

DO-HEALTH – VitaminD3-Omega3-Home Exercise- HeALTHy Ageing and Longevity Trial

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Coordinator: Prof. Dr. med. Heike A. Bischoff-Ferrari, DrPH, UZH

DO-HEALTH – Publishable summary**Period covered: from M1 to M18**Periodic report: 1st 2nd 3rd 4th **Author(s):** All DO-HEALTH partners**Approved by the Coordinator** **Date:** 02/09/2013**Keywords:** DO-HEALTH publishable summary**Number of pages:** 7**Document Identifier:** DO-HEALTH_Publishable
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Document History

When	Who	What action
06/2013	NOVAMEN	Templates sent to the partners
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I. List of beneficiaries

Beneficiary Number*	Beneficiary name	Beneficiary short name	Country
1	UNIVERSITAET ZUERICH	UZH	CH
2	UNIVERSITÉ DE GENÈVE	UGE	CH
3	UNIVERSITAETSSPITAL BASEL	UHB	CH
4	CENTRE HOSPITALIER UNIVERSITAIRE DE TOULOUSE	CHUT	FR
5	CHARITE - UNIVERSITAETSMEDIZIN BERLIN	CHARITE	DE
6	FRIEDRICH-ALEXANDER-UNIVERSITAT ERLANGEN NURNBERG	FAU	DE
7	MAX RUBNER INSTITUT BUNDESFORSCHUNGSINSTITUT FUR ERNAHRUNG UND LEBENSMITTEL	MRI	DE
8	MEDIZINISCHE UNIVERSITAET INNSBRUCK	IMU	AT
9	UNIVERSIDADE DE COIMBRA	UCO	PT
10	THE UNIVERSITY OF MANCHESTER	UNIVERSITY OF MANCHE	UK
11	THE UNIVERSITY OF SHEFFIELD	USFD	UK
12	INTERNATIONAL OSTEOPOROSIS FOUNDATION	IOF	CH
13	NOVAMEN SAS	NOVAMEN	FR
14	FERRARI STEPHEN MARIO	FDS	CH
15	ULTRA IMAGES AG	ULTRA	CH
16	TECHNISCHE UNIVERSITAET DRESDEN	TUD	DE
17	PHARMALYS LTD	Pharmalys	UK
18	MAETZEL ANDREAS - MAETZEL CONSULTING	Maetzel	CH
19	DSM NUTRITIONAL PRODUCTS LTD	DNP	CH
20	NESTEC S.A.	NESTEC	CH
21	ROCHE DIAGNOSTICS (SCHWEIZ) AG	ROCHE	CH
22	GUT PICTURES	Gut pictures	CH

II. Publishable summary

II.1. Summary description of project context and objectives

The European population is ageing, and the number of adults age 70 and older is predicted to increase from 25% to 40% by 2030¹⁻⁵ as will the number of people with age-related chronic diseases. Thus interventions that prolong the number of years during which **seniors are in good health and free from disabilities** will have a striking impact on public health.

The goal of DO-HEALTH is to extend healthy life expectancy by delaying physiologic aging at multi-organ sites in European seniors and to reduce healthcare costs via the implementation of effective and broadly applicable disease prevention interventions. This will be achieved within a large multi-centre clinical trial enrolling 2152 community-dwelling men and women aged 70 and older, when chronic diseases increase substantially. The randomized-controlled trial will test the **individual and the additive (“multi-modal”) benefit** of 2000 IU vitamin D/day, 1 gram of omega-3 fatty acids per day and a simple home exercise program in an efficient factorial trial design. **DO-HEALTH will establish evidence for 5 primary endpoints:** (1) the risk of incident non-vertebral fractures; (2) the risk of functional decline; (3) the risk of blood pressure increase; (4) the risk of cognitive decline; (5) and the rate of any infection.

Key secondary endpoints include risk of hip fracture, rate of falls, knee pain in symptomatic knee osteoarthritis, glucose tolerance, oral health, gastro-intestinal symptoms, mental health, quality of life, and mortality. The trial duration will be 3 years to establish long-term efficacy and safety data for the 3 interventions. Follow-up will be in-person and in 3-monthly intervals (4 clinical visits and 9 phone follow-up calls). **DO-HEALTH will further assess the comparative effectiveness of the interventions** by evaluating reasons why or why not seniors adhere to them; and **will assess their cost-benefit** in a health economic model based on documented health care utilization and observed incidence of chronic disease.

II.2. Description of the work performed since the beginning of the project and the main results achieved so far

Regulatory approval for all 7 recruitment centers

All 7 centers have achieved ethical and regulatory approval for the DO-HEALTH clinical trial by April 2013. Recruitment was initiated in December 2012 at the University of Zurich site (Centre on Aging and Mobility). The DO-HEALTH study approval has been delayed as DO-HEALTH has been evaluated as a drug study in 6 of the 7 centres. This is in part explained by the higher dose of vitamin D than currently recommended in diet guidelines (2000 IU per day instead of 800 IU per day) and the aspect that DO-HEALTH tests disease prevention. The only country that approved DO-HEALTH as a dietary supplement study is Austria.

All center are actively recruiting

Due to the need to undergo regulatory approval for DO-HEALTH at 6 of 7 sites (see above), we have a 6-month delay of recruitment initiation. This has been communicated in the first amendment to the EC in February 2013. Since July 8th 2013, all 7 DO-HEALTH centers are actively recruiting. From December 2012 to August 31st 2013, we have enrolled 532 participants in DO-HEALTH and thereby successfully achieved the milestone of 25% recruitment. The recruitment status is updated continuously for the public and partners of DO-HEALTH at the DO-HEALTH website: <http://do-health.eu/wordpress/>

Study investigational product manufactured and distributed to the recruiting centers

First batch of the DO-HEALTH capsules:

DSM Nutritional Products sent the first batch of the active ingredients Vitamin D3 and Omega-3 fatty acid to the manufacturer (Swisscaps/ Anova) for encapsulation in soft gel capsules. The filling of the softgel capsules into plastic containers was performed by NextPharma.

Capsule release:

The DSM analytical services laboratory performed from the produced softgel capsules analytical testing for the correct content of vitamin D3 and/ or omega-3 fatty acids.

Capsule release in EU:

Pharmacy of the Charitè was in charge of the capsule release in Europe

Home exercise video and Booklet:

The DO-HEALTH Avatar for exercise program instruction (video and booklet) was designed and animated by partner gut pictures (Benno Gut).

The content (exercise + text in 3 languages) was provided by UZH.

Randomization:

Study capsules and exercise kits were blinded and relabeled by the DO-HEALTH logistic centre (NextPharma).

Diet Assessment tool (FFQ)

We developed an electronic food frequency questionnaire (FFQ) as a tool that is consistent across countries in DO-HEALTH and targeted at the senior population. The content development was led by Prof. Walter Willett (collaborator and advisor to DO-HEALTH) and Simonetta Salvini (diet expert and trainee of Prof. W. Willett at the Dept. of Nutrition at Harvard School of Public Health) in collaboration with the DO-HEALTH coordinating centre at the University of Zurich (Prof. Heike A. Bischoff-Ferrari). The interactive electronic format of FFQ was developed by partner FDS and the food pictures taken by partner gut pictures.

DO-HEALTH central training and certification of the study staff

All the centres have sent their staff members to the DO-HEALTH training and certification sessions at the coordinating site in Zurich. We held 4 central DO-HEALTH training sessions at the University of Zurich, and one additional session at the Toulouse recruitment center (CHUT) for MDs, PTs, study nurses and administrators of DO-HEALTH between August 2012 and May 2013. The training covered the screening procedure, clinical visit, dental examination, osteoarthritis examination, biological sample procedure, physical performance tests and home exercise program. See report on central training on the DO-HEALTH website: <http://do-health.eu/wordpress/central-training/>

Detailed SOPs have been created by coordinating team at UZH

The coordinating centre has taken great care in writing detailed SOPs (standard operating procedures) for all tasks of DO-HEALTH clinical visits including blood handling, labeling, all tests and examinations of DO-HEALTH and a critical SOP for data quality in DO-HEALTH.

Development of DO-HEALTH randomization software by partner FDS

Our FDS partner has created a direct data entry software on tablet computers in 4 languages for the DO-HEALTH study (English, German, French, and Portuguese). The developed software includes the ability to assign subjectIDs, schedule subject visits, screen subjects in or out, print labels for vials, collect data on the tablets for most forms (comorbidities, EQ5D-3L, FFQ, GDS, GOHAI, HOOS, KOOS, Joint map, Knee buckling, McGill, NHS, PROMIS-HAQ, participant survey, QuickDash, Romell, SHARE-FI, sunlight, and MOCA scoring), collect additional data (height, weight, sample collection time, etc.), randomize subjects to a treatment and assign supplies (medication and exercise packets). Eventually also the CRFs will be electronically available for DO-HEALTH recruitment partners (gradual start October 2013, final items in March 2014).

DO-HEALTH website

Mid October 2012 the website DO-HEALTH was opened to the public. The website is designed to serve as a communication platform for all partners (a portal for DO-HEALTH partners and EU only) but also to support the recruitment at the local recruitment centers (information for participants). The website was created by partner FDS with support by partner gut pictures. The content was written and is updated by the Coordinator (Prof. H.A. Bischoff-Ferrari). See the website: <http://do-health.eu/wordpress/>

First annual partner meeting / Governing Board Meeting on the 25th of February

The first DO-HEALTH Annual Meeting and Governing Board Meeting took place on February 25th at the University of Zurich (Congress Forum Waid City Hospital, Zurich, Switzerland). Key partners of DO-HEALTH attended this meeting to discuss the progress of DO-HEALTH (see 2 reports on DO-HEALTH website: <http://do-health.eu/wordpress/update-do-health-by-investigators/> ; <http://do-health.eu/wordpress/annual-partner-meeting-2013/>).

II.3. Expected final results and potential impacts

The DO-HEALTH trial is designed to clarify the role of 3 promising interventions (vitamin D, omega3-fats, home exercise program), both individually and combined as a multi-modal combined intervention in chronic disease prevention at older age. DO-HEALTH will establish evidence in 5 following primary endpoints: 1) the risk of incident non-vertebral fractures; 2) the risk of functional decline; 3) the risk of blood pressure increase; 4) the risk of cognitive decline; 5) and the rate of any infection.

- 1) *The risk of incident non-vertebral fractures:* Fractures are a major problem in seniors and the findings of DO-HEALTH may provide critical evidence in the prevention of fractures at older age. 75% of all fractures occur in the population of 75 years and older and the consequences of fractures are severe, and often result in a second fracture. Recent research suggests that in order to reduce fractures at older age, we need to support bone and muscle health. DO-HEALTH will test 3 promising treatments that have shown promise in this dual concept.
- 2) *The risk of functional decline:* Adequate level of mobility and muscle strength is crucial for healthy aging and maintaining quality of life well into the advanced age. There is growing body of evidence that vitamin D and simple physical exercise can significantly improve functional mobility, gait, and balance reducing likelihood of falls in seniors. Effects of omega-3 fatty acids on muscle function are also promising, but long term data are lacking. DO-HEALTH has functionality, mobility and muscle health among its main focus. DO-HEALTH aims to provide evidence that will help seniors live their lives more actively, safer and, ultimately, more enjoyable.
- 3) *The risk of blood pressure increase:* Blood pressure rises with age and lowering systolic blood pressure in seniors with hypertension may reduce cardiovascular events and mortality. DO-HEALTH will test 3 promising treatments that have shown promise in the reduction of blood pressure.
- 4) *The risk of cognitive decline:* Dementia and Alzheimer disease has a prevalence of over 30% among seniors age 80 years and above. DO-HEALTH will test 3 promising treatments that have shown promise in the reduction of cognitive decline.
- 5) *The rate of any infection:* **Infections** increase with age, and premature deaths from influenza and pneumonia in older adults are rising. DO-HEALTH will test 3 promising treatments that have shown promise in the reduction of infections by immune-stimulation and anti-inflammatory effects.

Other key endpoints include risk of hip fracture, rate of falls, pain in symptomatic knee osteoarthritis, glucose tolerance, gastro-intestinal symptoms, mental and oral health, quality of life, and mortality. Follow-up will be in-person and in 3-monthly intervals (4 clinical visits and 9 phone calls). DO-HEALTH will further assess the comparative effectiveness of the interventions by evaluating reasons why or why not seniors adhere to them, and will assess their cost-benefit in a health economic model based on documented health care utilization and observed incidence of chronic disease.

DO-HEALTH will be the largest aging study to date designed to extend healthy life expectancy by delaying physiologic aging at multi-organ sites.

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