Upon confirmation of biochemical hypothyroidism, the participant will be withdrawn from the study treatment and referred to the General Practitioner (GP) for usual care.
- If overt biochemical hyperthyroidism is identified (TSH < 0.4 mIU/L) in the placebo group, or consecutively in the treatment group despite down titrations, the participant will be withdrawn from the study treatment and referred to the GP for usual care.
- If for clinical reasons (e.g. major illness) a proposed change in study medication or placebo is deemed inappropriate the algorithm is overridden by the local principal coordinator and no change in study medication takes place.

Randomisation

Participants are randomised to either the levothyroxine or placebo treatment arm (ratio 1:1) using the randomly permuted block method, stratified by site, sex and starting dose. The data

centre (Robertson Centre for Biostatistics, University of Glasgow, Scotland) independently provides the randomisation schedule. Mawdsley Brooks & Co. implements the schedule through identical packaging of levothyroxine and matching placebo tablets.

Patient allocation is conducted via the dedicated trial web portal by the study nurses. When a participant is eligible based on entering the eligibility criteria in an electronic case report form (eCRF) supervised by a medically certified Principal Investigator, a central computer will trigger the decision.

Blinding

Participants are blinded to treatment allocation by using matching tablets and packaging for levothyroxine and placebo. All study personnel remain blinded for the duration of the trial through remote analysis of laboratory results of TSH in the data centre, ensuring the trial stays double blinded. GPs will remain blinded to treatment allocation and TSH tests unless otherwise required in the event of an emergency medical situation. An Interactive Voice Response System at the data centre allows for individual emergency allocation information to be released to an unblinded study physician through 24-h telephone access. All participants will learn the treatment allocation within 15 working days of receiving the final visit and completing all the data to aid in any further treatment decisions with the GP.

All laboratory tests for TSH and fT4 are performed at the local GP and clinical laboratories. The results in the treatment phase are uploaded to the independent data centre which in turn advises the study site on dose titration through the dedicated trial web portal. The study team remains unaware of the results of the thyroid function testing. Additionally, all cooperating GPs were asked to refrain from additional thyroid function measurements to ensure adequate blinding.

Data collection

Data collection will be performed by study research nurses at baseline and predetermined follow-up visits at the participant's home or place of residence. All participants are followed up for a minimum of 1 year with a likely average of 2 years. Participants are reviewed face-to-face by the study nurses at recruitment, study baseline, 6–8 weeks, 12 months, 24 months, 36 months and at the final visit. This personal approach ensures data quality and promotes participant retention and complete follow-up. In addition, interim telephone contact or visits (depending on the desire of the patient) are made by study nurses at 6, 18 and 30 months (depending on total duration of follow-up), including recording of possible cardiovascular and serious adverse events (SAEs). For a timeline of assessments and visits see Table 1.

Table 1. Detailed schedule of assessments.

Months of follow up	**0 visit**	**6-8 wks**	**6m**	**12m**	**18m**	**24m**	**30m**	**36m**	**Final[a] visit**
		visit	**call/visit**	**visit**	**call/visit**	**visit**	**call/visit**	**visit**	
Participant characteristics & medical history	x								
Weight, height, waist circumference and BMI	x			x					x
Concomitant medication	x	x		x		x		x	x
Home support	x								x
Safety and monitoring									
Morbidity, mortality, hospitalisation and GP contacts		x	x	x	x	x	x	x	x
Serious Adverse Events		x	x	x	x	x	x	x	x
Single-lead ECG (for AF)	x			x		x		x	x
Drug adherence		x	x	x	x	x	x	x	x
Outcomes									
Thyroid related quality of life (ThyPRO)	x	x		x					x
Generic quality of life (EQ-5D-3L)	x	x		x					x
Cognitive function									
MMSE	x								
Letter Digit Coding Test	x								x
Functional ability									
ADL (BI), IADL (OARS), falls questionnaire	x								x
Handgrip strength & 6-meter gait speed	x			x					x
Blood pressure	x			x					x
Fatal and non-fatal cardiovascular events		x	x	x	x	x	x	x	x
Arthritis complaints									x
Treatment Satisfaction (TSQM vII)									x
Laboratory analysis									
Thyroid function	x	x		x		x		x	x
Haemoglobin	x			x					
Blood samples for biobank	x			x					

[a] the final visit assessments may substitute for any assessment time between 12 and a maximum of 42 months

All study nurses are trained simultaneously on the data to be assessed. All measuring equipment is calibrated before the start and annually thereafter to safeguard reliability and validity. The Data centre will develop and manage a dedicated, anonymised trial web portal, including the electronic case report forms in Dutch and Swiss Standard German. This portal is based on the dedicated trial web portal from the TRUST trial to maximise the homogeneity of data and to allow for pre-planned pooled analysis of the results. Personal information used for trial logistics is collected and stored in a separate electronic study database in accordance with legal and ethical requirements.

Data validation checks give study personnel immediate feedback on missing or out of range values. Logic checks reduce the possibilities of entering invalid data. Database validation checks are run routinely and are tracked and escalated as appropriate. Data will be locked at the end of the study according to preregistered lockdown procedures by the data centre. The data centre will provide the independent data monitoring committee (IDMC) and the authorities with (annual) safety reports on the Data.

Outcomes

At 6–8 weeks we expect most patients allocated to levothyroxine to be biochemically euthyroid, and at this time point short-term improvements (such as in thyroid-related quality of life) will be assessed. By 1 year the medium-term effects of levothyroxine treatment should emerge (such as muscle function). The long-term effects of treatment of SCH will be determined by assessment over the full course of the study, with a mean of 2 years treatment duration.

In the screening phase, results from TSH and fT4 tests, exclusion criteria, informed consent for the screening phase of the study, informed consent for the trial phase of the study are obtained by the study nurses.

During the baseline phase of the study the following data are recorded:

- Participant characteristics: age, sex, ethnicity, information on alcohol and tobacco use, height.
- Any clinical changes that would violate the inclusion or exclusion criteria
- Concomitant drugs used: prescribed medication, over-the-counter non-steroidal anti-inflammatory drugs and aspirin
- History of disease: Cardiovascular disease including history of ischaemic heart disease (angina pectoris or previous myocardial infarction), cerebrovascular disease (ischaemic stroke, transient ischaemic attack) or peripheral vascular disease (intermittent claudication), or any revascularisation procedure for ischaemic vascular disease. History of atrial fibrillation, epilepsy, hypertension, diabetes mellitus or osteoporosis.

- Single lead ECG: to check for atrial fibrillation.
- Cognitive function: Mini-mental state examination (MMSE [11]) score as an indicator of general cognitive function. This will not be used as an outcome measure due to insensitivity to change during the trial.
- Home support services: (e.g. home help, meals-on-wheels, district nursing) and home circumstances (e.g. living alone, co-habiting, standard or sheltered housing, or entry to care home)

Primary study endpoints

The main study primary endpoints are mean change from baseline scores in thyroid-related quality of life and symptom burden assessed using the hypothyroid symptoms scale score and tiredness symptoms scale score on the thyroid-related quality of life patient-reported outcome (ThyPRO) [12] at 12 months after recruitment. The primary analyses will be done in the 80 years and over group (IEMO and TRUST participants). The results will be compared through subgroup analysis with those in the 79 years and under group (TRUST participants) as a secondary analysis. The ThyPRO is an 85-item patient-reported outcome measure, evaluating symptoms, well-being and function on 85 items summarised in 14 scales, ranging 0–100, with higher scores representing more symptoms or impact of disease. For this study three scales with 19 items are evaluated: Tiredness, Hypothyroid physical symptoms and Hyperthyroid physical symptoms.

Secondary study endpoints

- Generic quality of life: EuroQOL EQ-5D-3 L [13] at baseline, 6–8 weeks, 12 months and final follow up.
- Thyroid-related quality of life ThyPRO [12] at baseline, 6–8 weeks and at final follow-up.
- Thyroid-related quality of life: ThyPRO-39 [14] recorded at final follow-up (additional 28 questions).
- Executive cognitive function: Letter Digit Coding Test [LDCT] [15] at baseline and final follow-up.
- Handgrip strength: Jamar hand dynamometer (best of 3 measures in dominant hand) at baseline, 12 months and final follow up.
- Functional ability: Activities of Daily Living (Barthel Index [BI] [16,17]), Instrumental Activities of Daily Living (Older Americans Resources and Services [OARS] [18]), 6-m gait speed [19], independent living status and falls questionnaire at baseline and final follow up.
- Blood pressure: systolic and diastolic measured at baseline, 12 months and final follow up
- Height, weight, waist circumference and body mass index: recorded at baseline, 12 months and final follow up

- Mortality: all-cause and cardiovascular are requested through national mortality registries
- Fatal and non-fatal cardiovascular events: including acute myocardial infarction, stroke, amputations for peripheral vascular disease and revascularisations for atherosclerotic vascular disease (including for acute coronary syndrome and heart failure hospitalisations).

Additional measurements

- Treatment satisfaction with trial medication: Treatment Satisfaction Questionnaire for Medication vII (TSQM [20]) and desire of post-trial medication continuation recorded at final follow up.
- Arthritis: data regarding joints, skeletal functioning and arthritis are recorded through an arthritis questionnaire at final follow up.
- Haemoglobin: measured on a full blood count at baseline and 12 months.

See Table 1 for detailed schedule of assessments.

Safety

Full details of all Serious Adverse Events (SAEs), Adverse Events (AEs) of special interest (atrial fibrillation, heart failure, fractures, new diagnosis of osteoporosis), study treatment withdrawals and ThyPRO hyperthyroid symptoms are recorded at all visits and telephone contacts. Participants and GPs have 24-h access to an emergency trial phone number operated by a certified physician for the reporting of SAEs.

Biobank

Blood samples for the IEMO biobank are collected at baseline (40 ml venous blood) and at 12 months (10 ml venous blood). The following 19 aliquots (0.75 ml each) are stored per participant at baseline: 3 EDTA plasma, 1 whole blood, 2 citrated plasma, 1 NaF plasma, 1 buffy coat, 3 heparin plasma, and 8 serum aliquots. The 12 months bloods are stored in four serum 0.75 ml aliquots per participant.

Analyses in the IEMO biobank will be performed in combination with the TRUST biobank. Both biobanks are organised by the same biobank committee. The IEMO biobank will be stored at the Department of Clinical Chemistry of Leiden University Medical Center (LUMC), the Netherlands. The biobank consists of all plasma, serum, and DNA material of all randomised IEMO participants that provide consent for storing biobank material. The Department of Clinical Chemistry of the LUMC is fully accredited (EN ISO 15189:2012) by the Dutch Accreditation Council. The Biobank adheres to all necessary quality assurance standards and legal guidelines.

Sample size calculation

The total number of participants in all published trials on SCH before 2017 is 450 across 12 studies, including only a small number of older people and very heterogeneous endpoints across studies. We aim to study endpoints that are of particular relevance for the oldest old, including endpoints in those with considerable comorbidity.

Originally, the IEMO 80-plus thyroid trial had set out to analyse 450 participants with SCH aged 80 years and over. Additionally, a pre-planned pooled analysis of 900 participants was agreed upon, of which 450 were recruited directly through this study and a subset over the age of 80 years from the TRUST trial would add another 450 participants, to further increase the statistical power to detect significant changes in this subgroup. The power calculations were based on two main study endpoints:

1. Fatal and non-fatal cardiovascular events.
2. Change in thyroid-related quality of life (ThyPRO Tiredness and Hypothyroid physical symptoms).

Due to several limiting factors including delays in starting the studies, caused by difficulties procuring study medication and matching placebos, it proved impossible to reach this number, similar to the experiences in the TRUST trial [10]. Therefore, in 2015, revised power calculations were proposed (study protocol amendment 8, 04/06/2015) and accepted by the funding agent, sponsor, medical ethical committee (15/07/15) and competent authority (03/07/2015). These revisions detailed the change of primary study endpoint cardiovascular events into a secondary study outcome, accepting the possibility of being underpowered to answer this secondary endpoint. This allowed the power calculations to be revised according to the remaining primary outcome thyroid-related quality of life.

The resulting revised sample-size calculation is based on the pre-planned pooled analysis of one of the co-primary endpoints of thyroid-related quality of life (ThyPRO Hypothyroid physical symptoms and Tiredness scale score). According to previous studies applying the ThyPRO, a study should be adequately powered for at least a difference of 9 points to be clinically meaningful. Using an expected standard deviation of the difference of 26 [21] and a power of 80%, 132 participants are required per trial group adding to a total of 264 participants to be included in the combined 80-plus analyses. For all secondary continuous endpoints this sample size is deemed large enough to provide statistically robust results. For the secondary endpoints on cardiovascular events and mortality the possibility of being underpowered is accepted.

Over a recruitment period of almost 3 years the TRUST trial recruited 737 participants to the trial of which 146 participants were aged 80 and over. Assuming 10% loss to follow-up in

both trials a projected 145 additional participants will be recruited in the IEMO trial. The follow up phase of the trial is expected to be complete in May 2018 with one additional month of SAE recording.

Data analysis

The data centre (Robertson Centre for Biostatistics, Glasgow, ISO 9001/2008 certified) is responsible for writing, implementing and revising a statistical analysis plan that is agreed upon before locking the study database and will have full access to the final study database for the planned analyses. A copy of the statistical analysis plan is appended to this manuscript as Additional file 1. All analyses are based on a modified intention-to-treat principle and the primary time-point for analysis is after 12 months of treatment. The main analyses will be based on the combined IEMO and TRUST 80-plus participants (n = 291).

Analyses will be presented separately for:

- the IEMO 80-plus participant cohort (n = 145)
- the TRUST 80-plus participant subset (n = 146)
- the combined IEMO and TRUST 80-plus participants compared with the TRUST 80-minus participants (n = 291 vs n = 591)

Summary information for all participants and between the treatment groups will be made available. Similar to the TRUST trial [10], continuous variables measured at baseline and follow-up will be analysed at each time point comparing treatment groups adjusting for stratification variables and baseline levels of the same variable using analysis of covariance. Additionally, repeated measures regression analysis will be performed with regards to the primary time-point and final assessment for each participant. For calculating ThyPRO scores, raw total scores containing valid missing items will be scaled to maintain the maximum possible score. Clinical outcome data will be analysed using time-to-first-event Cox proportional hazards regression analysis in models that contain the randomised treatment allocation and stratification variables as covariates. Treatment effect will be analysed using the Wald-test and corresponding point estimates and 95% confidence intervals for the hazard ratio for treatment will be estimated. The assumption of proportionality of hazards will be tested.

Analysis of the primary outcomes will be performed in the modified intention to treat (ITT) population, based on participants with data available on the outcome of interest. The ITT population will be used for analyses on efficacy and safety. In addition, analyses using mixed effects models and multiple imputations will be used for sensitivity analysis. The per protocol population will also be used for all primary and secondary outcomes as exploratory analyses.

Owing to the intended similarities in study design between the IEMO 80-plus thyroid trial and the TRUST trial, the data allow for a pooled subgroup analysis of the TRUST and IEMO 80-plus participants compared with the TRUST 80-minus participants. Outcome differences between these groups will highlight the additional clinical merits or adverse effects of levothyroxine replacement therapy for older participants aged 80 and over.

Other pre-planned subgroup analyses include: baseline TSH in two groups (< 10/ ≥ 10 mIU/L) or in three groups (< 7/7–9.99/ ≥ 10 mIU/L), sex (male/female). However, we accept that our study will be underpowered for some of the smaller subgroups, such as male participants, TSH above 10.0 and below 19.9 mIU/L. We should however have sufficient statistical power in the combined analysis to detect beneficial effects in the larger or dominant subgroups, such as female and TSH in the range above 4.6 and below 10.0 mIU/L.

Monitoring and committees

To secure the highest quality of participant care and safety, the careful titration algorithm avoids the possibility of prolonged periods of levothyroxine over-replacement. Similarly, the system guards against participants developing overt hypothyroidism that might require open-label levothyroxine use.

All SAEs, AEs and AEs of special interest are recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and the study protocol. All events are followed up until resolution or stabilization occurs, and are assessed for seriousness, expectedness and causality by the chief investigator. Serious adverse events are reported to the sponsor by thorough recording in the eCRF and to the local accredited Medical Ethics Committee and competent authority. Annually and at the end of the trial 100% study monitoring visits are conducted by independent clinical research associates, in accordance with the Netherlands Federation of University Medical Centres' report 'Kwaliteitsborging van Mensgebonden onderzoek'. All important decisions made leading to protocol modifications are communicated to all relevant parties, including the trial registry, ethical committees and competent authorities.

All main decisions for the study were made by the steering group. Its members are: Dr. Simon P Mooijaart, Dr. Jacobijn Gussekloo, Dr. Olaf M Dekkers, Dr. Jan Smit, Dr. J Wouter Jukema, Dr. Anton. JM de Craen (Leiden, the Netherlands, Deceased).

Each national site was supervised by a local organising committee and Principal Investigator. For the Netherlands the organising committee was: Dr. Simon P Mooijaart (PI), Dr. Rosalinde KE Poortvliet, Dr. Iris Postmus, Robert S Du Puy, MSc, Professor Robin. P Peeters, Professor

Bruce. HR Wolffenbuttel and Dr. Barbara. C van Munster. For Switzerland the organising committee was: Professor N Rodondi (PI) and Dr. Manuel Blum,

An Independent Data Monitoring Committee (IDMC) assesses safety data in order to protect the ethical and safety interests of the participants recruited into the study, while safeguarding, as far as possible, the scientific validity of the study. The IDMC reviews annual safety and efficacy data and may request additional data if considered necessary. The IDMC meets at least once a year and is composed of medical experts and a biostatistician without any involvement in the study as investigators or as study participant care physicians. The committee is empowered to make a recommendation on early stopping when there is overwhelming evidence of benefit for the primary outcome or when it considers there is adequate evidence of harm. The IDMC members are: Professor Gary Ford (Chair; Chief Executive Officer of the Oxford Academic Health Science Network, Oxford), Professor Thompson G Robinson (University Hospitals of Leicester NHS Trust, Department of Cardiovascular Sciences, Leicester Royal Infirmary, Leicester), Professor Colin Dayan (Institute of Molecular and Experimental Medicine, Cardiff University School of Medicine, Heath Park, Cardiff), Professor Kathleen Bennett (Department of Pharmacology and Therapeutics, Trinity Centre for Health Sciences, St James's Hospital, Dublin).

A study Endpoint Committee, blinded to treatment allocation, provides independent and unbiased review of clinical endpoint events which occur during the study, ensures unified and unambiguous events evaluation practices across the study and compensates for regional diversity in medical practice at the site of endpoint evaluation and classification. All causes of death, stroke, myocardial infarction and heart failure hospitalisations are potential endpoints to be reviewed on the data supplied through the eCRF and if necessary, acquired source documentation. The Endpoint Committee members are: Professor Peter Langhorne (Chair; Professor of Stroke Care, Institute of Cardiovascular and Medical Sciences, University of Glasgow), Professor J Wouter Jukema (Vice-chair; Professor of Cardiology, Leiden University Medical Center, The Netherlands), Dr. Tinh-Hai Collet (Department of Ambulatory Care and Community Medicine, University of Lausanne, Switzerland), Professor Olaf M Dekkers Leiden University Medical Center, The Netherlands) and Dr. Anne Marie O'Flynn (Department of Epidemiology and Public Health, UCC, Ireland).

A TRUST/IEMO Biobank committee supervises the storage and analysis of the biobank samples. Members are: Professor Patricia M Kearney, Dr. H Anette van Dorland (Bern, Switzerland), Dr. Wendy PJ den Elzen.

Each national study site is supervised by a local sponsor, responsible for the oversight of the clinical trial and supplying proper insurance to cover any liabilities during and after the trial

arising from trial conduct and participation. The sponsors are not involved in the preparation, or approval of any scientific outputs.

Dissemination

This study is well suited to promote effective dissemination of the results and implications. Arrangements regarding sharing of data and joint publication are laid down in a Memorandum of Understanding between the TRUST trial and IEMO 80-plus thyroid trial project group. Due to its role as a knowledge centre with an education and research program in the field of ageing, vitality and geriatric medicine, the Leiden Academy on Vitality and Ageing is well placed to play a coordinating role in the dissemination activities. Schildklier Organisatie Nederland, the patient advocacy group, will closely collaborate with the study team to help align the study outputs with the patients and public need.

The Institute for Evidence-based Medicine in Old Age (the Netherlands) is ideally placed to ensure that the results of the study are considered by relevant professionals, and will be included in the leading clinical guidelines. In cooperation with the Cochrane collaboration the results of the trial will be offered for the update of the Cochrane systematic review of treatment of subclinical hypothyroidism, allowing for independent scientific interpretation, placing results in context and maximising understanding of the implication of the trial.

To comply with the general social responsibility associated with clinical research, the trial results will be proactively disseminated to the general public and key public health stakeholders through established media networks.

DISCUSSION

In the latest Cochrane review of levothyroxine replacement therapy for SCH (12 studies, only 491 participants in total) most studies excluded those who suffered from multimorbidity, none of the studies reported on oldest old separately and two trials excluded those over the age of 80 years.[22] Robust evidence for the potential clinical merits or adverse effects in 80-plus persons with SCH is greatly needed to help guide clinical practice.

The IEMO 80-plus thyroid trial is a representative randomised controlled trial on levothyroxine treatment for SCH, with representative 80-plus persons and a wide range of characteristics and morbidities, studying end-points that are relevant to the older population and clinical practice. The combined analysis of participants in the IEMO 80-plus thyroid trial with those aged over 80 who participated in the TRUST trial will provide the largest experimental evi-

dence base on the multimodal effects of levothyroxine treatment in 80-plus persons to date. Trial results are expected to be publicly disseminated in the fall of 2018.

Online supplemental material

https://bmcendocrdisord.biomedcentral.com/articles/10.1186/s12902-018-0285-8

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