# Supplementary Online Content

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**Supplement 1.** Trial protocol

This supplementary material has been provided by the authors to give readers additional information about their work.

# RESEARCH PROTOCOL

IEMO 80-plus thyroid trial

**June 14th 2016**

**Version 9**

## PROTOCOL TITLE 'IEMO 80-plus thyroid trial'

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## LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

| | |
|---|---|
| **ABR** | **ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)** |
| **ADL** | **Activities of daily living** |
| **AE** | **Adverse Event** |
| **AF** | **Atrial fibrillation** |
| **ALDS** | **Amsterdam Linear Disability Scale** |
| **AR** | **Adverse Reaction** |
| **BI** | **Barthel Index** |
| **BMI** | **Body Mass Index** |
| **CA** | **Competent Authority** |
| **CCMO** | **Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek** |
| **CHD** | **Coronary Heart Disease** |
| **CI** | **Chief investigator** |
| **CRF** | **Case report form** |
| **CV** | **Curriculum Vitae** |
| **CTIMP** | **Clinical Trial of Investigational Medicinal Product** |
| **DSMB** | **Data Safety Monitoring Board** |
| **DSST** | **Digital Symbol Substitution test** |
| **EC** | **Ethics Committee** |
| **ECG** | **Electrocardiogram** |
| **eCRF** | **Electronic case report form** |
| **EU** | **European Union** |
| **EudraCT** | **European drug regulatory affairs Clinical Trials** |
| **GCP** | **Good Clinical Practice** |
| **GP** | **General Practitioner** |
| **IB** | **Investigator's Brochure** |
| **IC** | **Informed Consent** |
| **ICH GCP** | **International Conference on Harmonization of Good Clinical Practice** |

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| **IDMC** | **Independent data monitoring committee** |
| **IMP** | **Investigational Medicinal Product** |
| **IMPD** | **Investigational Medicinal Product Dossier** |
| **HR** | **Hazard ratio** |
| **METC** | **Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)** |
| **MMSE** | **Mini mental state** |
| **(S)AE** | **(Serious) Adverse Event** |
| **NYHA** | **New York Heart Association** |
| **OARS** | **Older American resources and services measure of activities of daily living** |
| **PI** | **Principal investigator** |
| **PROSPER** | **Prospective study of pravastatin in the elderly at risk** |
| **QoL** | **Quality of life** |
| **RCT** | **Randomised controlled trial** |
| **SAE** | **Serious adverse event** |
| **SAP** | **Statistical analysis plan** |
| **SAR** | **Serious adverse reaction** |
| **SCH** | **Subclinical hypothyroidism** |
| **SOP** | **Standard operating procedure** |
| **SPC** | **Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)** |
| **Sponsor** | **The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.** |
| **SSAR** | **Serious suspected adverse reaction** |
| **SUSAR** | **Suspected Unexpected Serious Adverse Reaction** |
| **$T_4$** | **Levothyroxine** |
| **ThyPRO** | **The Thyroid-specific Quality of Life patient-reported outcome measure** |

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| **TSH** | **Thyroid stimulating hormone** |
| **ULN** | **Upper limit of normal** |
| **Wbp** | **Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)** |
| **WMO** | **Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen** |

## SUMMARY

**Rationale:** Subclinical hypothyroidism (SCH) is a common condition (8-18%) among older men and women. Although by definition SCH comprises biochemically mild thyroid hormone deficiency, 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. This is especially the case for the oldest old, because observational studies are conflicting and very few oldest old are included in clinical trials, although they have the highest prevalence of SCH and its potentially related symptoms and diseases. Therefore, the aim of this study is to test the efficacy of thyroxine replacement for subclinical hypothyroidism (SCH) in the oldest old adults to provide the necessary evidence to properly inform best practice for treatment of SCH in the oldest old.

**Objectives**: To test the efficacy of thyroxine replacement for subclinical hypothyroidism (SCH) in the oldest old (i.e. over 80 years old).

**Primary Objective:**

To determine multi-modal effects (cognitive; musculoskeletal; quality of life and cardiovascular) of Levothyroxine treatment for SCH in the oldest old.

**Secondary objectives:**

1) To determine adverse effects associated with SCH treatment with particular focus on arrhythmia and heart failure

2) To build experience in tailoring a randomised controlled trial to the oldest old participants

3) To store biomaterials, to be used in future research into causes and mechanisms of health, disease and disability in later life.

**Study design:** Randomised double-blind placebo-controlled parallel group trial of Levothyroxine for older people with subclinical hypothyroidism.

**Study population:** 145 people.

**Study centres:** Leiden University Medical Center (project leader) and University Hospital Bern (Switzerland).

**Inclusion criteria:** Community-dwelling subjects aged ≥80 years with SCH, diagnosed on the basis of elevated TSH plus free thyroxine within the laboratory reference range, measured on a minimum of two occasions at least 3 months apart.

**Exclusion criteria:**

- Subjects currently on (anti)thyroid drugs, amiodarone or lithium
- Recent thyroid surgery or radio-iodine therapy
- Grade IV NYHA heart failure
- Prior clinical diagnosis of dementia
- Recent hospitalisation for major illness
- Recent acute coronary syndrome

- Acute myocarditis or acute pancarditis
- Untreated adrenal insufficiency or adrenal disorder
- Terminal illness
- Patients known to have rare hereditary problem of galactose intolerance
- 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

**Screening:** Potential subjects will be identified through clinical laboratory databases as having biochemical features consistent with SCH (Thyroid stimulating hormone [TSH] of ≥4.6 and ≤19.9 mU/L plus free thyroxine levels within the laboratory reference range).
**Randomisation:** Randomisation (1:1 thyroxine versus placebo) will be stratified by site, gender and starting dose of Levothyroxine and carried out using the method of randomly permuted blocks.
**Intervention:** Oral Levothyroxine 50 µg daily (reduced to 25 mcg daily in subjects < 50 kg body weight or if known coronary heart disease) versus matching placebo. At baseline the dose will be changed according to the serum TSH level measured at 6-8 weeks after starting medication and after each dose change. Dose titration will be according to a predefined dosing schedule.
**Duration of treatment**: minimum 1 years, maximum 4 years, on average 2 years.
**Main study parameters/endpoints:**
1) Change in disease specific QOL and symptom burden
2) Fatal and non-fatal cardiovascular events
3) General QOL
4) Handgrip strength
5) Cognitive function
6) Total mortality and cardiovascular mortality
7) Functional ability (basic and extended activities of daily living; gait speed)
8) Hemoglobin

**Statistical analysis:** The participants of the present project will be included in a pre-planned combined analysis with the international TRUST consortium, of which the LUMC is the Dutch member (protocol number P12.203), who includes a total number of 738 participants over the age of 65 years. The present project adds 145 80-plus year old participants to perform an adequately powered sub-group analysis in the over eighties age group. The main analysis will be the association between thyroid specific quality of life and treatment in the combined study population of IEMO and the 80-plus participants of TRUST. Treatment effects will be assessed using analysis of covariance (ANCOVA) adjusting for gender and baseline levels of the same variable. To assess for associations with cardiovascular events, time to first event Cox regression analysis are used stratified by gender in models containing the randomised treatment allocation as a covariate (intention-to-treat). Tests of treatment effect will be based on the Wald test and corresponding point estimates and 95% confidence intervals for the hazard ratio for treatment will be calculated. The assumption of proportionality of hazards will

be tested. Additional end points relevant to older people will be assessed for the present study alone and in combination with the 80-plus participants in TRUST.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:**

Adverse events (atrial fibrillation, heart failure and fractures in particular) are likely to occur only in the context of over replacement of Levothyroxine. Our dose titration scheme and study processes of careful monitoring of thyroid function tests are designed to ensure we avoid prolonged periods of thyroid hormone excess.

For the group allocated to placebo, there is risk of developing overt clinical hypothyroidism; however, our study processes of careful monitoring of thyroid function tests are designed to avoid this scenario. Specific measures are taken to minimise the burden and risk for the oldest old, such as home visits, and more frequent face-to-face contact.

# 1. INTRODUCTION AND RATIONALE

## 1.1 Background

Subclinical hypothyroidism (SCH) is a common finding in older people across Europe. It is defined as an elevated serum thyroid stimulating hormone (TSH) with normal circulating thyroid hormone levels (1). The prevalence is around 8% in adult women and 3% in men, but the proportion of the population affected rises markedly with increasing age. Approximately 8-18% of adults over 65 years have SCH, prevalence being higher among women than men (2-4). SCH is a likely contributor to multiple problems in older age. From a biological point of view thyroid hormone has multiple pleiotropic effects, acting as an essential regulatory factor in numerous physiological systems, including the vascular tree and the heart, brain (including cognition and mood), skeletal muscle and bone. Health consequences of overt thyroid disease range from mild non-specific symptoms such as tiredness (5) that can adversely affect quality of life, to coronary heart disease (CHD).

There are data to suggest adverse health effects of SCH. The most convincing epidemiological associations of SCH with poor health are with CHD events and deaths. We performed an individual patient data analysis from over 50,000 subjects in 11 prospective cohorts (3); the age and sex-adjusted hazard ratio (HR) for CHD mortality was 1.09 (95% CI 0.91-1.30) for a TSH of 4.5-6.9 mU/L, 1.42 (1.03-1.95) for a TSH of 7.0-9.9 mU/ L and 1.58 (1.10-2.27) for a TSH of 10.0-19.9 mU/ L; corresponding HRs for CHD events were 1.00 (0.86-1.18), 1.17 (0.96-1.43) and 1.89 (1.28-2.80) respectively. Interestingly, in one study in the oldest old (85-plus year old), subclinical hypothyroidism associates with better survival compared to euthyroidism (6), suggesting a protective instead of detrimental effect in the oldest old. However, these observational results should be interpreted with caution. Other risk factors, such as high blood pressure and high cholesterol levels, also associate with better survival in the highest age group (7-9) but treatment of the risk factors does in fact improve survival also in this age group (10,11). Furthermore, in the meta-analysis the association with better survival was not reported in the pooled analysis of 80-plus year olds, nor was there a significant interaction with age, of the cardiovascular mortality risk that associated with subclinical hypothyroidism (3).

There is considerable symptom burden in hypothyroid states. Patients with overt hypothyroidism are most bothered by hair problems, weight gain, depression, fatigue and feeling cold. Of these symptoms, depression, feeling cold, and tiredness are significantly correlated with their ratings of poorer present quality of life (12). Although by definition SCH comprises biochemically mild thyroid hormone deficiency, it is a possible contributor to multiple problems in older age. Subjects with subclinical hypothyroidism do not have the full symptom cluster of overt hypothyroidism, however they often report non-specific symptoms such as tiredness (5). Health-related quality of life (as measured by the Short Form-36 questionnaire) is reduced in subjects with SCH compared to euthyroid controls (13). Muscle symptoms such as cramps, weakness and myalgia are more common in SCH than in euthyroid controls (14). SCH has also been linked with adverse psychiatric outcomes (including cognition and mood disorder (15)) although data are inconsistent (5) and

associations are less strong than for cardiovascular disease. Reduced exercise capacity in SCH may be due to impaired skeletal muscle function (14) and increased oxygen requirements of exercise (16) SCH has also been associated with systolic and diastolic cardiac dysfunction and with an increased incidence of clinical heart failure (17). These adverse effects are likely to reduce maximal exercise capacity, and might have important effects in the elderly on abilities to perform activities of daily living, although reduced functional capacity in SCH has not been demonstrated in epidemiological studies (18).

Evidence is lacking about the benefits of Levothyroxine replacement in the elderly with SCH, as no large randomised clinical trials (RCT) on the full range of relevant clinical outcomes have been performed (4). The indications for screening and threshold TSH for treatment of SCH are areas of clinical controversy. The Cochrane systematic review of Levothyroxine replacement for SCH summarises the evidence from RCTs up to 2006 (4). It concluded that there was some evidence for improved cardiac function and blood lipids with Levothyroxine replacement, but a lack of data for improved survival, reduced cardiovascular morbidity or improved health-related quality of life; data were available for only a total of 350 patients in twelve RCTs, often of short duration (range 6-14 months). The review explicitly recommends that future "studies should also analyse patients older than 85 years of age"

Thus there is the potential for multisystem benefits from treatment of SCH with Levothyroxine. The high prevalence of SCH in later life gives the prospect that the population attributable benefit of treatment could be large. However, definitive evidence from RCTs is lacking.

It is common that older individuals with comorbid conditions are excluded from RCTs. In a meta-analysis of RCTs on Acute Coronary Syndromes (ACS) for instance, of 14% participants of a total of over seventy thousand participants were over the age of 75 years, whereas of the patients who suffer from ACS, 42% belongs to this older age group (19). This is a problem, because the clinical guidelines that are based on these RCTs are used to treat the older population with multi-morbidity, resulting in abundant treatment (20). Because of the poor generalizability of trial results or the limited relevance of the end point they study for the older population, it is questionable whether the treatment of older individuals meets the standard of evidence-based medicine.

### 1.2 Study rationale - hypothesis

There is reason to believe that treatment of SCH in older adults may have multi-modal health benefits. However definitive trial evidence is lacking. Strong recommendation was made in the Cochrane review of 2007 (4), by international experts (21) and by the US Preventive Services Task Force (22) for further RCTs in larger groups and with longer follow-up for clinically relevant endpoints, including in the oldest old.

To definitively solve this clinical uncertainty, we propose to conduct an RCT with power to detect clinically worthwhile benefits from Levothyroxine replacement for SCH in the oldest

old. Critical elements of the study design include inclusion of participants over 80 years of age, longer follow-up than previous RCTs, recruitment of subjects with persisting SCH (excluding those in whom it is a temporary phenomenon, who are less likely to benefit), and clinically important outcomes. We will recruit subjects with a wide range of characteristics (gender, TSH levels) to allow pre-planned subgroup analysis and potential targeting of treatment to subjects with specific characteristics. We also propose a wide range of outcome assessments reflecting the potential multi-system effects of Levothyroxine replacement for SCH.

We propose a randomised double-blind placebo-controlled parallel group trial of Levothyroxine for older people with SCH. We propose a pragmatic study that studies relevant end points in representative elderly patients, resulting in data that are generalizable and therefore will directly influence clinical practice. This includes a study population with that is representative for the older population, a target TSH within the laboratory reference range (reflecting common clinical practice) and simple inclusion criteria (for example not including thyroid auto-antibodies). We have selected a wide range of clinical endpoints to reflect the potential multi-system and multi-modal effects of thyroid hormone. The study (reporting) will conform to CONSORT guidelines (www.consort-statement.org).

The trial will comprise one of the largest RCTs in older age ever performed, concentrating on participants over 80 years old in the presence of comorbid conditions. The present trial sets an example how to perform a clinical trial in older age, studying representative older people and end-points that are relevant to the older population. The trial can serve as a template for future trials in old age. The national infrastructure that is set up as well as the knowledge and experience with optimizing the trial for 80-plus year old participants is a valuable asset for future trials. The Institute for Evidence-based Medicine in Old Age aims to consolidate this infrastructure and expertise and initiate and coordinate multiple trials among older patients in the future. With the built-up national network, the Netherlands is ideally placed to take the lead in generating large amounts of clinical evidence and improve the healthcare for older people throughout the world.

## 2. OBJECTIVES

### 2.1 Main study objectives

There are four main study objectives:

1. Does Levothyroxine treatment for SCH give multi-modal benefits for the oldest old people with SCH?

2. Are benefits seen across a wide range of outcomes, including improving health-related quality of life, muscle function, cognition and prevention of cardiovascular disease?

3. Are benefits seen in specific subgroups of oldest old people with SCH, including women, and those with mild degrees of SCH (TSH 4.6-10 mU/L)?

4. Are any benefits offset by adverse effects, such as atrial fibrillation or heart failure?

### 2.2 Additional study objectives

A. To obtain experience and expertise in performing a randomised controlled clinical trial in the oldest old and to build a national network to perform such a trial as a basis for future trials.
B. To store study samples, to be used in future research into causes and mechanisms of health, disease and disability in later life (this is not directly funded through this research application). The biomaterials will be maintained by the department of Clinical Chemistry of the LUMC and will be managed in line with all applicable and current regulations.

# 3. STUDY DESIGN

This is a randomised double-blind placebo-controlled parallel group trial of Levothyroxine for 145 older people with subclinical hypothyroidism. The trial will run over three years in the Leiden University Medical Centre (the Netherlands) and University Hospital Bern (Switzerland). We propose a minimum one year of follow-up, with a likely average of two years. A schedule of assessments and time points is provided in the Appendix. The Institute for Evidence-Based Medicine in Old Age will be the coordinator of the trial, with the LUMC as its formal legal representative.
This protocol is written for all 145 Dutch participants that will be recruited via the Dutch centre.
The protocol of the present study mirrors that of a European FP7 funded TRUST trial, of which the LUMC is the Dutch beneficiary (LUMC CME protocol number P12.203) and which recruitet 738 older participants over the age 65 years. Using identical protocols between the studies will allow for pre-planned pooled analyses on all end-points, which is of particular relevance for the 80-plus subgroup analysis. Furthermore, our will add to that a number of end points that are of particular interest for the oldest old.

# 4. STUDY POPULATION

## 4.1 Population (base)

The trial will recruit 145 community-dwelling patients aged ≥80 years with SCH, diagnosed on the basis of persistently elevated TSH levels, measured on a minimum of two occasions at least 3 months apart, over 3 years. Potential subjects will be identified from clinical laboratory databases as having biochemical features consistent with SCH. In total, 145 participants will be included in the study.

We have defined SCH as persistently elevated TSH levels (≥4.6 and ≤19.9 mU/L) and free thyroxine (fT4) in normal range measured on a minimum of two occasions at least 3 months apart. Given the epidemiology of SCH, we anticipate around two-thirds of subjects will be female.

We will aim for data to be gathered for over 95% of patients followed up for cardiovascular events and deaths, and over 90% for all other outcomes (including thyroid specific and general health-related quality of life, muscle strength and cognition).

## 4.2 Inclusion criteria

Community-dwelling patients aged ≥80 years with SCH.

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

### 4.3 Exclusion criteria

- Subjects currently on Levothyroxine or antithyroid medication (e.g. Carbimazole, methimazole, propylthiouracil, potassium percholate), 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 ore acute pancarditis
- Untreated adrenal insufficiency or adrenal disorder
- Terminal illness.
- Patients known to have rare hereditary problem of galactose intolerance.
- Subjects 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.

Atrial fibrillation (sustained or paroxysmal) will not be an exclusion criterion, as in itself this cardiac arrhythmia is not a contra-indication to Levothyroxine treatment. In addition, AF is a common finding in the studied age groups and exclusion of subjects with it would potentially compromise the generalizability of our results.

Adherence to treatment allocation: drop-ins (where subjects allocated to placebo are prescribed Levothyroxine) and drop outs (where subjects allocated to Levothyroxine stop this treatment) are each estimated at less than 5% at 1 year and less than 10% at the end of the study (mean 2 years follow-up).

### 4.4 Sample size calculation

The present power calculation is based on the progress of recruitment on June 1st 2015.

The total number of participants in all published trials on SCH to date is 350 across 12 studies, with few older people included and very heterogeneous end points across studies. We aim to include 145 participants of 80 years and older and study end points that are of particular relevance for the oldest old, including those in those with considerable comorbidity. We will analyze these participants in a pre-planned pooled analysis with the TRUST study of all participants aged 80 years and older.

As the trial aims to combine analyses with the TRUST study, samples size calculations were made based on the number of participants currently included in TRUST. Currently, in total 452 participants are included in TRUST of which 23% is over the age of 80 years (n=104). The inclusion of TRUST is running till end of 2015, with expectation of higher inclusion rates in the coming months. Based on the current number of participants the inclusion of minimal

184 more participants is expected, making a total of at least 636 participants of which 146 participants will be over the age of 80 years. (Update dec. 2015 – 738 participants included of which 146 aged >80 years). These participants over the age of 80 years will be added to the combined 80-plus year old subgroup analyses.

The main sample-size calculation is based on the co-primary endpoint, “Thyroid specific Quality of Life”. This endpoint will be assessed in both the “IEMO 80-plus thyroid trial” as the TRUST trial.

**Thyroid specific Quality of Life**

The thyroid specific Quality of Life is a self-reported questionnaire, rating symptoms on 83 items in 13 categories (29). Categories can be divided into three domains: tiredness, hypothyroidism and hyperthyroidism. Each of this domains scores can range from 0 to 100. In the table below we give several scenarios using different effect sizes of the treatment. According to the developer of the test (Torqil Watts) a study should be powered at least at a difference of 9 points to be clinical meaningful. Thus, to have a power of 80% at least 264 participants should be included in the combined 80-plus subgroup analyses together with the TRUST 80-plus participants. With a drop-out rate of 10%, the total number of patients to include is 291. IEMO will therefore include a minimum of 145 participants.

For all secondary endpoints the participants will contribute to the combined analysis of the TRUST and IEMO trials (expected total of 781 participants). The 12 randomized clinical trials on SCH to date investigated various patient groups regarding age of the participants and comorbidities and various endpoints. The total number of participants in these trials combined was 350. Therefore, the IEMO 80+ plus Thyroid study will largely contribute to the our understanding of the clinical practice in elderly with subclinical hypothyroidism in general, and in the oldest old in particular.

## 5. TREATMENT OF SUBJECTS

### 5.1 Investigational product/treatment

The investigational medicinal product will be Levothyroxine (T4) as tablet for oral administration.

Oral Levothyroxine is widely used as the sole treatment for overt hypothyroidism and is the obvious intervention to trial for subclinical hypothyroidism. The main possible alternative (or additional treatment) is tri-iodothyronine, however this short-acting hormone is less tried and tested and is likely to carry increased risk of adverse effects (particularly with over-replacement). It is therefore not an attractive option.

Levothyroxine will be compared with placebo. A mock titration will be performed in the placebo group (tablet, oral use) aiming for approximately the same frequency of dose changes as that likely to be required in the thyroxine-treated group.

# 6. INVESTIGATIONAL MEDICINAL PRODUCT

## 6.1 Name and description of investigational medicinal product(s)

The investigational medicinal product will be Levothyroxine (T4) as tablet for oral administration.

Each tablet will contain Levothyroxine Sodium anhydrous also known as thyroxine sodium. Matching placebo will also be produced.

### 6.1.1 Pharmacodynamic properties Levothyroxine

Levothyroxine is deiodinated in peripheral tissues to form triiodothyronine which is thought to be the active tissue form of thyroid hormone. Triiodothyronine has a rapid action but a shorter duration of activity than Levothyroxine. The chief action of Levothyroxine is to increase the rate of cell metabolism.

### 6.1.2 Pharmacokinetic properties Levothyroxine

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 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.

## 6.2 Summary of findings from non-clinical studies

See sIMPD and SmPC

## 6.3 Summary of findings from clinical studies

See sIMPD and SmPC

## 6.4 Summary of known and potential risks and benefits

Evidence is lacking about the benefits of Levothyroxine replacement in the elderly with SCH, as no large randomised clinical trials (RCT) on the full range of relevant clinical outcomes have been performed. However, potential for benefits from thyroxine includes prevention of cardiovascular disease, and improved quality of life, cognition, and muscle function.

Side-effects are usually indicative of excessive dosage and usually disappear on reduction of dosage or withdrawal of treatment for a few days. Such effects include:

- General: Headache, flushing, fever and sweating
- Immune system disorders: hypersensitivity reactions including rash, pruritus and oedema
- Metabolic: weight loss
- Nervous system: tremor, restlessness, excitability, insomnia.
- Rarely, seizures can occur in patients with a known history of epilepsy.
- Cardiac: anginal pain, cardiac arrythmias, palpitations, tachycardia
- Gastrointestinal: diarrhoea, vomiting
- Musculoskeletal and connective tissue: muscle cramps, muscle weakness.
- Reproductive: menstrual irregularities
- Fever, heat intolerance, transient hair loss in children, hypersensitivity reactions including rash, pruritus and oedema also reported.

### 6.5 Description and justification of route of administration and dosage

The daily dose of Levothyroxine used in all studies of treatment of SCH included in the Cochrane review ranged from 50-100 µg, with a mean dose in most studies of 50-70 µg/day. (4). There is no good evidence that starting with a dose lower than 50 µg improves tolerability or reduces risk of adverse effects, and there are no short-medium term differences in changes in heart rate or blood pressure between a low dose (25 µg) and replacement dose (50 µg) strategy of initiation of Levothyroxine. Full replacement doses of Levothyroxine for overt hypothyroidism are 1.6 µg / Kg body weight (approximating to 100 µg for a 70Kg individual). While such a dose can be used right from the start, even in older subjects, we have taken a cautious approach, and have chosen 50 µg daily as the initial dose of Levothyroxine in the IEMO 80-plus thyroid study. For those persons with a low body weight (i.e. below 50 kilograms) or a history of coronary heart disease (as evidenced by a history of previous myocardial infarction or angina pectoris), we will use a starting dose of 25 mcg.

We have chosen to set a target TSH of 0.4-4.6mU/L with thyroxine treatment, within the standard laboratory reference range. Some authorities have recommended a tighter target, e.g. 0.4-3.0mU/L, to try and ensure strict biochemical euthyroidism, although this remains controversial (30). We considered modifying our approach to adopt a narrower therapeutic target, but decided against this for the following reasons;

- There is no consensus about TSH target and no direct evidence that achieving a lower target TSH with thyroxine gives added therapeutic benefit in treating hypothyroidism.
- There were concerns about increased risk of over-treatment and potential adverse events (such as new-onset atrial fibrillation and heart failure; problems associated with subclinical hyperthyroidism in the PROSPER study cohort (31).
- More frequent therapeutic monitoring with thyroid function tests would be required to achieve these TSH levels while avoiding biochemical hyperthyroidism

- We would more reflect routine clinical practice as most primary and secondary care physicians in Europe accept a TSH within the laboratory reference range as evidence of adequate thyroxine dosing for hypothyroidism.

### 6.6 Dosages, dosage modifications and method of administration

The intervention will start with Levothyroxine 50 µg daily (reduced to 25 mcg in subjects <50 kg body weight or if known coronary heart disease - previous myocardial infarction or symptoms of angina pectoris) versus matching placebo for 6-8 weeks.

The dose will be changed according to the serum TSH level as follows; at 6-8 weeks a blood sample will be taken for serum TSH, with 3 possible actions;
1) TSH <0.4 mU/L; treatment dose 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 patients will have a further TSH check after 6-8 weeks; if TSH remains <0.4 mU/L patient will be withdrawn from randomised treatment.
2) TSH >0.4 and <4.6 mU/L; no change to the treatment dose; patient to be reviewed at 12 months.
3) TSH remains elevated (>4.6mU/L); additional 25 micrograms Levothyroxine, 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; further TSH check after 6-8 weeks repeating this cycle one more time; if TSH <0.4 mU/L; treatment dose reduced by 25 micrograms, with further repeat at 6-8 weeks as per 1) above. If TSH remains elevated (>4.6mU/L); additional 25 micrograms Levothyroxine, giving a total daily dose of 100 micrograms Levothyroxine for those starting on 50 micrograms, or a total daily dose of 75 micrograms Levothyroxine for those starting on 25 micrograms; after these dose changes a further TSH check will be performed after 6-8 weeks, and if TSH <0.4 mU/L; treatment dose reduced by 25 micrograms, with further repeat at 6-8 weeks as above. This strategy is designed to avoid over-replacement of levothyroxine.

The above process (but with only a single up-titration) will be repeated at 12 months then annually with further dose increments of 25 micrograms if TSH elevated (>4.6 mU/L), and 25 micrograms dose reductions if TSH suppressed (<0.4 mU/L). For all patients who have a dose increase (including at annual review) further TSH check will be performed after 6-8 weeks, and if TSH <0.4 mU/L; treatment dose reduced by 25 micrograms, with further repeat at 6-8 weeks as above. If TSH remains <0.4 mU/L on 2 consecutive measurements (6-8 weeks apart) the patient will be withdrawn from randomised treatment.

Therefore in summary there will be a maximum of 2 up-titrations of dose at the start

of the study (each at 6-8 week intervals), and a maximum of only 1 up-titration at each annual review. If a patient is found to have a suppressed TSH level, the dose of Levothyroxine will be reduced by 25 micrograms, and they will be required to attend for repeat TSH measurement in 6-8 weeks to confirm that their TSH is no longer suppressed.

A mock titration will be performed in the placebo group aiming for approximately the same frequency as that likely to be required in the Levothyroxine-treated group. We will adopt an adaptive schedule, in which the data centre will allocate the same proportion of placebo patients to have dose adjustment (up and down) as prove to be required in the Levothyroxine group. This will ensure that the burden of assessment, and number of tablets to be taken, will be the same in both the Levothyroxine and placebo groups. This will also ensure that the clinical investigators will remain blind to treatment allocation.

Where a proposed up-titration of levothyroxine (or placebo) is thought to be clinically inappropriate (eg known non-adherence to IMP, recent major illness) the algorithm will be 'over-ridden' and the patient will not be up-titrated.

The maximum possible dose of Levothyroxine that will be prescribed is 150 micrograms. Patients will be advised to take their prescribed dose once daily in the morning before breakfast.

### 6.7 Preparation and labelling of Investigational Medicinal Product

See sIMPD.
A QP batch release will be available for all ""IEMO 80-plus thyroid trial"" IMP's. There is no requirement to submit the batch analysis for the euthyrox product as this has a marketing authorisation in the EU.

### 6.8 Formulation and Source of Drug

The investigational medicinal products in this study are Levothyroxine 25 and 50 microgram tablets and matched placebo for oral use. The tablets will be white and round in shape with the strength imprinted on the active and matched placebo tables. All IMPs will be manufactured in accordance with Good Manufacturing Practice with the final Qualified Person release and shipment provided by Mawdsleys UK to study sites.

### 6.9 Storage and Stability

The levothyroxine/placebo tablets must be stored in the original container at room temperature below 25$^{o}$C in a secure location. A shelf life of 36 months will be assigned. The

study medication must only be used in accordance with the trial protocol and only for subjects enrolled into the study.

## 6.10 Drug Procurement

Study medication supplies will only be released to study site once all the appropriate regulatory and governance approvals are in place. The study web portal will be used to track drug use, shipment and receipt.

### 6.10.1 Packing and Distribution

The medication will be supplied in blister strips (28 tablets per blister), and packaged as 4 blister strips per cardboard carton for patient distribution. All investigational medicinal products will be packaged in such a way as to maintain the study blind. All study medication will be labeled in accordance with national regulatory requirements and will have a unique pack identifier with labeling including randomisation code as supplied by the data centre. Supplies will be distributed to study centres in each study location.

Detailed written information will be available to sites on study drug management including the supply of medication via post (if applicable).

The Dutch trial medication will be sent and stored in the LUMC trial pharmacy (trial manager Mrs Linda van der Hulst).

### 6.10.2 Drug Accountability

A record of study drug movements will be maintained for accountability purposes in accordance with GCP and local regulatory requirements. The records will include the quantity of investigational medicinal product dispensed to and returned from study subjects and final disposal including batch number and expiry date information.

Accountability logs will be made available for inspection by the Sponsor or their designee and Regulatory Inspectors. Detailed written information will be provided to study sites on study drug management.

## 6.11 Disposal of Unused Drug

Systems will be put in place for disposal of any unused study drug. Detailed written information will be provided to study sites.

## 6.12 Unblinding of Treatment Allocation

This will include immediate response to requests for unblinding from treating physicians or general practitioner. In this event attempt will be made to maintain blinding of the clinical research team.

### 6.13 Criteria for Withdrawal of Participants on Safety Grounds and Withdrawal

If overt biochemical hypothyroidism is identified (TSH ≥20 mU/L or fT4 below the reference range), the data-centre will require a 2nd TSH measurement with fT4 within 2 weeks; if overt biochemical hypothyroidism is confirmed (free T4 levels below the reference range), the patient will require to stop the study treatment and attend GP for consideration of open treatment with Levothyroxine.

If biochemical hyperthyroidism (TSH<0.4 mU/L) develops in the placebo group, or occurs at 2 consecutive follow-up visits in a patient in the Levothyroxine group; i.e. persisting despite down-titration of the Levothyroxine dose the patient will require to stop the study treatment and attend GP for consideration of further assessment and treatment of hyperthyroidism.

### 6.14 Maintenance of trial treatment randomisation codes, procedures for unblinding.

Detailed SOPs will be developed for maintenance of trial randomisation codes and unblinding of treatment allocation.

### 6.15 Special warnings and precautions for use

Subclinical hyperthyroidism is associated with bone loss, increased risk of osteoporotic fractures, atrial fibrillation, heart failure and possibly worsening angina. For this reason we propose careful monitoring of thyroid function tests throughout the study, with reduction in dose of Levothyroxine in those with early biochemical evidence of over-replacement (TSH < 0.4 IU/L).

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. However this study effectively excludes subjects with panhypopituitarism, by requiring an elevated TSH level as a condition of entry.

Initiation or discontinuation of anti-convulsants therapy may alter levothyroxine dosage requirements.
There are further special precautions relating to pregnancy, lactation and use in paediatric subjects. Such considerations are not relevant to this trial.

### 6.16 Interactions with other drugs

The drugs listed below may interact with the IMP given as part of the '"IEMO 80-plus thyroid trial"'. However it should be noted that interactions are generally weak, and have very limited clinical relevance for the treatment of mild or subclinical hypothyroidism, with doses of Levothyroxine that avoid over-replacement (iatrogenic hyperthyroidism).

*Anticoagulants*
Levothyroxine increases the effect of anticoagulants and it may be necessary to reduce the anticoagulation dosage if excessive hypoprothrombinaemia and bleeding are to be avoided. However clinically relevant effects are unlikely in the context of treating subclinical hypothyroidism, as long as overtreatment with Levothyroxine is avoided.
The SOPs for the study will include detailed recommendations for monitoring of oral anticoagulants (warfarin, fenprocoumon, acenocoumerol) for patients who are on these drugs, ensuring the INR is checked soon after initiating or changing Levothyroxine dose.

*Anti-convulsants*
Anti-convulsants, such as carbamazepine, primidone and phenytoin, enhance the metabolism of thyroid hormones and increase requirement for thyroid hormones in hypothyroidism.

*Anti-arrhythmics*
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. However subjects on this drug are excluded from this study.

*Antidiabetics*
Blood sugar levels are raised and dosage of anti-diabetic agents may require adjustment. However clinically relevant effects are unlikely in the context of treating subclinical hypothyroidism, as long as overtreatment with Levothyroxine is avoided. The SOPs for the study will include detailed recommendations for diabetes monitoring, however it is anticipated that this will not require significant changes to the diabetic monitoring that is occurring as part of routine clinical practice.

*Beta Blockers*
Levothyroxine (thyroxine) accelerates metabolism of propranolol. Beta blockers may decrease the peripheral conversion of levothyroxine.

*Antidepressant*
Levothyroxine increases receptor sensitivity to catecholamines thus accelerating the response to tricyclic antidepressants (e.g. amitriptyline, imipramine). Concomitant use of tricyclic antidepressants and Levothyroxine may precipitate cardia arrhythmias.
Effects of Levothyroxine may be decreased by concomitant sertraline.

*Sympathomimetics*
The effects of sympathomimetic agents (e.g. adrenaline) are enhanced.

*Cardiac glycosides*
In theory, 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. However heart rate changes in treatment of subclinical hypothyroidism are likely to be negligible, and as long as overtreatment is avoided it is expected any interaction with digoxin will not be of any clinical significance.

*Antineoplastics:*
Plasma concentration of Levothyroxine (thyroxine) is possibly reduced by imatinib.

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

*Sex Hormones*
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.

*Lipid regulating drugs*
Lovastatin has been reported to cause one case each of hypothyroidism and hyperthyroidism in two patients taking Levothyroxine.

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

*Drugs affecting metabolism or absorbtion of Levothyroxine*
Metabolism of Levothyroxine (thyroxine) is accelerated by rifampicin, barbituarates (these may increase dose requirements for Levothyroxine (thyroxine) in hypothyroidism).
Absorption of Levothyroxine (thyroxine) is possibly reduced by antacids, calcium salts, cimetidine, oral iron, sucralfate, colestipol, polystyrene sulphonate resin and cholestyramine (if possible administration should be separated by 4-5 hours).

*Prohibited concomitant medication*
Thyroxine; antithyroid medications (carbimazole, methimazole, propylthiouracil, potassium perchlorate); amiodarone; lithium.

# 7. METHODS

## 7.1 Study parameters/endpoints

### 7.1.1 Main study parameter/endpoint

Change in disease specific QOL (measured using symptom and fatigue domains from the Thyroid-specific Quality of Life patient-reported outcome measure (ThyPRO) published by Watt (29) – measured at baseline; 6-8 weeks; 12 months and close-out.

### 7.1.2 Secondary study parameters/endpoints (if applicable)

- General QOL (measured using EuroQOL) at baseline; 6-8 weeks; 12 months and final follow up.
- Comprehensive thyroid quality of life assessment ThyPRO39 – recorded at final visit (additional 28 questions).
- Fatal and non-fatal cardiovascular events (this will include acute myocardial infarction; stroke; amputations for peripheral vascular disease; revascularisations for atherosclerotic vascular disease, including for acute coronary syndrome and heart failure hospitalisations).
- Handgrip strength (measured using the Jamar hand dynamometer) at baseline; 12 months and final follow up.
- Cognitive function, particularly executive function (measured using Letter Digit Coding Test [LDCT] at baseline and final follow-up.
- Total mortality and cardiovascular mortality
- Functional ability (basic Activities of Daily Living (ADL) measured using Barthel Index [BI]; extended activities of daily living measured using the older American resources and services [OARS] and gait speed) at baseline and final follow-up.
- Haemoglobin, measured on a full blood count at baseline and 12 months.
- Participant's treatment satisfaction with trial medication at final study (closeout) visit.

## 7.2 Randomisation, blinding and treatment allocation

### 7.2.1 Randomisation

Randomisation (1:1 Levothyroxine versus placebo) will be stratified by site, gender and starting dose of levothyroxine and carried out using the method of randomly permuted blocks. The randomisation schedule will be prepared by the data centre (independent of the clinical investigators), implemented by the manufacturer of the matching placebo (they will package Levothyroxine and placebo), and patient allocation conducted via the trial web portal by the study nurses.

### 7.2.2 Blinding

The study will be double blinded. Subject blinding to treatment allocation will be ensured through use of matching tablets for Levothyroxine and placebo. Clinicians / study centres blinding to treatment allocation will be ensured by remote analysis of laboratory results of TSH in the Robertson Centre for Biostatistics in Glasgow, with corresponding titration advice.

All blood tests for in-study thyroid stimulating hormone (TSH) and free thyroxine (fT4) levels will be performed by the local laboratories. All TSH and fT4 results from the follow-up phase of the study will be directly transferred by the laboratories to the data-centre in the Robertson Centre for Biostatistics in Glasgow. The data-centre in Glasgow will advise the clinical research team and I on any dose titration. The clinical research team will not be informed of the actual results of thyroid function testing. Detailed algorithms for titration of Levothyroxine and placebo, including dosing of Levothyroxine and numbers of tablets to be consumed daily, will be prepared in the initial planning and implementation phase of the study.

These processes are designed to ensure the integrity of blinding, with the research and the clinical teams kept unaware of results of repeat thyroid function tests. Drug and placebo supplies will be delivered to patients after 3-monthly after each dose alteration and 6-monthly at intermediate visits.
During the '"IEMO 80-plus thyroid trial"' study there will be risk of unblinding through additional unscheduled GP or hospital testing of thyroid function. We intend to minimise the risk of this happening by effective communication, through the study website and phone access for patients and their physicians. In this communication we will discourage the practice of unnecessary interim testing of thyroid function.

## 7.3 Study procedures

### 7.3.1 Identification of participants and informed consent

Screening process:
Potential subjects will be identified from clinical laboratory databases as having, within the last 36 months, biochemical features consistent with SCH with a TSH level $\geq$4.6 and $\leq$19.9 mU/L and age $\geq$80 years. There will be a minimum delay of 3 months between the last measure of TSH and the laboratory screening visit.

The initial laboratory identification of potentially eligible subjects will be for the previous 15 to 3 months, with subsequent new summary laboratory reports of potential cases at 3 monthly intervals (at 15, 18 and 21 months after commencement of the randomised controlled trial), allowing inclusion of 2 years of laboratory data for study recruitment.

Study participants will be recruited through primary care laboratories or clinical (in-hospital) laboratories. The identification of eligible persons for the screening phase of the study will be

executed by the laboratory and GPs or treating physicians; the study centers will not be involved in the selection of eligible participants and does not have access to names and addresses of potential participants, and can therefore never directly contact eligible persons, prior to their consent to participate in the screening phase of the study.

The procedures differ slightly between primary care and hospital laboratory settings.

1. Primary Care Laboratories:

Prior to the study, all GPs referring patients to the above mentioned laboratories will be notified about the study and are asked to recruit participants for the study.

During the study we anticipate 2 potential recruitment algorithms, based on local factors (magnitude of the laboratory, degree of participation of General Practices). The first algorithm is identical to TRUST and is suitable for smaller.

Algorithm 1.
In this algorithm, we will use a 2-stage consent process, with the first stage for screening and the second stage for participation in the randomised controlled trial. There will be a minimum of 1 week and maximum of 6 weeks between the screening and baseline visit by the research nurse.
The laboratory will forward laboratory results and patient names to the GPs for each potentially eligible patient, including a simple questionnaire to check in- and exclusion criteria (using information from their medical records), plus, an invitation letter and screening information and simple information sheets on the randomised-controlled trial to be sent out by the GP to the patient. The GP invites the patient to participate in the study. The patient will be asked to indicate their willingness to be considered for entry to the study, by signing the first informed consent form for the laboratory screening phase of the study and visiting the laboratory for thyroid function retesting. For those unable to visit the laboratory for thyroid testing, we will offer a visit by trained staff of the laboratory within their own home. Subjects who do not respond, whose GP believes are eligible, will be sent a single reminder (again by the GP).
When visiting the laboratory for thyroid function retesting, a venous blood sample for baseline thyroid function tests (TSH and fT4) is taken.
Results of the thyroid function testing are then sent to the study center at the Institute of Evidence Based Medicine in Old Age. Those eligible subjects found to have both a TSH level >4.6 and ≤19.9 mU/L L and fT4 in the laboratory reference range will be assumed to have persistent biochemical SCH. The research nurses will contact them by phone to invite them to take part in the study, with a suggested date and time for a baseline study visit within their own home. The research nurses will send detailed information about the trial phase of the study before the baseline study visit.
Subjects whose repeat screening thyroid function tests show TSH has reverted to within the normal range will be sent an information letter explaining them that the results are normal and that it would not be appropriate for them to enter a trial of thyroid hormone treatment.

This letter will be copied to the GP or treating physician in the hospital. Subjects whose repeat screening thyroid function tests show high TSH and low fT4 will be sent an information letter advising them that their thyroid gland shows overt hypothyroidism and that it would not be appropriate for them to enter a trial of thyroid hormone treatment; they may wish to discuss these results with their GP or treating physician in the hospital. Again this letter will be copied to the GP or treating physician in the hospital.

Algorithm 2.
The laboratory will forward laboratory results and patient names to the GPs for each potentially eligible patient and advise the GP to repeat the measurement in line with clinical guidelines of the Nederlandse Internisten Vereniging and present International consensus. Of potentially eligible participants who have repeated subclinical hypothyroidism, the laboratory will inform the GP that the patient is potentially eligible for the study. This notification will include a simple questionnaire for the GP to check in- and exclusion criteria (using information from their medical records), plus, an invitation letter and screening information and simple information sheets on the randomised-controlled trial to be sent out by the GP to the patient. The GP invites the patient to participate in the study. The patient will be asked to indicate their willingness to be considered for entry to the study, by signing the answer card to the study center, to be contacted for further information, including patient information sheet and Informed Consent form. Subjects who do not respond, whose GP believes are eligible, will be sent a single reminder (again by the GP). After receipt of the answering card, the study center will contact the eligible patient to answer any questions, and to plan a baseline visit which includes signing of the Informed Consent form.

2. Clinical (in-hospital) laboratories:

Prior to the study, all specialists ordering TSH and fT4 measurements will be notified about the study and are asked to recruit participants for the study.

When an older patient with a TSH level $\geq$4.6 and $\leq$19.9 mU/L is identified by the clinical laboratory, the specialist that requested the TSH and fT4 measurement is notified. The specialist is to repeat the measurement in line with clinical guidelines of the Nederlandse Internisten Vereniging and present International consensus (Lancet, American guidelines). Of potentially eligible participants who have repeated subclinical hypothyroidism, the laboratory will inform the specialist that the patient is potentially eligible for the study. This notification will include a simple questionnaire to check in- and exclusion criteria (using information from their medical records), plus, an invitation letter and screening information and simple information sheets on the randomised-controlled trial to be sent out by the specialist to the patient. The specialist invites the patient to participate in the study. The patient will be asked to indicate their willingness to be considered for entry to the study, by signing the answer card to the local study center, to be contacted for further information, including patient information sheet and Informed Consent form. Subjects who do not respond, whose GP believes are eligible, will be sent a single reminder (again by the GP). After receipt of the answering card, the local study center will contact the eligible patient to

answer any questions, and to plan a baseline visit which includes signing of the Informed Consent form.

Informed consent procedure:
The first act at the baseline study visit will be to obtain written informed consent for participation in the randomised controlled trial.

Information sheets and consent forms will be in Dutch. Full written contact details and telephone support will be available for participating patients, which they will be encouraged to use if they have concerns or questions about the study.

The time between screening (and provision of information sheets) and signing of formal consent for participation in the randomised controlled trial (prior to study baseline assessments) will allow ample opportunity for prospective entrants to reflect on participation and consider / ask further questions. There will be no time or other pressure to give informed consent.

Participants will have the right:

- To know that participation is voluntary
- To ask questions and receive understandable answers before making a decision.
- To know the degree of risk and burden involved in participation
- To know who will benefit from participation
- To know the procedures that will be implemented in the case of incidental findings
- To receive assurances that appropriate insurance cover is in place
- To know how their data will be collected, protected during the project and either destroyed or reused a the end of the research, if plan to reuse the data exist, participants should be duly informed, and consented also for this further usage,
- To withdraw themselves and their data from the project at any time
- To know of any potential commercial exploitation of the research

The study center will notify the GP and treating physician in the hospital (if recruited through the hospital) of every older person that signs informed consent for the treatment phase of the trial. If the participant is using anti-coagulation, the anticoagulation clinic will be notified. Each participant will be receiving an information card, including information about the trial, type of medication that is prescribed, and contact information of the principal investigator and the national coordinator as well.

### 7.3.2 Data collection

Data collection will be performed by study research nurses at baseline and predetermined follow-up as outlined previously. Data will be collected in the patient's home own / place of residence.

For the screening phase; we will record results of repeat TSH and fT4, consent / decline to take part in the screening phase of the study and for those who have consented, their contact details. For participants in the randomised controlled trial, we will first obtain informed consent for the trial phase of the study, and then generate the following data:

- Baseline visit; subject characteristics, including prior cardiovascular disease, smoking, home support and Mini Mental State Examination
- Concomitant drug treatment at baseline, 6-8 weeks and 12 months and annually thereafter
  Thyroid specific Quality of Life measured (ThyPRO symptom and fatigue domains) (29)), and the EuroQol5D at study baseline, 6-8 weeks and 12 months post-recruitment and at final review.
  The ThyPRO39 will be recorded at the final study (closeout) visit. It provides an extended dataset covering a comprehensive range of thyroid-related quality of life issues. To preserve the integrity of the validated ThyPRO39 scale we will include all domains even though some (eg goitre and eye symptoms) are not likely to be major issues in subclinical thyroid disease.
    Memory concentration (3 items)
    Nervousness and tension (3 items)
    Psychological well-being (3 items)
    Coping and mood swings (3 items)
    Relationships with other people (3 items)
    Daily activities (3 items)
    Appearance (3 items)
    Overall impact (1 item)
    Goitre (3 items)
    Eye Symptoms (3 items)
- The letter-digit coding test, isometric handgrip strength (best of 3), gait speed, and Activities of daily living (ADL, IADL) at study baseline, 12 months and at final review
- Blood pressure (systolic and diastolic) at study baseline, 12 months and at final review
- Drug accountability data will be gathered for each patient including distribution date, quantity of study drug supplied, and drug supply returns including date, and quantity of tablets returned
- At the final study (closeout) visit we will evaluate participant's treatment satisfaction with the trial medication, desire of post-trial medication continuation and proportion of patients opting for continuation of study medication. The Treatment Satisfaction Questionnaire for Medication (TSQM vII) and four additional questions will be asked.

Report forms for possible cardiovascular endpoints and SAEs will be generated for the study nurses to complete; these will be entered via the trial web portal which will have an in-built notification to the Endpoints Committee. Adjudicated endpoints will also be entered via the trial web portal using separate adjudication record forms. Anonymised source documents can be uploaded by the study nurses via the trial web portal, to assist in the adjudication process, in accordance with the committee's requirements.

Detailed information about the questionnaires and tests can be found in the Appendix.

### 7.3.3 Data collection process

The Robertson Center for Biostatistics (Glasgow University) will function as the data center for the “IEMO 80-plus thyroid trial”. The RCB has the same function for the TRUST trial and will develop and manage a trial web portal, including the electronic case report form (eCRF).

The eCRF for the “IEMO 80-plus thyroid trial” will be identical to that of the TRUST trial, with the exception of additional end points to be entered for the IEMO 80-plus trial participants. Data for the “IEMO 80-plus thyroid trial” will be stored separately from the TRUST database. The identical eCRF and database infrastructure ensures maximal homogeneity of data, allowing for the pre-planned pooled analysis.

Data entry will be electronic on laptops using internet access through a secure connection. The trial web portal will be in English, however, for nurse-led questionnaires and patient completed questionnaires these forms will be in Dutch. Data will be entered via the eCRF or in some cases transferred to the data centre via the trial web portal.

Data validation checks will be implemented within the eCRF to give users immediate feedback on mandatory items that are missing and ‘out of range’ values. In addition, logic checks will be put in place to ensure no invalid data are entered. Further database validation checks will result in data queries being flagged to the sites for correction. These checks will be run routinely and will be tracked and escalated as appropriate. Any third party data validations that result in data queries will be required to be dealt with by the data source. Data will be locked at the end of the study and the lockdown procedures will be managed by the data centre. Routinely snapshots of the data will be taken in order to report to an independent data monitoring committee (IDMC) and to the authorities (annual safety reports).

All data will be securely stored for the duration of the contract and archived beyond this time for a minimum period of 10 years after study database lock. The study database will be held by RCB for the duration of the study and for a minimum period of 10 years after study close.

### 7.3.4 Assessment and follow-up

We propose a minimum of one year of initial follow-up, with a likely average of 2 years. Subjects will be reviewed face-to-face by the study nurses at recruitment, study baseline, 6-8 weeks and 12 months and annually thereafter. In addition interim telephone contact or visits (depending on the desire of the patient) will be made by study nurses at 6, 18, 30 and up to 42 months (depending on total duration of follow-up), including recording of possible cardiovascular and serious adverse events (SAEs). Patients may also be contacted if

required in addition to the planned visits, e.g. to arrange delivery of study drug and ensure that supplies have been received. The final review will be face-to-face.

The follow-up time points listed below were chosen to reflect the following; at 6-8 weeks we expect most patients allocated Levothyroxine to be biochemically euthyroid, and at this time point short-term improvements (such as in thyroid-specific quality of life) will be apparent. By one year the medium-term effects of Levothyroxine treatment should emerge (such as on 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.

Detailed information about the tests and questionnaires that will be administered during the home visits can be found in the appendix. The items on the list may be subject to changes as a result of piloting or local factors. Based on these factors, the Project Group will establish a "minimal dataset" that is required for proper functioning of the trial. A tolerable burden on the patient will be the leading and limiting determinant of the amount of data to capture.

Descriptive data to be recorded at baseline

- Age and gender.
- Lifestyle; smoking, alcohol intake and usual exercise.
- All exclusion criteria listed in section 4.3.
- Known 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. The exact criteria for prior cardiovascular disease will be similar to those used in PROSPER (32).
- History of atrial fibrillation (AF).
- History of epilepsy.
- History of hypertension, diabetes mellitus or osteoporosis.
- Patients with hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorbtion.
- Prescribed medicines and over-the counter medicines will be recorded at each study visit; medicine count will be used as an assessment of baseline co-morbidity.
- Mini-mental state examination (MMSE) score (33) will be recorded at study baseline as a descriptor of general cognitive function. However it will not be repeated or used as an outcome measure as it is insensitive to change over the time-span planned for this study.
- Weight, height and waist circumference at baseline.
- 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), at study baseline and final review.

Outcome measures recorded at baseline and during follow-up:

- Prescribed and over the counter medications will be recorded at baseline, 6-8 weeks and 12 months, then annually until after review.
- Disease specific quality of life will be assessed using the symptom and fatigue domains from the Thyroid-specific quality of life Patient Reported Outcome (ThyPRO) questionnaire (29); Of the 13 ThyPRO domains, some are not relevant for subclinical hypothyroidism (e.g. goitre, eye symptoms and cosmetic complaints), and some overlap with the general health related quality of life questions in the Euroqol; these questions therefore will be omitted from the study. The ThyPRO symptom and fatigue questionnaire will be applied at study baseline, 6-8 weeks and 12 months and at study closeout. This questionnaire will give summary scores for symptoms and for fatigue, but in addition allow for analysis of specific individual symptoms, including weight gain, depression, cold, and tiredness.
- General quality of life will be assessed using the EuroQol5D, recorded at study baseline, 6-8 weeks and 12 months and at final follow up.
- Handgrip strength will be measured using isometric dynamometry (Jamar hand dynamometer, using best of 3 attempts of dominant hand) recorded at study baseline, 12 months and final follow up.
- Executive cognitive function will be assessed using the letter-digit coding test recorded at study baseline and at final follow up.
- Blood pressure (systolic and diastolic phase V), measured at baseline, 12 months and final follow up (mean of 2 measurements taken after 5 minutes sitting).
- Ability to perform basic activities of daily living (ADL) will be recorded using the 10 item, 20 point Barthel index, at study Baseline and final follow up.
- Instrumental or extended activities of daily living (IADL) will be recorded using a short (7-item) questionnaire derived from the OARS instrument. This will be recorded at study Baseline and final follow up.
- Gait Speed at baseline and final follow-up
- Home support services (e.g. home help, meals on wheels, district nursing) and home circumstances (e.g. living alone, cohabiting, standard or sheltered housing, or entry to care home, will be recorded at study baseline and final review
- History of falls through the Falls Questionnaire at baseline and at 12, 24 and 36 months follow-up. During follow-up, only the first 2 questions of the questionnaire will be asked.
- Weight and waist circumference at baseline and at 12 months follow-up.

Outcome measures additional recorded at final study (closeout) visit

- Disease specific quality of life will be assessed using the Thyroid-specific quality of life Patient Reported Outcome (ThyPRO39) questionnaire.
- Participant's treatment satisfaction with trial medication will be assessed using the Treatment Satisfaction Questionnaire for Medication (TSQM vII).
- Questionnaire about arthrosis

Causes of death

In addition to the above, consent will be sought before randomization to obtain information on the causes of death from Statistics Netherlands for those who participate in the RCT allowing long term (post trial) analysis of cause specific mortality.

Medical records review
Information will be obtained from GPs and treating physicians in the hospital at baseline (i.e. medical history) and during the study (for endpoint adjudication, e.g. hospital discharge letters, ECG results, laboratory results etc)

At study baseline and after 12 months a standard venous blood sample (40mls) will be collected for storage for future analyses (see section 7.3.5).

### 7.3.5 Sample storage

The extra “IEMO 80-plus thyroid trial” blood samples will be collected from participants who have provided consent to participate in the IEMO 80-plus thyroid trial and who provided consent to collect the extra blood samples. The aim of this extra collection of blood samples is to establish a repository of blood samples from which potential biomarkers and/or genes may be identified that better predict those older people with SCH who are at risk of dying or developing ill-health, including cardiovascular and cerebrovascular disease. The extra blood samples - assigned with a unique 2D barcode - will be stored for max. 15 years in a depository in the Leiden University Medical Center. Blood samples will be stored with patient ID coded to allow merging of data with outcomes of the study. At a time in the future (no earlier than the inclusion of the last patient), the stored blood samples, together with other information obtained about these participants (in relation to their health, lifestyle and other circumstances) will be analysed to address specific questions regarding the association of biomarkers and major health outcomes. After having provided informed consent, participants of the study will not be informed about future analyses of the samples, as analyses will likely take place years after blood drawing and thus clinical relevance of individual findings is limited. The future analyses that will be performed will be notified to the METC and to the competent authority in an amendment.

The materials are stored in an identical manner (yet physically separate) as the TRUST samples, allowing for future combined use.

Samples taken at baseline study visit and 12 months:
- 1 EDTA tube (6 ml) (for EDTA plasma and whole blood);
- 2 serum separation tubes (2*8,5 ml) (for serum and buffy coat)
- 1 sodium citrate tubes (4 ml)(for citrated plasma)
- 1 NaF tube (2 ml) (for NaF plasma)
- 1 lithium heparin tube (8,5 ml);
- 1 EDTA tube (3 ml)(for haematology / cell counts)

Definition:

The “IEMO 80-plus thyroid trial” samples consists of:

- all plasma and DNA samples from randomised participants held at –70°C either in the main study sample depository in Leiden University Medical Center, or in the different laboratories where samples have been handled during the study.
- all data derived from analyses of these samples.

### 7.4 Withdrawal of individual subjects

The participant can decide to withdraw from the study at any time. The researcher also has the right to withdraw participants from the study if he/she feels that it is in the best interest of the participant. Full details of the reasons for withdrawal should be recorded on the CRF. Withdrawn participants should be followed up in accordance with the protocol. If a patient withdraws consent from treatment and from follow-up this should be clearly documented in the CRF.

### 7.5 Replacement of individual subjects after withdrawal

Participants that withdraw from the study will not be replaced. Drop-outs have been taken into account in the sample size calculation.

### 7.6 Follow-up of subjects withdrawn from treatment

All subjects will be followed to allow an ‘intention to treat’ analyses.

### 7.7 Premature termination of the study

The safety of patients enrolled in the study will be monitored by an Independent Data and safety Monitoring Committee (IDMC) (See section 8.5). The IDMC will advise the “IEMO 80-plus thyroid trial” Project Group, Sponsor (LUMC) and Competent Authority (CCMO) if it is safe and appropriate to continue with the study.

# 8. SAFETY REPORTING

## 8.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

## 8.2 Assessment and reporting of adverse events / serious adverse events

### 8.2.1 Definition of adverse events

Adverse Event (AE)
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject

### 8.2.2 Definitions of Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any adverse event or adverse reaction that

- results in death;
- is life threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- is otherwise considered medically significant by the investigator

i.e. 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

### 8.2.3 Definition of Suspected Serious Adverse Reaction (SSAR)

Any adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC)

### 8.2.4 Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC)

### 8.2.5 Recording and Reporting AEs/SAEs

We have taken particular care in devising a titration algorithm to avoid any possibility of prolonged periods of thyroid hormone over-replacement in those allocated to Levothyroxine. This should substantially reduce the risks in this group, such as of AF or cardiac failure; in epidemiological studies these problems are observed in association with biochemical hyperthyroidism and not with TSH within the reference range. Similarly for those allocated to placebo we have developed an algorithm for review that is designed to detect those who develop overt hypothyroidism who require to start open-label Levothyroxine. These measures are designed to ensure the highest quality of patient care, including safety, of those who are randomised into the trial.

If the study demonstrates a convincing pattern of SAEs with either Levothyroxine or placebo, this would be an important endpoint in its own right. If SAEs are observed with Levothyroxine this would counterbalance any benefits observed, and would directly influence recommendations for treatment that are generated by the study.

If an association of AEs is noted with either Levothyroxine or placebo allocation this would require careful consideration as to whether it is ethical and appropriate to continue with the trial. It is necessary to ensure that any such recommendation is not influenced by the gains obtained from direct involvement in the running of the study. Therefore this is a primary remit of the IDMC, who will comprise an independent group including medical experts and an independent biostatistician.

SAEs and AEs of special interest will be recorded at all visits and telephone contacts. Patients' GPs will also be asked to report SAEs to the research center at the department of Public Health and Primary Care. Patients can phone the department to report symptoms or concerns.

Adverse events (AEs) will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and this protocol.

Full details of all AEs of special interest (atrial fibrillation, heart failure, fractures, new diagnosis of osteoporosis) including the nature of the event, relationship to study drug and outcome will be recorded in the eCRF. AEs of special interest will be monitored and followed up until satisfactory resolution or stabilization.

All adverse events will be assessed for seriousness and causality. SAEs will also be assessed for causality, expectedness and severity. This assessment will be carried out by the Chief Investigator (Dr. Mooijaart) or designated medical practitioner.

**Severity**
This should be assessed and described using the following categories:

- **Mild**- awareness of event but easily tolerated
- **Moderate**-discomfort enough to cause some interference with usual activity
- **Severe**-inability to carry out usual activity.

All SAEs arising during the clinical trial will be reported to the sponsor by entering the details into the eCRF as soon as reasonably practicable and in any event within 24 hours of first becoming aware of the event. Any follow up information should also be reported.

Serious adverse events recorded in the eCRF will be reported through the web portal *ToetsingOnline* (https://toetsingonline.ccmo.nl) to the accredited Medical Ethics Committee of the Leiden University Medical Center that approved the protocol.

All SUSARS will be reported through the web portal *ToetsingOnline* to the accredited Medical Ethics Committee of the Leiden University Medical Center and competent authority within the following timelines:

**Fatal or life threatening SUSARs**: not later than 7 days after the sponsor has information that the case fulfilled the criteria for a fatal or life threatening SUSAR, and any follow up information within a further 8 days.
**All other SUSARs**: not later than 15 days after the sponsor has information that the case fulfilled the criteria for a SUSAR.

The sponsor (LUMC) will report the SAE or SUSAR of all participants to Eudravigilance. Lareb will report the SAE or SUSAR of the Dutch participants to Eudravigilance.

The Lead Investigator at each site will be informed about any SUSARs, which have occurred during the study.

Specific regulations regarding pregnancy are not applicable to this trial. There are no risks to the foetus; male participants who have a partner of childbearing age do not need to take any contraceptive precautions and female participants are beyond the childbearing age.

SAEs that occur at any time after the inclusion of the subject in the study (defined as the time when the subject signs the informed consent) up to 30 days after the subject completed or discontinued the study will be reported.

The subject is considered to have completed the study EITHER after the completion of the last visit or contact (e.g. phone contact with the investigator or designee), OR after the last dose of the study medication, whichever is later. The date of discontinuation is when a subject and/or investigator determine that the subject can no longer comply with the requirements for any further study visits or evaluations.

Stopping guidelines will be developed by the Independent Data and Safety Monitoring Committee (IDMC); it is assumed any recommendations for early stopping, such as because of overwhelming benefit for the primary outcome, will be conservative and will have no impact on the sample size calculations.

### 8.2.6 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

### 8.2.7 Unblinding

If the clinical investigator or attending physician deems that unblinding is necessary, they will have 24-hour access to telephone unblinding through the data-center (Robertson Centre). In the event of a SUSAR, the sponsor (but not the investigators) will be unblinded to facilitate reporting to the accredited Medical Ethics Committee.

### 8.2.8 Specific adverse events of interest

Certain potential adverse events are anticipated or likely as a result of the study and study population. The adverse events detailed below are likely to occur in the context of over replacement of Levothyroxine. Our dose titration scheme and study processes of careful monitoring of thyroid function tests are designed to ensure we avoid prolonged periods of thyroid hormone excess.

For the group allocated to placebo, there is risk of developing overt clinical hypothyroidism; again our study processes of careful monitoring of thyroid function tests are designed to avoid this scenario.

(A) Atrial fibrillation (AF)
AF is associated with subclinical hyperthyroidism (34) and therefore is a potential risk of thyroid over-replacement for SCH. It should not occur if TSH is maintained in the normal range, however we will pay particular attention to identifying this possible adverse event.

We have developed a robust mechanism to ensure detection of atrial fibrillation. Cardiac rhythm will be determined at study baseline, and new onset AF, paroxysmal or persisting, will

be diagnosed from an annual single-lead electrocardiograph, or if noted on 12-lead electrocardiograph or telemetry performed as part of hospitalisation or other clinical care, identified by inquiry about hospitalisations and out-patient visits (including for cardiac arrhythmias) at all patient contacts.

This general process of screening for atrial fibrillation has been found to be very sensitive for identifying new cases (35).

We propose to use a single-lead recorder (Omron HeartScan HCG-801-E). This provides a simple and quick assessment of cardiac rhythm; it has been shown to have high diagnostic accuracy for AF (sensitivity 99%, specificity 96%) compared to a standard 12-lead electrocardiograph.

(B) Heart failure. Prevalent heart failure and incident heart failure diagnosis / hospitalisations will be recorded, as this outcome is a potential risk of thyroid hormone over-replacement.

(C) Fracture. Musculoskeletal effects of Levothyroxine are described, including osteopenia/ osteoporosis. We will record all new fracture diagnosis and all new diagnoses of osteoporosis. Formal screening for osteoporosis is not required for this trial.

## 8.3 Annual safety report

An annual safety report (in the format of a Development Safety Update Report) must be submitted to the accredited METC and competent authority, as soon as is practicable and within 60 days of the anniversary of the issue of the Clinical Trials Authorisation. The Chief Investigator (Dr. Mooijaart) will prepare this document in liaison with the data-center.

### 8.3.1 End of trial

The subject is considered to have completed the study EITHER after the completion of the last visit or contact (e.g. phone contact with the investigator or designee), OR after the last dose of the study medication, whichever is later. The date of discontinuation is when a subject and/or investigator determine that the subject can no longer comply with the requirements for any further study visits or evaluations.

For the purposes of regulatory requirements the end of the trial is defined as the date of the last investigational visit for the last patient undergoing protocol treatment.

Participants who either complete or withdraw from the study treatment will be referred back to their general practioner for their ongoing care. Any future treatment will be at the discretion of the patient's general practitioner or treating physician in the hospital.

Within 15 working days of completing a participant's final study visit it is intended to inform the participant (if they wish) and their general practitioner (GP) which arm of the study they had been allocated to i.e. placebo or Levothyroxine. This should aid discussions between the participant and their GP regarding any further treatment. If a participant does not agree with waiting for maximal 15 working days to be unblinded, we have 24-hr access to telephone unblinding through the data-centre (Robertson Centre).
Only one member of the study team will be "unblinded" and this individual will not be involved in a gathering information or assessing Serious adverse events or Endpoints.

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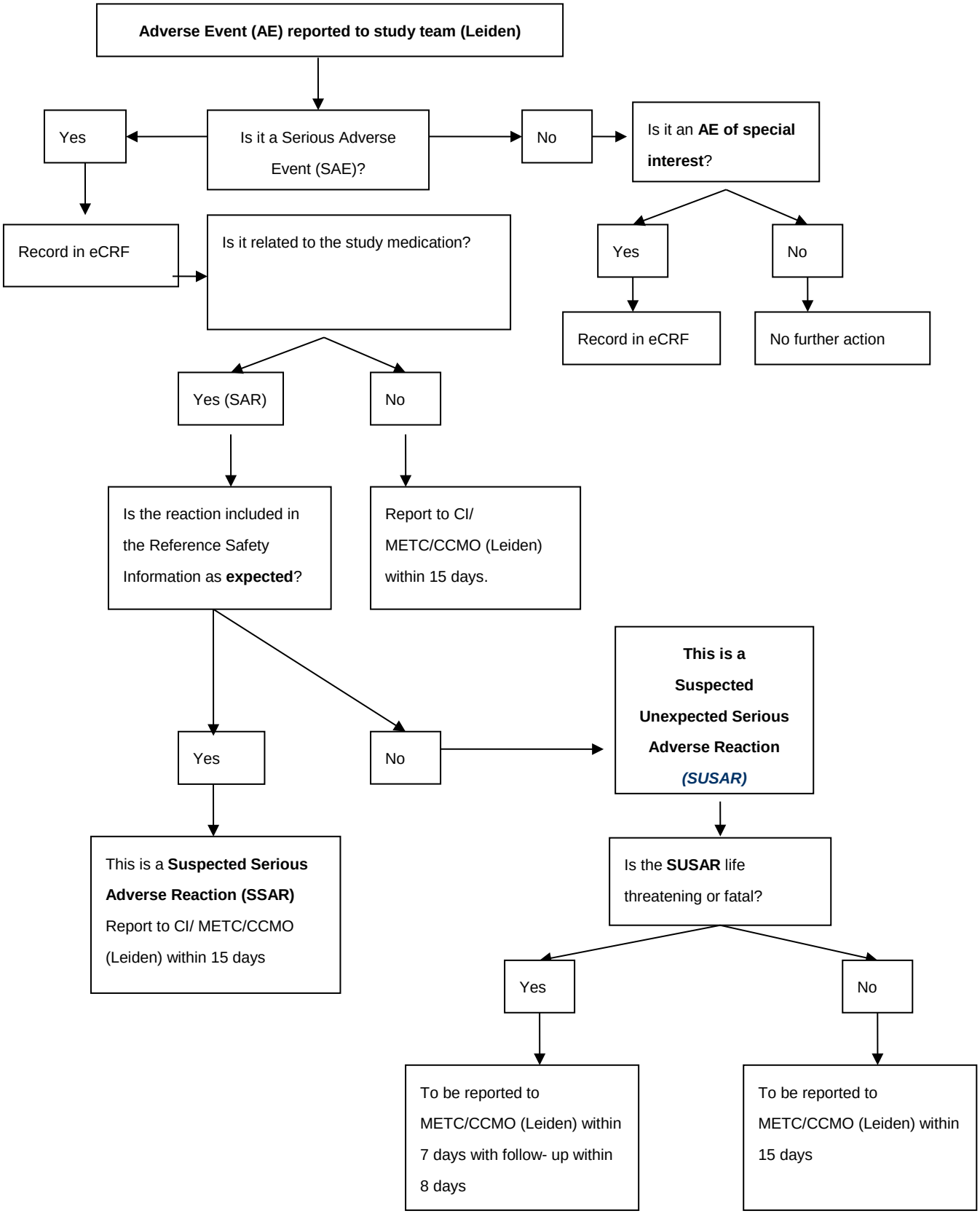
## 8.4 Safety flow-chart



### 8.5 Independent Data and Safety Monitoring Committee (IDMC)

The IEMO 80-plus thryroid trial and the TRUST trial will be using the same IDMC. As a result data of both trials will provide a more accurate estimated of patient safety.

The IDMC will have a formal charter; this will outline the responsibilities of the IDMC members, Data Centre and the sponsor. Responsibilities include:

- To protect the safety of patients recruited to the trial.
- Advising Project Group and Sponsor if it is safe and appropriate to continue with the study.
- Scrutinising recruitment and endpoint rates, and providing reports for the Project Office to forward to the Project Group, ethical committees and regulatory bodies.
- Examining information provided by the Data Centre on study recruitment, adverse events and outcomes and providing reports for the Project Office to forward to the "IEMO 80-plus thyroid trial" Project Group, ethics committees, regulatory bodies, and study sponsor.

## 9. TRIAL MANAGEMENT

The investigators institution(s) will permit trial related monitoring and audits, ethical reviews and regulatory inspections by providing direct access source data/documents.

### 9.1 Study administrative team

A study administrative office will be sited in the Institute for Evidence-Based Medicine in Old Age (IEMO). The study will be guided by a central Project Group, which will include representatives from all partners: one representative of IEMO (Chief Investigator) and one representative of the recruitment site. The Project Group will seek advice on a regular basis from external expert advisors, patient advocacy (Schildklier Organisaties Nederland), independent ethics advisor and representatives from all partners. Potential cardiovascular endpoints will be reviewed and adjudicated by an endpoints committee. The endpoints committee of the IEMO 80-plus Thyroid Trial functions together with that of the TRUST Study. The endpoints committee will have a formal charter that will outline the responsibilities of the committee members, Data Centre and the sponsor. An Independent Data and Safety Monitoring Committee (IDMC) will be established, to review outcome and SAE data and advise the Project Group and sponsors on continuation of the study. Each of the participating sites will establish a local organizing committee to deal with operational issues. The research center in the Netherlands is located at the department of Public Health and Primary Care of the LUMC.

### 9.2 Trial Project Group

The Project Group is the ultimate scientific decision-making body for the study. It is chaired by the Chief Investigator (or Deputy), and will meet regularly throughout the lifespan of the project.

To be quorate, each beneficiary organization will be represented by at least one person (from the named collaborators), however all named collaborators from each of the main participants will be eligible to attend.

The Project Group will have a formal agenda. Responsibilities include:
• Providing overall project management policy.
• Making formal decisions on the project and project strategy (including changes to the work plan and / or the budget).
• Ensuring effective dissemination and knowledge management, including IPR and determining the publication strategy.

### 9.3 Independent Data and Safety Monitoring Committee (IDMC) (See section 8.5)

An Independent Data and Safety Monitoring Committee (IDMC) will be established, to review outcome and SAE data and advise the steering committee and sponsors on continuation of the study.

### 9.4 National organising committees

Each participating state will establish a National organising committee, chaired by one of main study applicants. National organising committee responsibilities will include:

- Obtaining national ethical committee approval including for protocol amendments.
- Establishing local standard operating procedures for screening, recruitment and follow-up of randomised patients (including endpoints).
- Pharmacovigilance reporting of SAE's and SUSARs to appropriate regulatory authorities (Medical Ethics Committee, CCMO (Competent Authority))
- Preparing language-specific website content, record forms (in consultation with the Data Centre), patient information sheets, consent forms, posters and newsletters.
- Budgetary management.
- Ensuring prompt information transfer to the Data Centre, including patient screening and recruitment, results of in-study TSH from the regional clinical laboratories, and follow-up including all study endpoints.
- To inform the 'Chief Investigator' of any significant problems in the conduct of the study.

### 9.5 Involvement of patients, service users/carers, members of the public

We are delighted to have support from, and collaboration with, Thyroid Federation International (TFI), an international umbrella patient support organisation with strong European links and Schildklier Organisaties Nederland.

# 10. STATISTICAL ANALYSIS

## 10.1 Statistical Analysis Plan

The Robertson Centre for Biostatistics (RCB) will be responsible for writing a formal statistical analysis plan (SAP) for the trial, submitting this for review by the Project Group and implementing revisions. The SAP will be agreed before the final locking and unblinding of the study database.

The general strategy will be as follows. Analyses will be based on the intention-to-treat principle. Continuous variables involving measurement at follow-up and baseline will be analyzed at each time point comparing treatment groups and adjusting for gender and baseline levels of the same variable using analysis of covariance (ANCOVA). In addition, such data will be analyzed using repeated measures analyses (standard analyses and repeated measures regression analyses) and in terms of the final assessment for each participant.Clinical outcome data will include time to first event Cox regression analysis stratified by gender in models containing the randomised treatment allocation as a covariate. Tests of treatment effect will be based on the Wald test and corresponding point estimates and 95% confidence intervals for the hazard ratio for treatment will be calculated. The assumption of proportionality of hazards will be tested.

RCB will also be responsible for creating a statistical analysis plan for the IDMC report and providing the independent IDMC statistician with pre-written and validated programs to facilitate the provision of unblinded reports for the IDMC.

## 10.2 Statistical methods

Continuous variables involving measurement at follow-up and baseline will be analysed at each time point comparing treatment groups and adjusting for gender and baseline levels of the same variable using analysis of covariance (ANCOVA). In addition, such data will be analysed using repeated measures analyses (standard analyses and repeated measures regression analyses) and in terms of the final assessment for each participant. For disease-specific and general quality of life, greatest effect will be expected after 1 year of treatment, and for these endpoints this will be the primary time-point for analysis. As an indicative power calculation each ANCOVA analysis will have 90% power to detect an effect size of 0.118 residual standard deviations in the ANCOVA model.

Clinical outcome data will include time to first event Cox regression analysis stratified by gender in models containing the randomised treatment allocation as a covariate. Analyses will be based on the intention-to-treat principle. Tests of treatment effect will be based on the Wald test and corresponding point estimates and 95% confidence intervals for the hazard ratio for treatment will be calculated. The assumption of proportionality of hazards will be tested.

We plan to pool our data with the participants of the TRUST trial (aged 65 years and over). The primary analysis will be a combined analysis of all participants. Specific attention will be paid to the subgroup analysis of the 80-plus year olds and older, for which we expect to have sufficient power to detect significant effects. Other subgroup analyses will include TSH above and below 10 mU/L, as recommended in the Cochrane Systematic Review (4), and also for known cardiovascular disease at study baseline. However we accept that our study will be underpowered for some of the smaller subgroups, such as men, TSH $\geq$10.0, $\leq$19.9 mU/L. We should however have sufficient statistical power in the combined TRUST and "IEMO 80-plus thyroid trial" on its own to detect beneficial effects in the larger or dominant subgroups, such as women, age above and below 80 years, and TSH in the range $\geq$4.6, <10.0 mU/L.

# 11. ETHICAL CONSIDERATIONS

## 11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (version 59, 2008, see for the most recent version: www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

## 11.2 Recruitment and consent

We will obtain written informed consent from all study participants prior to inclusion in the study. Participants will have a minimum of 1 week from the time of receipt of the letter of invitation for entry to the RCT before the baseline visit at which formal written consent will be obtained; they can decide to withdraw at any stage.

## 11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

## 11.4 Benefits and risks assessment, group relatedness

### 11.4.1 Benefits

Evidence is lacking about the benefits of Levothyroxine replacement in the elderly with SCH, as no large randomised clinical trials (RCT) on the full range of relevant clinical outcomes have been performed. However, potential for benefits from thyroxine includes prevention of cardiovascular disease, and improved quality of life, cognition, and muscle function.

Those allocated to placebo will potentially benefit from structured follow up and review of their thyroid function, identifying those who are developing overt hypothyroidism and therefore enabling prompt treatment (out of trial).

### 11.4.2 Risks

Adverse events (atrial fibrillation, heart failure and fractures in particular) are likely to occur in the context of over replacement of Levothyroxine. Our dose titration scheme and study processes of careful monitoring of thyroid function tests are designed to ensure we avoid prolonged periods of thyroid hormone excess.

For the group allocated to placebo, there is risk of developing overt clinical hypothyroidism; however our study processes of careful monitoring of thyroid function tests are designed to avoid this scenario.

## 11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The four participating recruitment centers have an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

- € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
- € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
- € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

### 11.6 Incentives (if applicable)

Participants will be visited at home. Travel expenses (taxi, public transport) to local laboratory will not be reimbursed.

### 11.7 Prescription of medication

The study physician (a qualified GP or internist affiliated to the IEMO 80-plus thyroid trial) will prescribe the study medication according to a strictly prepared schedule. We realise that a physician prescribing medication in a healthcare setting requires him/her to know the patient. However, we believe that in context of the strictly prepared study protocol, it will not be necessary for the physician to actually see the patient. All information about the patient that informs the physician whether to prescribe the study medication or not, is collected by the research team and available for the physician.

We consider this approach justified because of the safety measures that are embedded into the inclusion of participants and during follow-up in the trial:

- The exclusion criteria have already been checked by the GP or treating physician in the hospital before inviting the potential participant to participate in the trial.
- When a potential participant signs informed consent, but *before* randomization, the research nurse again checks the exclusion criteria with the GOP or treating physician in the hospital. This information should be entered into the electronic case report form (eCRF). Without this entry, the prescription of study medication is impossible.
- The study physician should check in the eCRF if the above-mentioned steps are taken. Only if the participant does not meet the exclusion criteria at the moment of randomization, the study physician will give permission to randomize.
- After randomization, the study physician will sign the recipe of the study medication.
- Several STOPs are embedded into the supply system of the study medication, as well as in the eCRF. As soon as a clinical incident in entered into the eCRF, it will be impossible to prescribe the study medication again. The study physician will then

judge the medical status of the participant and define whether it is justified to restart or continue with the treatment with study medication, and if so, with what dosage.

- In the study, an automated titration schedule is developed in order to register alterations in dosage of the study medication.
- In the study, a schedule for monitoring the thyroid function is initiated, wherein alterations of dosage after each monitoring can be entered. After an alteration of dosage, thyroid function will be monitored again after 8 weeks. If needed, the dosage of the study medication will be altered again.

## ADMINISTRATIVE ASPECTS AND PUBLICATION

### 11.8 Handling and storage of data and documents

The data from measurements of the research study outcomes will be registered anonymously in a database that will be designed specifically for the study. The Robertson Centre for Biostatistics in Glasgow will develop and manage a trial web portal, including an electronic case report form (eCRF). Data will be handled confidentially. A subject identification code list, not based on the patient initials or birth date, is generated by The Robertson Centre for Biostatistics in Glasgow and will be used to link the data to the subject. The key to the code will be safeguarded by the Chief Investigator (Dr. Mooijaart) and the lead 'local coordinator' per study site. Only the Robertson Centre for Biostatistics in Glasgow, the Chief Investigator and the 'local coordinator' in the Netherlands have access to the personal data of the participants. The handling of personal data will comply with the Dutch Personal Data Protection Act (WBP). The anonymised details and results will be shared with the collaborating investigators of the TRUST trial and in the future with the University of California, San Francisco, USA (Prof D Bauer, who is initiating a similar trial).

### 11.9 Monitoring

Annual 100% study monitoring visits 1 will be conducted by independent clinical research associates, in accordance with the NFU report 'Kwaliteitsborging van Mensgebonden onderzoek'.

### 11.10 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments (typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation) will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

### 11.11 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

### 11.12 End of study report

The investigator will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

### 11.13 Public disclosure and publication policy

The study will be registered with the clinical trials database http://isrctn.org/.

Together with TRUST, we are in a strong position to ensure effective dissemination of the results by the strong ties with the TRUST trial, including early adoption into clinical practice. Arrangements regarding sharing of data and joint publication are laid down in a Memorandum of Understanding between TRUST and the IEMO 80-plus thryoid trial project group.

TRUST partner Leyden Academy on Vitality and Ageing (LAVA) is well placed to play a coordinating role in this activity for TRUST, given its role as a knowledge centre with an education and research program in the field of ageing, vitality and geriatric medicine. The "IEMO 80-plus thyroid trial" project group will closely collaborate with TRUST and LAVA to ensure adequate dissemination of results.

The patient advocacy group Stichting Schildklier Organisaties Nederland will play a key role in planning the dissemination strategy and approving outputs to ensure methods and content fit with the public need.

The study team has an impressive record of publication of their research in high-quality peer-reviewed journals, and this will form a key part of the primary dissemination strategy. Furthermore, members of the Project Group are members of national and international guideline committees.

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, and included in the leading clinical guidelines. This will be facilitated by the inclusion of study data in high-quality systematic reviews; using links through the Cochrane Field for Older People (Prof. Stott, PI of TRUST) results of the “IEMO 80-plus thyroid trial” and TRUST will be offered for the update of the Cochrane systematic review of treatment of subclinical hypothyroidism, allowing for independent scientific interpretation.

Scientific publications will be targeted for high ranking peer-reviewed journals; publication will be open access manner where possible. Scientific publications will include:

- The trial rationale and design. This will be published in the first phases of the study to enhance visibility of the trial for researchers around the world and to ensure full transparency.
- A review of the current state of the art regarding the evidence for treatment of subclinical hypothyroidism in old age.
- The main study results will be published in a high ranking peer-reviewed journal reporting the primary study results and interpretation.
- The steering committee will actively search for collaborations with other trials (such as the USA NIH initiative) to jointly analyse results and publish on consensus regarding implications for treatment of subclinical hypothyroidism in old people around the globe.
- Scientific presentations

In parallel to the scientific publication, in first instance the rational, design and progress of the trial will be presented in leading conferences in various domains (cardiology, endocrinology, geriatrics). A standard presentation and slide-set in multiple languages will facilitate presentation of this information by all participating researchers.
Inclusion of study results in high quality systematic reviews and 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.

Subjects will be informed by letter of any substantive relevant information that becomes available during the course of the research that is relevant to their continuing participation. Such information will also be placed on the study website.

## 12. REFERENCES

1. Jones DD, May KE, Geraci SA. Subclinical thyroid disease. Am J Med. 2010a;123:502-4.
2. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002b;87:489-99.
3. Rodondi N, den Elzen WPJ, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al. Subclinical Hypothyroidism and the Risk of Coronary Heart Disease and Mortality. JAMA. 2010c;304:1365-74.
4. Villar HC, Saconato H, Valente O, Atallah AN. Thyroid hormone replacement for subclinical hypothyroidism. Cochrane Database Syst Rev. 2007d:CD003419.
5. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. J Clin Endocrinol Metab. 2007e;92:1715-23.
6. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. JAMA. 2004d;292:2591-9.
7. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. Lancet. 1997e;350:1119-23.
8. Newson RS, Felix JF, Heeringa J, Hofman A, Witteman JC, Tiemeier H. Association between serum cholesterol and noncardiovascular mortality in older age. J Am Geriatr Soc. 2011f;59:1779-85.
9. van Bemmel T, Gussekloo J, Westendorp RG, Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. J Hypertens. 2006g;24:287-92.
10. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008h;358:1887-98.
11. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002i;360:1623-30.
12. McMillan C, Bradley C, Razvi S, Weaver J. Evaluation of new measures of the impact of hypothyroidism on quality of life and symptoms: the ThyDQoL and ThySRQ. Value Health. 2008d;11:285-94.
13. Vigário P, Teixeira P, Reuters V, Almeida C, Maia M, Silva M, Vaisman M. Perceived health status of women with overt and subclinical hypothyroidism. Med Princ Pract. 2009f;18:317-22.

14. Reuters VS, Teixeira Pde F, Vigário PS, Almeida CP, Buescu A, Ferreira MM, et al. Functional capacity and muscular abnormalities in subclinical hypothyroidism. Am J Med Sci. 2009g;338:259-63.
15. Valenti G, Fabbo A. Subclinical hypothyroidism in the elderly. Arch Gerontol Geriatr. 1996h;22 Suppl 1:585-92.
16. Mainenti MR, Vigário PS, Teixeira PF, Maia MD, Oliveira FP, Vaisman M. Effect of levothyroxine replacement on exercise performance in subclinical hypothyroidism. J Endocrinol Invest. 2009h;32:470-3.
17. Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, Bauer DC. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med. 2005i;165:2460-6.
18. Simonsick EM, Newman AB, Ferrucci L, Satterfield S, Harris TB, Rodondi N, et al. Subclinical hypothyroidism and functional mobility in older adults. Arch Intern Med. 2009j;169:2011-7.
19. Dodd KS, Saczynski JS, Zhao Y, Goldberg RJ, Gurwitz JH. Exclusion of older adults and women from recent trials of acute coronary syndromes. J Am Geriatr Soc. 2011e;59:506-11.
20. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA. 2005f;294:716-24.
21. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical Thyroid Disease. JAMA. 2004e;291:228-38.
22. Helfand M, U.S. Preventive Services Task Force. Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2004f;140:128-41.
23. Holman R, Weisscher N, Glas CA, Dijkgraaf MG, Vermeulen M, de Haan RJ, Lindeboom R. The Academic Medical Center Linear Disability Score (ALDS) item bank: item response theory analysis in a mixed patient population. Health Qual Life Outcomes. 2005g;3:83.
24. Weisscher N, Wijbrandts CA, de Haan R, Glas CA, Vermeulen M, Tak PP. The Academic Medical Center Linear Disability Score item bank: psychometric properties of a new generic disability measure in rheumatoid arthritis. J Rheumatol. 2007h;34:1222-8.
25. Studenski, S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, Brach J et al. Gait speed and survival in older adults. JAMA. 2011; 305: 50-58.
26. Taekema DG, Gussekloo J, Westendorp RG, de Craen AJ, Maier AB. Predicting Survival in Oldest Old People. Am J Med. 2012.
27. Figueiredo S, Finch L, Mai J, Ahmed S, Huang A, Mayo NE. Nordic walking for geriatric rehabilitation: a randomized pilot trial. Disabil Rehabil. 2012i.

28. Mooijaart SP, Sattar N, Trompet S, Polisecki E, de Craen AJ, Schaefer EJ, et al. C-reactive protein and genetic variants and cognitive decline in old age: the PROSPER study. PLoS One. 2011j;6:e23890.
29. Watt T, Hegedüs L, Groenvold M, Bjorner JB, Rasmussen AK, Bonnema SJ, Feldt-Rasmussen U. Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO. Eur J Endocrinol. 2010a;162:161-7.
30. Waise A, Price HC. The upper limit of the reference range for thyroid-stimulating hormone should not be confused with a cut-off to define subclinical hypothyroidism. Ann Clin Biochem. 2009e;46:93-8.
31. Nanchen D, Gussekloo J, Westendorp RG, Stott DJ, Jukema JW, Trompet S, et al. Subclinical Thyroid Dysfunction and the Risk of Heart Failure in Older Persons at High Cardiovascular Risk. J Clin Endocrinol Metab. 2012f.
32. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, et al. The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. Am J Cardiol. 1999b;84:1192-7.
33. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975c;12:189-98.
34. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, et al. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA. 2006b;295:1033-41.
35. Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, et al. Fish intake and risk of incident atrial fibrillation. Circulation. 2004c;110:368-73.

**13.** SCHEDULE OF ASSESSMENTS

(*the final visit assessments may substitute for any assessment time between 12 and a maximum of 42 months).

| | | Months of follow up | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **0** | **6-8 wks** | **6m** | **12m** | **18m** | **24m** | **30m** | **36m** | **Final*** |
| | visit | Visit | call/visit | visit | call/visit | visit | call/visit | visit | visit |
| Age and gender | x | | | | | | | | |
| Medical history | x | | | | | | | | |
| Weight and waist circumference | x | | | x | | | | | |
| Concomitant medication | x | x | | x | | x | | x | x |
| **Safety and monitoring** | | | | | | | | | |
| Morbidity, mortality; hospitalisation, GP contacts | | x | x | x | x | x | x | x | x |
| SAEs | | 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 |
| **Outcomes** | | | | | | | | | |
| Cardiovascular events | | x | x | x | x | x | x | x | x |
| Quality of life | x | x | | x | | | | | x |
| Grip strength; Gait speed | x | | | x | | | | | x |
| Cognitive function | | | | | | | | | |
| MMSE | x | | | | | | | | |
| Letter Digit Coding Test | x | | | | | | | | x |
| Blood pressure | x | | | x | | | | | x |
| Functional status | | | | | | | | | |
| ADL; IADL | x | | | | | | | | x |
| Home support | | | | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Falls | x | | x | x | x | x |
| Institutionalisation | x | | | | | X |
| Treatment Satisfaction | | | | | | x |
| **Laboratory analysis** | | | | | | |
| Thyroid function | x | x | x | x | x | x |
| Hemoglobin | x | | x | | | |
| Blood samples for storage | x | | x | | | |

## Appendix Questionnaires

Appendix 1
Outcomes scales – application and scoring rules

a) Mini-mental State Examination
b) The Thyroid-specific Quality of Life Patient Reported Outcome Questionnaire (ThyPRO)
c) EuroQOL-5D
d) Hand Grip Strength
e) Letter Digit Coding Test
f) The Barthel Index of Activities of Daily Living
g) Older Americans Resources and Services (OARS) 7-item instrument
h) Gait speed
i) Treatment Satisfaction Questionnaire for Medication (TSQM vII)
j) Arthrosis questionnaire

**Folstein Mini Mental State Examination**

Overview
The mini-mental state examination (MMSE) is a popular screening test for cognitive impairment and is standard in many health-care systems. Using direct questioning, 8 different cognitive domains are tested across 11 items - with a total sum-score of 0-30. A total core of 24 or less is usually taken to represent dementia.

**Gestandaardiseerde MMSE** *RM Kok, FRJ Verhey (2002)*

1. a. Welk jaar is het?
   b. Welk seizoen is het?
   c. Welke maand van het jaar is het?
   d. Wat is de datum vandaag?
   e. Welke dag van de week is het? (0-5) ____

2. a In welk land zijn wij nu?
   b. In welke provincie zijn wij nu?
   c. In welke plaats zijn wij nu?
   d. In welke straat woont u?
   e. Wat is uw huisnummer? (0-5) ____

3. Ik noem nu drie voorwerpen. Wilt u die herhalen nadat ik ze alle drie gezegd heb? Onthoud ze want ik vraag u over enkele minuten ze opnieuw te noemen. Noem "appel, sleutel, tafel"; neem 1 seconde per woord. (max. 5 keer herhalen) (0-3) ____

4. Wilt u van de 100 zeven aftrekken en van wat overblijft weer zeven aftrekken en zo doorgaan tot ik stop zeg? (Laat 5 aftrekkingen maken en geef max. 1min de tijd. (Score: per goed antwoord)
   of:
   Wilt u het woord “worst” achterstevoren spellen?.
   (Score: per goede letter). (0-5) ____

5. Wilt u nogmaals de drie voorwerpen van zojuist noemen.
   (Score: Eén punt voor elk goed antwoord). (0-3) ____

6. Wat is dit? En wat is dat?
   (Wijs een pen en een horloge aan. Eén punt per goed antwoord). (0-2) ____

7. Wilt u de volgende zin herhalen: "Nu eens dit en dan weer dat".
   (Eén punt als de complete zin goed is) (0-1) ____

8. Wilt u deze woorden lezen en dan doen wat er staat'?
   (papier met daarop in grote letters: "Sluit uw ogen") (0-1) ____

9. Wilt u dit papiertje pakken met uw rechterhand, het dubbelvouwen
   en het op uw schoot leggen? (Eén punt voor iedere goede handeling). (0-3)
   ____

10. Wilt u voor mij een volledige zin opschrijven op dit stuk papier?
    (Eén punt wanneer de zin een onderwerp, gezegde en betekenis heeft) (0-1)
    ____

11. Wilt u deze figuur natekenen? Twee vijfhoeken die elkaar overlappen,
    zodat er een vierhoek tussen de vijfhoeken overblijft. Score: 1 punt (0-1)
    ____

TOTALE TEST SCORE (0-30):

*Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.*

**The Thyroid-specific Quality of Life patient-reported outcome measure (ThyPRO).**

Overview
The thyroid-specific quality of life (QoL) patient-reported outcome (PRO) measure for benign thyroid disorders has strong clinical validity and good test–retest reliability. The full scale consists of 84 items (plus a general quality of life question) and takes on average 14 minutes to complete.

Of the 13 ThyPRO domains, some are not relevant for subclinical hypothyroidism (e.g. goitre [11 questions], eye symptoms [8 questions] and cosmetic complaints [6 questions]) and other questions overlap with the general health related quality of life questions in the Euroqol; we have omitted these questions from the primary outcomes of the study.

We will ask the ThyPro questions for 2 domains (symptoms, fatigue), adding up to 19 questions.
In addition, at study close out only, we will ask an additional 28 questions to allow calculation of the ThyPRO39 as a secondary outcome measure. This comprehensive assessment has 12 domains, including 10 that are additional to our primary ThyPRO assessments. These domains are:

1. Memory concentration (3 items)
2. Nervousness and tension (3 items)
3. Psychological well-being (3 items)
4. Coping and mood swings (3 items)
5. Relationships with other people (3 items)
6. Daily activities (3 items)
7. Appearance (3 items)
8. Overall impact (1 item)
9. Goitre (3 items)
10. Eye symptoms (3 items)

*Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO. Watt T., Hegedus L., Groenvold M., Bjorner J.B., Rasmussen A.K., Bonnema S.J., Feldt-Rasmussen U. Journal of Endocrinology, Supplement. 162 (1) (pp 161-167), 2010.*

*Development of a Short Version of the Thyroid-Related Patient-Reported Outcome ThyPRO. Watt T, Bjorner JB, Groenvold M, Cramon P, Winther KH, Hegedus L, Bonnema SJ, Rasmussen K, Ware Jr JE, Feldt-Rasmussen U. Thyroid, 25 (10)(pp1069-1079), 2015.*

Quality of Life Questionnaire for Patients with Thyroid Disease

1. De eerste vragen gaan over klachten.
In de afgelopen 4 weken
1a) heeft u trillende handen gehad?
1b) heeft u veel moeten zweten?
1c) heeft u hartkloppingen (een zeer snelle hartslag) gehad?
1d) bent u kortademig geweest?
1e) bent u gevoelig geweest voor hitte?
1f) bent u gevoelig geweest voor kou?
1g) heeft u een toegenomen eetlust gehad?
1h) heeft u diarree gehad?
1i) heeft u last van uw maag gehad?
1j) heeft u gezwollen handen of voeten gehad?
1k) heeft u een droge huid gehad?
1l) heeft u een jeukerige huid gehad?

2. De volgende vragen gaan over vermoeidheid.
In de afgelopen 4 weken
2a) bent u moe geweest?
2b) bent u uitgeput geweest?
2c) heeft u moeite gehad om zichzelf te kunnen motiveren om wat dan ook te doen?
2d) heeft u zich helemaal 'op' gevoeld?

3. In de afgelopen 4 weken
   3a. Heeft u zich vol levenslustigheid gevoeld?
   3b. Heeft u zich vol energie gevoeld?
   3c. Heeft u kunnen omgaan met wat uw leven van u vergt?

Antwoordmogelijkheden; helemaal niet, een beetje, engiszins, redelijk veel, zeer veel

**Scale content of the ThyPRO-39**

The twelve ThyPRO-39 scales consist of the following items, summarized within each scale to form a scale score for each scale ranging 0-100. All question responses are graded as Not at all, A little, Some, Quite a bit, Very much.

Eleven questions (numbers 4, 5, 6, 7, 8, 9, 10, 11, 15, 16, 17) that have already been included in the assessment of hyperthyroid or hyperthyroid symptoms or tiredness will not be repeated. Therefore we will ask an additional 28 questions to complete the ThyPRO-39.

*Goitre symptoms:*
In de afgelopen 4 weken:
1) heeft u een gevoel van volheid in uw hals gehad?
2) Heeft u druk in uw keel gevoeld?
3) Heeft u een vervelend gevoel bij het slikken gehad?

*Hyperthyroid symptoms:*
In de afgelopen 4 weken:
4) heeft u trillende handen gehad?
5) heeft u veel moeten zweten?
6) heeft u hartkloppingen (een zeer snelle hartslag) gehad?
7) heeft u last van uw maag gehad?

*Hypothyroid symptoms:*
In de afgelopen 4 weken:
8) bent u gevoelig geweest voor kou?
9) heeft u gezwollen handen of voeten gehad?
10) heeft u een droge huid gehad?
11) heeft u een jeukerige huid gehad?

*Eye symptoms:*
In de afgelopen 4 weken:
12) heeft u droge ogen of het gevoel van “zand in de ogen” gehad?
13) heeft u slechter kunnen zien?
14) bent u erg gevoelig geweest voor licht?

*Tiredness:*
In de afgelopen 4 weken:
15) bent u moe geweest?
16) heeft u moeite gehad om zichzelf te kunnen motiveren om wat dan ook te doen?
17) heft u zich vol energie gevoeld?*

*Cognitive problems:*
In de afgelopen 4 weken:
18) heeft u moeite met onthouden gehad?
19) zijn uw gedachten traag of vaag geweest?
20) heeft u moeite geahd om zich te concentreren?

*Anxiety:*
In de afgelopen 4 weken:
21) heeft u zich bang of angstig gevoeld?
22) heeft u zich gespannen gevoeld?
23) heeft u zich niet op uw gemak gevoeld?

*Depressivity:*
In de afgelopen 4 weken:
24) heeft u zich verdrietig gevoeld?
25) heeft u zich ongelukkig gevoeld?
26) heeft u zelfvertrouwen gehad?*

*Emotional Susceptibility:*
In de afgelopen 4 weken:
27) heeft u opgemerkt dat u zich snel gestresst voelde?
28) heeft u stemmingswisselingen gehad?
29) heeft u het gevoel gehad controle te hebben over uw leven?*

*Impaired Social life:*
Is uw schildklieraandoening er in de afgelopen 4 weken de oorzaak van geweest dat:
30) u moeite had samen te zijn met anderen (bijvoorbeeld echtgenoot/echtgenote, kinderen, vriend/vriendin of anderen?
31) u het gevoel had anderen tot last te zijn?
32) u conflicten had met andere mensen?

*Impaired Daily life:*
Is uw schildklieraandoening er in de afgelopen 4 weken de oorzaak van geweest dat:
33) moeite had uw dagelijks leven in geode banen te leiden?
34) niet kon deelnemen aan wat er om u heen gebeurde?
35) het gevoel had alsof alles meer tijd in beslag nam?

*Cosmetic Complaints:*
In de afgelopen 4 weken:
36) heeft uw schildklieraandoening een invloed gehad op uw uiterlijk (bijvoorbeeld zwelling van de hals, veranderingen aan de ogen, veranderingen in gewicht?
37) heeft u er last van gehad dat andere mensen naar u keken?
38) heeft uw schildklieraandoening beïnvloed wat voor kleren u draagt?

In addition, ThyPRO contains one item not included in any multi-item scale:
In de afgelopen 4 weken:
39) had uw schildklieraandoening een negatief effect op uw kwaliteit van leven?

*Positively worded items are scored reversely when constructing scales

## The EuroQol5D

Overview
EQ-5D™ is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.
EQ-5D is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face-to-face interviews. It is cognitively simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.
The EQ-5D self-report questionnaire (EQ-5D) essentially consists of two pages comprising the EQ-5D descriptive system and the EQ Visual Analogue Scale. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a one-digit number expressing the level selected for that dimension. The digits for five dimensions can be combined in a five-digit number describing the respondent's health state.

*Adapted from: EQ-5D homepage http://www.euroqol.org/ (last accessed July 2011). EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990 December;16(3):199-208.*

1. Mobiliteit
    - Ik heb geen problemen met lopen
    - Ik heb enige problemen met lopen
    - Ik ben bedlegerig
2. Zelfzorg
    - Ik heb geen problemen om mijzelf te wassen of aan te kleden
    - Ik heb enige problemen om mijzelf te wassen of aan te kleden
    - Ik ben niet in staat mijzelf te wassen of aan te kleden
3. Dagelijkse activiteiten (bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)
    - Ik heb geen problemen met mijn dagelijkse activiteiten
    - Ik heb enige problemen met mijn dagelijkse activiteiten
    - Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren
4. Pijn/klachten
    - Ik heb geen pijn of andere klachten
    - Ik heb matige pijn of andere klachten
    - Ik heb zeer ernstige pijn of andere klachten
5. Stemming
    - Ik ben niet angstig of somber
    - Ik ben matig angstig of somber
    - Ik ben erg angstig of somber

EQ Visual Analogue Scale score

### Hand Grip Strength

Will be measured using isometric dynamometry. A Jamar hand dynamometer will be used, recorded score will be best of 3 attempts using dominant hand.

*Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J et al. Frailty in older adults: evidence for a phenotype. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2001 March;56(3):M146-M156.*

**Letter Digit Coding Test (LDCT)**

The letter digit coding test is used to measure the speed of processing of general information and draws upon several cognitive processes simultaneously, such as visual scanning, perception, visual memory, visuoconstruction and motor functions.

The subject is given a piece of paper with nine symbols corresponding with nine digits. Next on this piece of paper are three rows of digits with empty spaces below them. The subject is asked to fill in as many corresponding symbols as possible in 90 seconds

*Smith A. The Symbol Digit Modalities Test. A neuropsychological test for economic screening of learning and other cerebral disorders. Learning Disorders 1968;3:82-91.*

**The Barthel Index of Activities of Daily Living**

Overview
The Barthel Index (BI) is an ordinal scale describing basic (or personal) activities of daily living (ADL).
First used around 1955, Barthel's eponymous scale quickly became popular in rehabilitation, such that it is now arguably the most popular ADL scale in clinical practice.
The scale describes ten tasks and is scored according to amount of time or assistance required by the patient. Total score is from 0-100, with lower scores representing greater nursing dependency.
Several authors have proposed modifications to Barthel's original scale. Distinguishing between these BI scales is crucial, as even minor changes to scales can produce substantial differences in scoring. It is unfortunate that many of these BI variations maintain the descriptor "Barthel Index". There is no consensus on the optimal version. For this study we will use the 10 item scale, scoring 0-20 as described by Collin and Wade.

*Adapted from: Quinn TJ, Langhorne P, Stott DJ. Barthel Index for stroke trials–development, properties and application. Stroke 2011; 42:1146-1151.*

| Onderwerp | Omschrijving | Score | Patiënt-score |
|---|---|---|---|
| **Darm** | Incontinent | 0 | |
| | Af en toe een ongelukje | 1 | |
| | Continent | 2 | |
| **Blaas** | Incontinent of catheter en niet in staat daarmee om te gaan | 0 | |
| | Af en toe een ongelukje (max 1 maal / 24 uur) | 1 | |
| | Continent (gedurende meer dan 7 dagen) | 2 | |
| **Uiterlijke verzorging** | Heeft hulp nodig | 0 | |
| | Onafhankelijk ten aanzien van: gezicht, haar, tanden, scheren | 1 | |
| **Toiletgebruik** | Afhankelijk | 0 | |
| | Heeft enige hulp nodig maar kan sommige dingen zelf | 1 | |
| | Onafhankelijk (op en af; uit- en aankleden, afvegen) | 2 | |
| **Eten** | Niet in staat tot zelfstandig eten | 0 | |
| | Heeft hulp nodig bij snijden, smeren van boter, enzovoort | 1 | |
| | Onafhankelijk | 2 | |
| **Transfer (van bed naar stoel gaan** | Niet in staat tot zelfstandige transfer | 0 | |
| | Veel hulp nodig (1-2 mensen, lichamelijk) | 1 | |

| | | | |
|---|---|---|---|
| **en omgekeerd)** | Weinig hulp nodig; met woorden of lichamelijk | 2 | |
| | Onafhankelijk | 3 | |
| **Mobiliteit** | Kan zich niet verplaatsen | 0 | |
| | Onafhankelijk met rolstoel, inclusief hoeken, enzovoort | 1 | |
| | Loopt met hulp van 1 persoon; met woorden of lichamelijk | 2 | |
| | Onafhankelijk (maar mag gebruik maken van een hulpmiddel, bijv. een stok) | 3 | |
| **Aan-/uitkleden** | Afhankelijk | 0 | |
| | Heeft hulp nodig maar kan ongeveer de helft zelf | 1 | |
| | Onafhankelijk | 2 | |
| **Trappen lopen** | Niet toe in staat tot trappenlopen | 0 | |
| | Heeft hulp nodig (met woorden, lichamelijk, met het dragen van een hulpmiddel) | 1 | |
| | Onafhankelijk naar boven en naar beneden | 2 | |
| **Baden / douchen** | Afhankelijk | 0 | |
| | Onafhankelijk | 1 | |
| | | **Totaal** | …….. |

*Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. Maryland State Medical Journal 1965;14:61-5.*
*Collin C, Wade DT, Davis S, Horne V.The Barthel ADL index:a reliability study.Int Disabil Studies.1988;10:61-3.*
*Klinimetrische evaluatie van de Barthel-index, een maat voor beperkingen in het dagelijks functioneren. De Haan, R. et al. Ned Tijdschr Geneeskd 1993; 137:917-921*

**7-item OARS**

Instrumental activities of daily living will be described using a short (7-item) questionnaire derived from the Older Americans Resources and Services (OARS) instrument.

Kunt u de telefoon gebruiken:
2. Zonder hulp, waaronder nummers opzoeken, draaien en bellen.
1. Met enige hulp (kan de telefoon beantwoorden of de telefoniste bellen in geval van nood, maar heeft een speciale telefoon of hulp nodig om het nummer te vinden of te bellen).
0. Geheel niet in staat om de telefoon te beantwoorden / te gebruiken.
- . Niet beantwoord.

Kunt u plaatsen bereiken die buiten loopafstand liggen:
2. Zonder hulp (bijv. door met uw eigen auto te rijden of alleen te reizen met de bus of taxi).
1. Met enige hulp (iemand nodig om u te helpen of met u mee te gaan als u reist).
0. Niet in staat te reizen tenzij er noodregelingen zijn getroffen voor speciaal vervoer zoals een ambulance.
- . Niet beantwoord.

Kunt u boodschappen doen of kleding kopen (in de veronderstelling dat u vervoer heeft):
2. Zonder hulp (zelf voorzienend in al uw winkelbehoeften).
1. Met enige hulp (iemand nodig om met u mee te gaan als u gaat winkelen).
0. Geheel niet in staat te winkelen.
- . Niet beantwoord.

Kunt u uw eigen maaltijden bereiden:
2. Zonder hulp (zelf volledige maaltijden voorbereiden en koken).
1. Met enige hulp (in staat sommige dingen te bereiden maar niet in staat zelf volledige maaltijden te koken).
0. Geheel niet in staat enige maaltijd te bereiden.
- . Niet beantwoord.

Kunt u zelf het huishouden doen:
2. Zonder hulp (in staat de vloeren schoon te maken etc.).
1. Met enige hulp (in staat licht huishoudelijk werk te doen maar hulp nodig bij zwaarder werk).
0. Geheel niet in staat enig huishoudelijk werk te doen.
- . Niet beantwoord.

Kunt u uw eigen medicijnen beheren en innemen:
2. Zonder hulp (de juiste dosis op de juiste tijd).
1. Met enige hulp (in staat de medicijnen in te nemen als iemand ze voor u klaarlegt en u eraan herinnert ze in te nemen)

0. Geheel niet in staat medicijnen in te nemen.
- . Niet beantwoord.

Kunt u uw eigen geldzaken regelen?:
2. Zonder hulp (pinnen, cheques uitschrijven, rekeningen betalen etc.).
1. Met enige hulp (geen problemen met dagelijkse aankopen maar hulp nodig bij het beheren van het chequeboek en het betalen van rekeningen etc.).
0. Geheel niet in staat met geld om te gaan.
- . Niet beantwoord.

*Fillenbaum GG, Smyer MA. The development, validity and reliability of the OARS multidimentional functional assessment questionnaire. Journal of Gerontology 1981;36:428-34*.

### Gait speed

Gait speed is measured at the place of residence of the participants. A pre-measured 6-meter tape will be laid down on the floor by the research nurse. The participant is instructed to walk these 6 meters at regular speed, with or without walking aid. The time to finish the 6 meters is recorded in seconds. The time will be measured in three trials, of which the average will be used for further calculations.

*Measurement of Gait Speed of Older Adults is Feasible and Informative in a Home-care Setting. Bohannon, R. Journal of Geriatric Physical Therapy. 32(1). 22-23, 2009*

**Falls questionnaire**

DE VAL INVENTARISATIELIJST INVULDATUM ……

NAAM …….....GEBOORTEDATUM …….

Geeft s.v.p. met een vinkje het goede antwoord aan
Heeft U in het laatste jaar:

| | JA | NEE |
|---|---|---|
| één of meer keer een val gehad | | |
| zo ja, hoe vaak (eventueel schatting) | …….. | |
| | | |
| een breuk door een val gehad | | |
| zo ja, wat is er gebroken | …….. | |
| | | |
| angst om te vallen | | |
| | | |
| een loophulpmiddel nodig (stok, rollator ed.) | | |
| | | |
| moeite om uit een normale stoel op te staan | | |
| | | |
| hulp nodig van anderen bij de toiletgang | | |
| | | |
| een rolstoel nodig om u te verplaatsen | | |
| | | |
| spier of gewrichtspijn | | |
| | | |
| stijfheid in spieren en gewrichten | | |
| | | |
| zwakke spieren | | |
| | | |
| duizeligheid, evenwichtsstoornissen of licht gevoel in het hoofd | | |
| | | |
| gevoelloosheid in de voeten of benen | | |
| | | |
| slecht zien | | |
| | | |
| ongewild urineverlies | | |
| | | |
| medicijnen voor angst, slapeloosheid of nervositeit gebruikt | | |
| | | |
| diabetes (suikerziekte) | | |
| | | |
| ziekte van parkinson | | |

**TSQM (version II) items:**

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication over the last two to three weeks, or since you last used it. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
□ Extremely Dissatisfied
□ Very Dissatisfied
□ Dissatisfied
□ Somewhat Satisfied
□ Satisfied
□ Very Satisfied
□ Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
□ Extremely Dissatisfied
□ Very Dissatisfied
□ Dissatisfied
□ Somewhat Satisfied
□ Satisfied
□ Very Satisfied
□ Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?
□ Yes
□ No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels, etc.)?
□ Extremely Dissatisfied
□ Very Dissatisfied
□ Somewhat Satisfied
□ Slightly Dissatisfied
□ Not at all Dissatisfied
□ Not Applicable

5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake, etc.)?
□ Extremely Dissatisfied
□ Very Dissatisfied
□ Somewhat Satisfied
□ Slightly Dissatisfied
□ Not at all Dissatisfied
□ Not Applicable

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?
□ Extremely Dissatisfied
□ Very Dissatisfied

□ Somewhat Satisfied
□ Slightly Dissatisfied
□ Not at all Dissatisfied
□ Not Applicable

7. How satisfied or dissatisfied are you with how easy the medication is to use?
□ Extremely Dissatisfied
□ Very Dissatisfied
□ Dissatisfied
□ Somewhat Satisfied
□ Satisfied
□ Very Satisfied
□ Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?
□ Extremely Dissatisfied
□ Very Dissatisfied
□ Dissatisfied
□ Somewhat Satisfied
□ Satisfied
□ Very Satisfied
□ Extremely Satisfied

9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?
□ Extremely Dissatisfied
□ Very Dissatisfied
□ Dissatisfied
□ Somewhat Satisfied
□ Satisfied
□ Very Satisfied
□ Extremely Satisfied

10. How satisfied are you that the good things about your medication outweigh the bad things?
□ Extremely Dissatisfied
□ Very Dissatisfied
□ Dissatisfied
□ Somewhat Satisfied
□ Satisfied
□ Very Satisfied
□ Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?
□ Extremely Dissatisfied
□ Very Dissatisfied
□ Dissatisfied
□ Somewhat Satisfied
□ Satisfied
□ Very Satisfied
□ Extremely Satisfied

**Side effects:**

12) If answered yes to Question 3, which side effects in particular?
……

**Post-trial continuation:**
13) "If offered, would you continue with this treatment after the trial?

| | | |
|---|---|---|
| Yes | No | Don't know |

**Therapy vs Placebo:**
14) "In your opinion, did you receive the active thyroid hormone or placebo during the trial?"

| | | |
|---|---|---|
| Active thyroid hormone | Placebo | Don't know |

**Other remarks:**
15) Would you like to report any other remark about the treatment?

**GEGEVENS OVER HET BEWEGINGSAPPARAAT/ARTROSE**

1a. Heeft u nu of in de afgelopen 12 maanden last gehad van ernstige of hardnekkige klachten in of rondom gewrichten (pijn, stijfheid en/of zwellingen)?

☐ Nee ☐ Ja, niet door arts vastgesteld ☐ Ja, door arts vastgesteld

1b. Kunt u aangeven welke gewrichten dit betreft (meerdere keuzes mogelijk)?

| | | |
|---|---|---|
| Schouder | ☐ Links | ☐ Rechts |
| Elleboog | ☐ Links | ☐ Rechts |
| Pols | ☐ Links | ☐ Rechts |
| Hand/vingers | ☐ Links | ☐ Rechts |
| Heup | ☐ Links | ☐ Rechts |
| Knie | ☐ Links | ☐ Rechts |
| Enkel | ☐ Links | ☐ Rechts |
| Voet/tenen | ☐ Links | ☐ Rechts |

2. Heeft een huisarts of specialist u ooit verteld dat u een vorm van reuma heeft? Zo ja, welke vorm?

☐ Nee ☐ Ja, namelijk

☐ Reumatoïde artritis
☐ Chronisch reuma
☐ Artritis psoriatica
☐ Ziekte van Bechterew
☐ Chronisch reuma
☐ Systemische lupus erythomatodes (SLE)
☐ Jicht
☐ Syndroom van Reiter
☐ Tendinitis/bursitis
☐ Carpaal tunnelsyndroom
☐ Fibromyalgie
☐ Anders, nl.

3. Heeft een huisarts of specialist u ooit verteld dat u gewrichtsslijtage of artrose heeft? Zo ja, in welke gewrichten?

☐ Nee ☐ Ja, namelijk

☐ Heupartrose
☐ Knieartrose
☐ Artrose handen
☐ Spondylartrose
☐ Anders, nl.

4. Bent u ooit geopereerd in verband met reuma of gewrichtsslijtage?

☐ Nee ☐ Ja, namelijk……