# Analysis plan PRODEMOS trial

Version date: 23 November 2020

## Contents

# 1. Background

In PRODEMOS we will investigate the effectiveness and implementation of an innovative mHealth intervention to optimize self-management of dementia risk factors in individuals at increased risk of dementia, aged between 55 and 75 years, of low SES in the United Kingdom (UK) and from the general population in greater Beijing, with the aim to reduce overall dementia risk.

This Analysis plan will be used as a work description for all the persons who are involved in the analyses of the PRODEMOS trial (ISRCTN15986016).

# 2. Study Objectives

## *Primary Objectives*

The study has two main objectives:

- To investigate whether an interactive mHealth intervention, designed to optimise the management of dementia risk factors, leads to reduction of dementia risk in middle-aged and older individuals (55 - 75 years old) of low SES / in a middle-income country, operationalised as the CAIDE dementia risk score.

- To evaluate the implementation of an mHealth intervention for dementia prevention, operationalised as the acceptability, adoption, appropriateness, feasibility, fidelity, cost, coverage, and sustainability. A separate analysis plan will be written for the implementation outcomes.

## *Secondary Objectives*

To evaluate the effectiveness of the mHealth intervention on the following secondary outcomes (questionnaires used to assess these outcomes are presented in table 1):

- Individual modifiable components of the CAIDE risk score (i.e. blood pressure, BMI, total cholesterol, physical activity)
- Smoking
- Diet
- Estimated 10-year cardiovascular disease risk
- Lifestyle for Brain Health (LIBRA) index
- Number of uncontrolled dementia risk factors
- Incident diabetes
- Incident dementia and Mild Cognitive Impairment (MCI)
- Incident cardiovascular disease (stroke, myocardial infarction)
- Mortality
- Disability
- Anxiety
- Self-management
- Medication adherence and number of medications
- Depressive symptoms
- Quality of life
- Number of hospital admissions
- Cost-effectiveness (a separate analysis plan is available on ISRCTN website)

**Table 1: Self-assessment questionnaires**

| **Domain** | **Questionnaire(s)** |
|---|---|
| Physical exercise | International Physical Activity Questionnaire (IPAQ short) |
| Diet | UK: Cleghorn short form food frequency questionnaire<br><br>China: China Kadoorie Biobank food frequency questionnaire |
| Disability | WHO Disability Assessment Schedule 2.0 (WHODAS 2.0, 12-item) |
| Anxiety | Hospital Anxiety and Depression Scale (HADS, anxiety only) |
| Depressive symptoms | Geriatric Depression Scale 15-item (GDS-15) |
| Self-management | Partners In Health (PIH) |
| Quality of Life (cost-effectiveness analysis) | EuroQol (EQ-5D 3L) |
| Wellbeing / capability (cost-effectiveness analysis) | ICEpop CAPability measure for Adults (ICECAP-A) |

The clinical outcomes - stroke, myocardial infarction, MCI, dementia and death - will be adjudicated by an independent outcome committee in each country.

# 3. Study Design

This chapter briefly describes the study design of the PRODEMOS trial.

## *The intervention*

The study is a multi-national, multicenter, investigator initiated, prospective, open-label blinded endpoint (PROBE) RCT with 12-18 months intervention and follow-up. Recruitment and inclusion of participants take place in two countries (United Kingdom (UK) and China) following a centralized randomization procedure coordinated from the Netherlands. Inclusion and exclusion criteria for the study population are similar in both countries, but recruitment strategies will differ, due to differences in local health care systems. The Amsterdam University Medical Centre (Amsterdam UMC), location AMC is the coordinator of the study.

The delays caused by the COVID-19 pandemic have forced us to rethink the original design of our PRODEMOS study. The original study duration was intended to be 18 months, with a recruitment period of 12 months, meaning, in total, 30 months would be required for complete recruitment and complete follow-up. This has become a major challenge due to the delays and the H2020 funding that will end by 31-12-2022 – and perhaps 6 months later if we will be granted a cost-neutral extension. We therefore incorporated a flexible design, meaning that people recruited later into the trial, may have a shorter follow-up, with a minimum of 12 months. This flexible design will allow a maximum number of person-months in the study to be achieved, given the current and potential future COVID-restrictions. This will not impact the implementation outcomes of our study. In fact, it will provide additional information on sustainability of the intervention.

## *Study population*

People aged between 55 and 75, of low SES in the UK and from the general population in China, with two or more dementia risk factors and in possession of a smartphone are eligible for participation.

### Inclusion criteria

The study aims to investigate the effectiveness and implementation of a mHealth intervention over 12-18 months. Few inclusion and exclusion criteria apply, to achieve maximal external validity towards a broad population. Eligibility is met when a potential participant meets the following criteria:

- Age ≥ 55 years ≤ 75 years
- Good proficiency of the national language (English in UK, Mandarin in China)
- Possession of a smartphone

- Persons who currently don't have good access to or use of preventive health care, including Low SES in the UK, operationalised as living in a postal code area ranked as equal to or less than the 3rd decile of the index of multiple deprivation (IMD) **OR** inhabitant of the Greater Beijing area irrespective of SES.
- ≥ two dementia risk factors defined as:
    - Manifest cardiovascular disease, as diagnosed by specialist or general practitioner
    - Lack of physical exercise (self-reported), defined as below the World Health Organization (WHO) norm (five times a week 30 minutes or a total of 150 minutes per week of intermediate exercise)
    - Active smoking (self-reported use of any sort of tobacco in any quantity)
    - Hypertension, defined by any of the following:
        - Diagnosis by specialist or general practitioner.
        - Currently on anti-hypertensive drugs.
        - Baseline blood pressure: ≥ 140/90 mmHg;
    - Overweight, defined by any of the following:
        - Body mass index (BMI) ≥ 30 (UK) or 28 (China)
        - Waist circumference men ≥ 102 cm (UK) or 90 cm (China), women ≥ 88 cm or 85 cm (China)
    - Diabetes mellitus, defined by any of the following:
        - Diagnosis by specialist or general practitioner
        - Use of insulin or other blood glucose-lowering medication
    - Depression
        - Current depression
            - Currently on anti-depressive medication or receiving psychotherapy
        - History of treatment (i.e. drug therapy, psychotherapy etc.) for depression
    - Dyslipidaemia, defined by any of the following:
        - Diagnosis by specialist or general practitioner
        - Use of lipid-lowering drugs
        - For UK: baseline total cholesterol ≥5.0 mmol/L (In China cholesterol levels will be obtained from full blood samples. Therefore, these cannot be incorporated in the inclusion criteria.)

### Exclusion criteria

- Previously diagnosed with dementia by a specialist or general practitioner
- Mini Mental State Examination (MMSE) < 24 for participants with International Standard Classification of Education (ISCED) levels > 1, MMSE < 21 for participants with ISCED level = 1.
- Any condition expected to limit 18-months compliance and follow-up, including metastasised malignancy or other terminal illness
- Smartphone illiteracy, defined as not being able to send a message from a smartphone
- Visual impairment interfering with operation of a smartphone
- Participating in another RCT based on lifestyle behavioural change
- Present alcohol or illicit drug abuse; binge drinking is not an exclusion criterion – this is a potential target for behaviour change

## *Sample size calculation*

In the Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial the mean difference in Cardiovascular risk factors, Aging and Incidence of Dementia (CAIDE) risk score after the first two years of follow up between the intervention and control group was 0.186. Attrition after the first two years of follow-up was 21%. With 80% power, a 0.05 two-sided significance level, accounting for an estimated 21% attrition, and a mean difference in change in CAIDE of 0.186, the required sample size is estimated to be 2319 participants in total. To allow for unexpected factors, this number was raised to 2400.

It is plausible that the shorter intervention duration in the flexible design will result in a larger effect on the primary outcome, due to the challenge of sustaining a healthy lifestyle over longer periods of time (Beishuizen C et al, JMIR 2016). We will perform a new sample size calculation if the number of people that will receive a significantly shorter intervention duration is substantial. Note: as the CAIDE score is not a time-to-event outcome, the reduced total number of person-months are not a part of the sample size calculation.

## *Randomisation procedures*

Randomisation will take place at the Department of Biostatistics at Amsterdam University Medical Centre, location AMC using a computer algorithm in a 1:1 manner, stratified by country. Participants whose partner also participates in PRODEMOS will automatically be allocated to the same treatment arm, to avoid contamination. Together those two partners allocated to the same treatment arm form the smallest conceivable cluster. Based on our experience in the Healthy Aging Through Internet Counselling in the Elderly (HATICE) study, this is not expected to affect the power of the study.

At the end of the baseline assessment randomisation takes place stratified by country. A computer algorithm will be used to generate an unpredictable allocation sequence which is built into the platform for a web-based randomisation system and will be concealed for participants, coaches and researchers alike. Due to the large sample within each participating region, no block-randomisation was deemed necessary. After randomisation, the participants randomised to the coach-supported interactive intervention are assigned a coach and granted access to the interactive app. The control participants get access to the app without interactive features and without coach.

The randomisation scheme is accessible at all hours, and in case of a technical emergency (like power failure) assessors are instructed to toss a coin to determine allocation.

More information about the intervention and the measurements can be found in the trial protocol.

# 4. Statistical Analysis

## *General*

Prior to analysis, all data will be checked for missing values and miscoding, and univariate analyses will be performed to compare the distribution of variables and to identify abnormalities/outliers.

Primary and secondary outcomes will be analysed according to the "intention to treat" principle for all participants who underwent baseline assessment and subsequent randomization and with available outcome data.

## *Primary outcome*

The PRODEMOS randomized controlled trial has two main objectives and two primary outcome measures 1) dementia risk as measured using the CAIDE score and 2) implementation of the mHealth application.

The main consideration for the decision to use dementia risk as measured using the CAIDE score as primary outcome is that in this population, no clinical outcome related to cognitive functioning can be designated as primary outcome within a reasonable follow-up duration and trial sample size. Therefore, within the hybrid trial design, PRODEMOS can be considered as a proof-of-principle trial.

The effect (i.e. the between-group difference in change from baseline to the end of follow-up) on the CAIDE score will be analyzed using linear mixed effects models according to the intention to treat principle taking clustering within partner pairs and country into account by testing best fit for random intercept and/or slope. For those participants who stopped participating in the study during follow-up and cannot be retrieved for a final study assessment, no information on the outcomes is available, precluding the use of their data in the analyses. If needed, we will adjust for baseline imbalances and take clustering of the intervention within centre or coach into account. No imputation of the CAIDE score will be done for the primary analysis.

### Sensitivity analyses

- A per protocol analysis will be performed.
- We will explore the interaction of intervention duration with the effect of the invention on the CAIDE score by adding an interaction term (intervention duration* randomisation group) to the main model. This will give insight into the potential additional intervention effect in participants for whom only a shorter follow-up time than 18 months was feasible.

- If one or more of the variables needed to calculate the CAIDE score is likely *not* missing not at random (MNAR), this variable (e.g. total cholesterol at the final assessment) will be multiple imputed in a sensitivity analysis.

## Predefined subgroup analyses

Separate analyses on the effect of the intervention on the primary outcome will be performed for:

- *Country (UK, China).* Due to cultural differences the intervention may have different effects in the two countries. Also, the coaching might be differently organised in both countries (e.g. located within the own GP practice, health care centre)
- *Gender.* Lifestyle change may have different effects on dementia risk factors by gender.
- *Age group.* Lifestyle change may have differential effects on dementia risk factors across age groups: there may be a smaller window of opportunity for prevention among the oldest old.
- *Participants with and without a history of cardiovascular disease (CVD).* The room for improvement may be larger in participants without CVD, as people with a history of CVD are as a rule already participating in disease management programs (including pharmacological treatment for high blood pressure and high cholesterol, and sometimes coaching for lifestyle change).
- *Number of risk factors.* Room for improvement is larger if people have more risk factors.
- *Willingness to change lifestyle at the start of the trial.* If people participate with the intention to change their lifestyle, the intervention is likely to be more effective.
- *Participation with partner.* The effect of a participating partner can be substantial as he or she can stimulate and support the other in behavioral changes.
- *Consistent coaching.* Compliance to and effect of the intervention may be higher, when baseline and coaching are performed by one and the same coach.
- *Number of goals.* A higher number of goals generally indicates higher compliance to the intervention.

Interaction terms will be included to test for between-subgroup differences in intervention effects.

## *Secondary outcomes*

Secondary outcomes are the individual modifiable components of the CAIDE risk score (i.e. blood pressure, BMI, total cholesterol, physical activity, all modelled continuously), smoking, incident diabetes, the estimated 10-year cardiovascular disease risk, the LIBRA score, the number of uncontrolled risk factors in the CAIDE risk score (0-4, using the cut-off values of the CAIDE score), dietary quality (country specific z-scores), disability, anxiety, self-management, medication adherence,

number of medications, number of hospital admissions, depressive symptoms, quality of life, incident dementia, incident MCI, incident cardiovascular disease (combination of stroke, and myocardial infarction: if the number of events allow for it, also the effect on the individual CVDs will be assessed), mortality (total, cardiovascular, other). For the cost-effectiveness a separate analysis plan was written.

The effect on the individual components of the CAIDE score and the 10-year CVD risk score will be analysed using linear mixed effects models according to the intention to treat principle taking clustering within partner pairs and country into account. Self-assessment scales, which are mostly ordinal, will be regarded as linear scales, if the instruments' characteristics reasonably allow for this. Poisson regression or zero-inflated models may be applied to distributions resembling count or zero-inflated data. The choice of the final model will be a compromise between optimal fit and interpretability of the results for a general clinical public.

Prevalence ratios will be used, in case a self-assessment instrument has a defined cut-off for the presence or absence of a condition. For (clinical) dichotomous outcomes, such as incident CVD, dementia or mortality, Cox-proportional hazard models will be used using time since baseline as timescale. A sensitivity analysis will be performed using age as timescale.