DO-HEALTH – VitaminD3-Omega3-Home Exercise- HeALTHy Ageing and Longevity Trial
Grant Agreement n° 278588
Start Date: 01/01/2012 - Duration: 66 months
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Publishable summary

I.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 2030[1-5] 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.

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

DO-HEALTH has reached 100% recruitment with 2159 seniors recruited in November 2014!
Despite issues and unexpected delays, *e.g.*, the assessment in period 1 of DO-HEALTH as a drug trial *vs* a food supplement trial (as originally thought) in all countries except Austria, the differences in regulatory and ethical requirements throughout Europe, the difficulty in recruiting 2152 participants aged 70+, furthermore with a low-trauma fall in the previous 12 months, the suspension of the recruitment in one DO-HEALTH centre for 5 months in period 2, DO-HEALTH has successfully met its recruitment goal, with over 2152 participants recruited in November 2014.

DO-HEALTH Biobank is created and operational
Fisher Bioservices, one of the largest and most experienced in biobanking services, host the DO-HEALTH biobank. The DO-HEALTH biobank is funded by UZH own resources. Fisher Bioservices organize the shipment of the biological samples from the recruiting centres to the biobank, the sorting of the samples and biobank the samples. The baseline samples collection of all the DO-HEALTH participants was completed in December 2014. Thermofisher has sorted the aliquots according to their use (analysis, back-up, biobank), and started to ship the aliquots for analyses to three laboratories:
- UZH: organ-specific biomarkers
- DNP: adherence - 25-hydroxyvitamin D and PUFA
- TUD: myostatin and sclerostin biomarkers

First baseline results are coming soon:
IDXA data from the IDXA sites of DO-HEALTH and first Tables on questionnaire results from all DO-HEALTH sites have been presented in a preliminary format to partners and collaborators present at the 3-year annual meeting!

Electronic Data Capture also for the elaborate DO-HEALTH CRFs
The initial plan was to have electronic data entry for the questionnaires and hopefully the CRFs. We have to date a versatile software allowing randomization, supply management, scheduling, trial monitoring, direct data entry of DO-HEALTH questionnaires (EQ5D-3L, PROMIS-HAQ , FFQ, SANGHA , SUNLIGHT, NHSexcerpt, SHARE-FI, KOOS, KNEE, JointMap, McGILL, GDSexcerpt, GOHAI, HOOS, QuickDASH, ROMEIII, MoCA), and data extraction. Plus a 7 day per week support for all software problems at all 7 DO-HEALTH centres, all provided by our partner FDS.
In addition, we will have a software for the elaborate CRFs (significant work programming and logistics) by Jnaurary 2015. With this, all of DO-HEALTH is electronic starting in 2015!

Unexpected regulatory issues were satisfactorily answered
Coimbra site was inspected by the Portuguese regulatory authority INFARMED on the 2nd to the 4th of April 2014. At the same visit, INFARMED found that the investigational medical product (IMP) may not comply with the product specification. Given this serious concern, the recruitment at Coimbra had to be suspended from 06/05/2014 to 26/09/2014, however the participants included in the study were allowed to go on with the IMP. INFARMED also informed all other regulatory authorities by sending a Fax "suspected quality defect IMP notification".
All the concerns raised by INFARMED during their regulatory inspection at UCO were answered. The Coordinating centre and DNP initiated additional actions (e.g., SOPs, analyses) to insure that trial participants are not placed at risk, and that the results of the trial are unaffected by inadequate safety, quality, or efficacy arising from unsatisfactory manufacture.
DO-HEALTH clinical trial is designed and conducted according to GCP, and the IMP is produced according to GMP!

Study investigational medical product: its shelf- life is adjusted following the stability program results
DNP is responsible for the DO-HEALTH study medication - vitamin D, omega-3 fatty acids and placebo (sunflower oil) provided in capsules, and DNP agreed to provide the capsules free of charge to DO-HEALTH sites. As the capsules are not commercially-produced capsules, their shelf life had to be estimated and was set to 3 years in alignment with. The stability program at the DSM Analytical Services laboratory in which the main ingredients of the capsules (*e.g.*, vitamin D / omega-3 fatty acids / high oleic Sunflower oil) are measured under standardized conditions (temperature and humidity) over the course of 4 years has now shown a shorter shelf live for the Capsules. Although the capsules do not constitute any health risk, DNP and the DO-HEALTH Coordination team decided to exchange the capsules earlier than planned. DO-HEALTH sites insure that the capsule batch number 2012 is exchanged by the capsule batch number 2014) between December 2014 and January 2015. The costs are supported by our partner DNP. This is very appreciated by the coordinating team and all other partners in DO-HEALTH!

DO-HEALTH website and dissemination
DO-HEALTH website was created in period 1 http://do-health.eu/wordpress/, and is regularly updated by DO-HEALTH Coordinator.

- **"DO-HEALTH in the media"** provides the links to videos, articles, newsletters, and the EU flyer for DO-HEALTH.
- **"News DO-HEALTH"** reports on DO-HEALTH recruitment status, public events, press releases and DO-HEALTH meetings.
- **"For partners"** includes information specific for DO-HEALTH partners, *e.g.*, recruitment, training, sharing of experiences, GB meetings minutes, newletters.

Annual meetings / Governing Board meetings
Annual meetings take place at at the University of Zurich (Congress Forum Waid City Hospital, Zurich, Switzerland). Two annual meetings were held in periods 1 and 2: http://dohealth.eu/wordpress/annual-partner-meeting-2013/, http://do-health.eu/wordpress/2014-annual-meeting-do-health/, and the next one will take place on February 5th 2015 (period 3). Confirmed speakers are to date Prof. Bess Dawson-Hughes from Tufts University, Prof. John E. Orav from Harvard School of Public Health and Prof. John Kanis (President IOF).

I.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 pressurein 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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