Sustaining Health After an Intensive Weight-loss Programme (SHAPe): A Real-world Study of Effects and Experiences of Treatment in Patients with Multimorbid Obesity

Project group:

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1.0 Background

Obesity is defined by the World Health Organization as a body mass index (BMI) ≥30 kg/m^2 and continues to be a threat to global health(1). Living with obesity enhances the risk of developing many potential symptoms and diseases such as cardiovascular disease, type II diabetes, sleep-disorders and cancer (1,2). The widespread implications of living with an elevated BMI and the rise in the global prevalence have promoted the development of various weight-loss strategies over the past decades. Historically lifestyle changes have been the preferred approach. Randomized clinical trials have demonstrated that intensive lifestyle changes can lead to a weight-loss of about 15 kg and remission of diabetes(3). In the Look AHEAD-trial a weight-loss of 8.6% from baseline was achieved but resulted in no difference in cardiovascular events compared with a control-group(4). These results are obtained in a patient population fit to participate in a rigorously controlled explanatory trial and outcomes represent clinical efficacy—not effectiveness (5). We need to know more about the effect we can expect in a real-life clinical setting where the patient population is more morbid, diverse, and weight regain is common(6–8). For that, we need pragmatic studies using real-life data, which was recently highlighted in the work by Thomsen, R. et.al. where 10 directions of real-world research are suggested (9).

To date bariatric surgery remains the most effective and gold-standard treatment for weight loss in patients living with obesity, leading to a 25-35% reduction in weight with only modest regain even after 15 years(10–12). The development of gut-hormone-based medications has brought non-surgical treatments closer to the efficacy of bariatric surgery, achieving weight losses at 15-20% when combined with lifestyle interventions including total dietary replacements (TDR) (6,13). While bariatric surgery is an effective intervention, it is associated with potential complications and necessitates lifelong medical monitoring and nutritional supplementation (14,15). Thus, not all patients are suitable candidates for surgery. This can be due to somatic or psychiatric conditions, that may complicate either the surgery, the anaesthesia or the patient's ability to follow the necessary postoperative care. This highlights the need for alternative treatment strategies as a stand-alone treatment or as a treatment on the way to surgery. Adding to this, research suggests that sustainable, healthy weight loss involves more than just pharmacotherapy and should include multimodal lifestyle changes with focus on healthy diet and physical activity to maintain muscle mass and stabilize weight(7).

Since 2021 Copenhagen University Hospital - Hvidovre, Denmark, has offered a 2-year, highly specialized, intensive clinical weight loss programme to patients living with severe and complex obesity, who due to somatic and/or psychiatric comorbidity are not eligible for bariatric surgery. This understudied group often lacks treatment options despite significant functional impairment and high healthcare costs. The clinical treatment in the weight loss programme is inspired by the results from the S-LiTE-study(6) and resembles the intensive weight loss-intervention from the LightCOM trials(16), although

participants in the LightCOM and S-LITE trials (and most trials generally) did not have the degree of obesity and multimorbidity as the ones offered our weight loss programme at Hvidovre Hospital. Thus, effects and durability of the treatment programme in this particular patient population can only be assessed by investigating real life cohorts

The programme is based on an intensive dietary and behavioural support provided by trained dieticians. It begins with an 8-week period of full TDR of 800 kcal/day. During this initial phase the patients have bimonthly consultations with the dieticians, a schedule which continues throughout the first year. At week 6-8 the patients begin the treatment with GLP-1 receptor agonist (GLP-1-RA). Until medio 2024 patients without diabetes were treated with Liraglutide, thereafter Semaglutide has been used. After week 8 the patients transition back to a normal balanced diet, guided by the dieticians. Shorter periods of TDR can be used as a rescue-strategy in cases of weight-regain during the treatment period (figure 2). In their second year of treatment the frequency of dietician consultations decreases to once a month. Patients are scheduled to see a physician at the beginning of the treatment, at 4 months, at 12 months and at 21 months. At the end of the programme dieticians and physicians' advice on weight loss maintenance strategies including possibilities for cessation/reducing dose of weight loss medication but there are no clinical follow up visits.

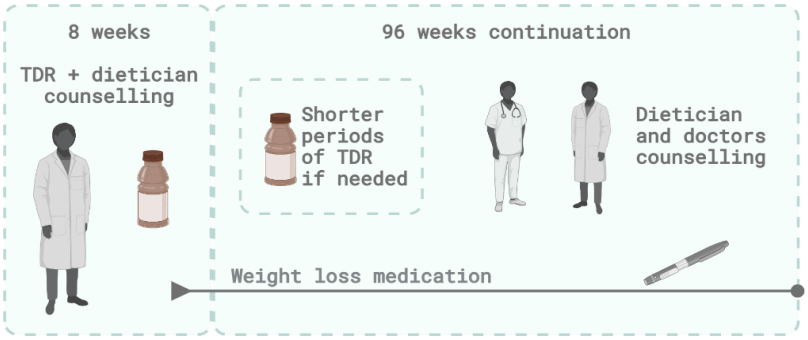


Figure 1: Intensive weight-loss treatment. Figure made with Biorender.

TDR products as well as weight loss medication are provided at no cost to the patients in the programme. Successful loss of 8-10% of body weight during the first 4 months of intervention is a requirement to stay in the programme. Approximately 75 patients are included in the programme each year.

1.1 SHAPe

It is well known that weight-regain is a common problem, when treating obesity without surgery(6), but it has never been investigated in a real life setting of patients living with this degree of multimorbidity. Also, in patients living with severe multimorbidity there could be sustained health effects even if weight is partly regained. The aim of this study is to assess health effects, feasibility and durability of the intensive weight loss programme. This study is named Sustained Health effects After intensive weight loss Programme (SHAPe) and consists of four interconnected sub-projects:

A. A prospective and exploratory quality-assurance-study: Exploring the health outcomes during the intensive weight-loss programme.

B. A post-intervention observational follow-up study: Exploring the durability of health outcomes following cessation of the intensive weight-loss programme.
C. A descriptive qualitative study exploring how psychosocial and socio-economic precarity mediate adherence to the programme and durability of health outcomes.
D. A societal and economic impact study to evaluate the impact on total health care costs and labour market attachment.

This protocol is for sub-project B – D (marked in yellow in figure 2). Sub-project A (marked in green in figure 2) has already been presented for the Capital Region's research ethics committee who determined that the study does not require formal approval (F-24080652) as it is a quality assurance project.

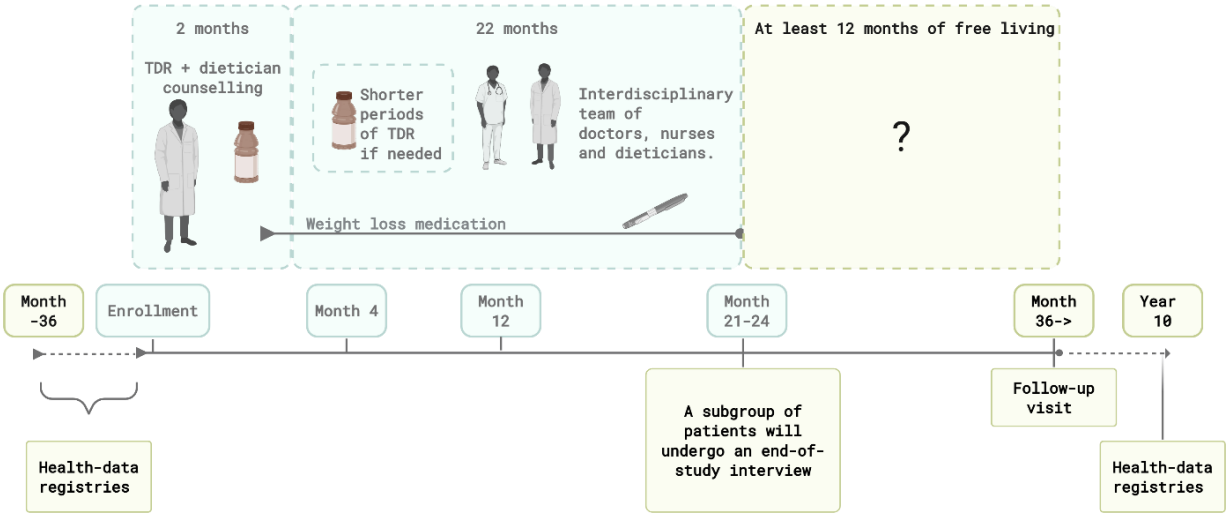


Figure 2 SHAPe timeline. Green: Project A, yellow: project B-D. Figure made with biorender.

2.0 Study design

2.1 Aim

Due to the clinical nature of the study, this cohort study is exploratory and descriptive and therefore does not include specific hypothesis testing but instead refer to a research question and aim.(17) The aim of subproject B-D is to assess the durability and long-term health effects including socio- and health-economic effects of the intensive weight loss programme. Exploring real-life effects of intensive weight-loss treatments in a vulnerable and understudied patient-population provides important knowledge that cannot be obtained in randomised clinical trials since these patients are typically not eligible(9). The overall research question can be found in chapter 4.0. Sub-project B aims to estimate

the durability of weight loss and selected long-term health outcomes after treatment cessation. Sub-project C aims to explore patient experiences and contextual factors influencing adherence and post-programme weight management. Sub-project D aims to describe long-term trajectories in healthcare utilisation, medication use, labour market attachment and public transfer payments using Danish registry data. Reporting of the study findings will adhere to the STROBE checklist using the extension for cohort studies (18). The study will be registered at clinicaltrials.gov.

2.2 Population and recruitment

Patients will be invited to participate before end of treatment and asked permission to contact them by phone. If permission is given the patient name and phone-number will be given to the primary investigator, who will contact the patient by phone and provide detailed information about the study. Should the patient wish to participate they will be invited to a visit where information is provided in person and they can sign the informed consent form.The follow-up visit will be scheduled at least 12 months after cessation of treatment. If the participants do not have any scheduled visits they will be offered the option of digital consent through RedCAP. Patients who have completed the programme prior to study-initiation and are part of the study-population for study A, will receive a letter (via e-boks) with information on the follow-up study and how to contact the study-team by email/phone for further information. This initial contact will be made by a certified quality assurance staff member, and no identifiable data on potential participants for project B will be shared with investigators outside the quality assurance team involved in study A. The letter will contain: cover letter, participant information, informed consent form, and the folder "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt". The initial letter will state that the potential participant will be contacted by the trial team by phone within 2 weeks. If participants are willing and eligible, they will be invited for the follow-up-visit where information is provided in person. All participants will be encouraged to bring an accompanying person for the visit, and they will all be given at least 24 hours of consideration before signing the consent form. If it will be necessary for other study personnel to obtain consent from the participants they will be trained on site and a delegationlog will be kept at site.

The study will recruit patients until the end of 2027, and the aim is to recruit 200 participants if feasible, but a minimum 65 participants. If 65 patients have not been reached by the end of 2027, the inclusion-period will be prolonged until 65 has been reached, or it is deemed unfeasible.

2.3 In- and exclusion criteria for project B, C and D.

Inclusion criteria:

1. Have completed the treatment programme at least 12 months before study-visit.
2. Have agreed to their data from the treatment programme being used for quality assurance.
3. Have signed the informed consent form.

Exclusion criteria:

1. Pregnant at time of the study-visit.

3.0 Data-collection

The study consists of one study visit that will be scheduled at least 12 months after completion of the treatment programme.

The study visit will consist of a single investigation day, which will take place in a clinical investigation room at Hvidovre Hospital. The participants will be asked to fast two hours prior to the visit, to avoid post-prandial blood-samples. At the visit they will have a blood-sample taken and provide a urine sample. Demographic data will be collected, and anthropometric measurement (weight, height, and waist circumference) conducted. Their blood-pressure will be measured using an automatic monitor and body-composition will be measured with a Seca Body Composition Analyzer 515/514. Lastly the participants will complete a SF36-questionnaire and a few questions regarding weight-management strategies and loneliness. These data are primarily for substudy B.

Moreover, participants will be asked to provide informed consent to link the study data to the clinical data from the electronic health records obtained during their clinical treatment period and to national registry data covering the period from 3 years prior to their enrolment in the treatment programme till 10 years after enrolment. These data will encompass detailed information on healthcare resource utilization across general practice, private specialist services, hospitals, and pharmaceutical consumption. Moreover, it will include data on labour market participation, receipt of public transfer payments, and a wide range of socioeconomic and demographic indicators for subproject B and D. From the electronic health records, we will collect data from visits during the treatment programme. These data will include weight, height, waist circumference, smoking status, alcohol use, history of cardiovascular disease, diabetes, and hypertension, as well as medication use related to these conditions. In addition, we will extract results from the sit-to-stand test, the Edmonton Obesity Staging System score, and the SF-36 questionnaire. These variables will serve as baseline measures for comparison with outcomes assessed at the follow-up visit

We also intend to reassess these data approximately 5 and 10 years after enrolment in the treatment programme to conduct additional linkage with registry data, including updated health care utilisation and mortality data. These long-term follow-ups are part of sub-project D.

A subgroup of patients will be asked to participate in project C. Project C will consist of two investigation days. The first day will be scheduled in conjunction with their final visit in the treatment programme and will consist of a semi-structured interview exploring their experiences with the programme and their psychosocial context and mental health status. This interview will be repeated at the follow-up visit with additional focus on the patients experience since completing the program including the possible health- and weight-management strategies they may have used.

4.0 Outcomes

To improve coherence between study aims and outcomes, outcomes are specified separately for each sub-project. For sub-project B, weight change from final programme assessment to follow-up is the primary clinical outcome, while body composition, health-related quality of life, medication use, selected biochemical markers, hospitalisations and exploratory proteomic signatures are secondary or exploratory outcomes. For sub-project C, the outcomes are thematic and concern patient experiences, perceived facilitators and barriers, and contextual factors relevant to weight management after programme completion. For sub-project D, the outcomes are registry-based and include healthcare utilisation, medication costs, labour market attachment and public transfer payments at prespecified follow-up intervals.

Sub-project B

Overall research question: What is the durability and long-term health effects of a hospital-based IWL-treatment programme, with specific attention to cardiometabolic health, body-composition and health-related quality of life, at least 1 year after cessation of treatment in a clinical cohort of patients living with severe obesity and multimorbidity?

Key outcomes:

- *Weight*: Change in weight from the final programme measurement (measured between 21 and 24 months) to follow-up-assessment. Will be presented in kg and as percent weight-change.
- *Biomarkers:* Identify potential proteomic biomarkers associated with weight loss maintenance vs weight regain.
- *Skeletal muscle mass*: We will calculate mean changes in skeletal muscle mass measured by bioimpedance from the final programme measurement (measured between 21 and 24 months) to follow-up-assessment.
- *Health related quality of life*: We will estimate health related quality of life using the short form survey questionnaire (SF36) at follow-up visit and compare this to the final programme measurement (measured between 21 and 24 months).

Additional outcomes:

- *Fat mass*: We will calculate mean changes in fat mass percentage measured by bioimpedance from final programme measurement to follow up.
- *Waist circumference*: Waist circumference will be measured between lowest palpable rib and top of the hip.
- *Use of weight-loss medication*: We will calculate the percent of patients who continued weight-loss medication after cessation of the programme and evaluate the dosages they use.
- *Lower body strength*: We will measure lower body strength with a 30-Seconds SST(19). The test will be performed by those of the patients who was tested at 21 months.

- *Changes in blood-pressure*: Will be measured at follow-up with an automatic monitor. We will then measure changes in blood-pressure from 21 months to follow-up.
- *Changes in Hba1c*: We will measure changes in HbA1c from 21 months to follow-up and combine this with data on medication requirements.
- *Changes in lipid levels*: We will measure changes in total cholesterol, HDL, LDL and triglycerides from 21 months to follow-up and combine this with data on medication requirements.

Sub-project C will explore

Overall research question: How do participants experience the intensive weight-loss programme and the period after programme completion, including the personal, social and structural factors that influence adherence and weight-management maintenance?

- How the participants experienced the treatment programme
- Which elements do they perceive as most effective in supporting their weight management
- Weight-management strategies used during and after the treatment programme
- Practices and routines around eating and exercise, living conditions and adversities, individual resources and adopted coping strategies.
- Further, the interview guide will include domains related to social connectedness, support networks, and experiences of loneliness.

Sub-project D will estimate

Overall research question: How do long-term trajectories in healthcare utilisation, medication use, labour market attachment and public transfer payments develop after enrolment in the intensive weight-loss programme?

- Healthcare costs (hospital costs, general practices costs, private specialist costs and medication costs) after two, three, five and ten years from baseline (program start).
- For hospitalisations we will obtain information on hospital admissions pr patient 3 years prior to enrolment in the treatment programme and till 5 years after enrolment in the treatment programme.
- We will obtain information on prescriptions at time of enrolment and at end of programme which will be compared to data from the follow-up visit, to explore the possible effect of the treatment on number of prescriptions needed pr patient. This will be a surrogate marker for overall disease burden.
- Labour market attachment after two, three, five and ten years from baseline (program start).
- Public transfer payments after two, three, five and ten years from baseline (program start).

5.0 Statistical analysis

Due to the descriptive study design, we will use descriptive statistics for all outcomes at all timepoints. Changes in outcomes from final programme measurement to follow up, will be reported and presented as mean changes with 95% confidence intervals. We will perform subgroup-analysis according to the comorbidities that made the patients ineligible for surgery, to determine the impact of type of comorbidity.

As descriptive studies usually do not test hypotheses or stipulate causal inference(17), they do not usually have a classic sample size estimation.(20) It is however still advisable to justify the sample size in some way. The target sample size is based primarily on feasibility and precision around the key outcome "weight change". We have calculated the number of participants needed that would give us a power of >90% to detect a weight change of 5 kg, which in the current population represents the minimal clinically relevant change. For this we need 62,48 participants, and we have therefore decided to include at least 65 participants (assumptions: delta 5 kg, SD 12 kg, significance level 0.05 two-sided, and paired study design). However, due to the heterogeneity of the participant-population we hope to include up towards 200 participants in order to be able to make exploratory sub-group-analysis and search for biomarkers.

6.0 Data management

Data will be managed using the Capital Region of Denmarks secure online platform REDCap.

Data will be entered directly into REDCap. The following source data will be used:

• Body composition from Seca Body Composition Analyzer 515/514.

• Blood sample data from patients' electronic records and clinical laboratory information system (LABKA).

Therefore, the informed consent, gives the investigator, the sponsor and sponsor's representatives and any regulatory authority direct access to obtain information in the patient's medical records, including electronic records from the treatment period, in order to view information about the subject's health conditions that is necessary for the conduct of the research project.

6.1 Information from Danish registries

In order to explore the outcomes of project D and the two outcomes from project B relating to hospitalisations and medication-use, data from the trial will be linked with Danish registry data to obtain additional information about health status, utilisation of healthcare services and medication, socio-economic and demographic characteristics, and sickness absence from a period stretching from 3 years prior to enrolment in the treatment programme until 10 years after enrolment in the programme. Information will be acquired from the following national health care registers: the National

Patient Register with Diagnosis Related Groups, the Health Service Register and the Pharmaceutical Database. In addition, data will be merged with the Population Register, the Income Register, the Education Register, and the DREAM database, for relevant demographic and socio-economic characteristics. Variables from these registers will be selected using a data minimization principle and in accordance with General Data Protection Regulation (GDPR). The health economics analysis will also use clinical outcomes from the trial. The entire health economics analysis is conducted at the Statistics Denmark secured research server and has its legal basis in GDPR ('databeskyttelsesforordningen' and 'databeskyttelsesloven'). These analyses will be performed by study-personnel at Southern Denmark University (SDU). Only relevant personnel will have access to the data and data will only be shared after all parties have entered into a collaboration agreement and data processing agreement.

7.0 Biological material

Sampling of biological material will take place at Hvidovre Hospital on the day of the study visit. Part of the samples will be analysed immediately, part of the samples will be stored in a research biobank, and after batch-analysis any remaining samples will be stored in a biobank for future research.

We will sample:

- Venous blood (45 ml)
    - For immediate analysis (25 ml).
    - For storage in a research biobank (20 ml).
- Urine (10-15 ml per assessment visit):
    - For immediate analysis (5 ml): creatinine, and albumin for estimation of urine albumin/creatinine ratio.
    - For storage in a research biobank (10 ml)

7.1 Samples for immediate analysis

Blood and urine samples for immediate analysis are collected from study participants and will be handled and processed within hours to 5 working days at most by the hospital's local department of clinical biochemistry. These samples will be destroyed immediately after analysis in accordance with the department's usual protocols.

The local biochemical department will be responsible for the immediate analysis of:

- Blood (plasma):
    - Lipid profile, haemoglobin A1c, alanine aminotransferase, aspartate aminotransferase, platelets, haemoglobin, ferritin, transferrin, mean corpuscular volume, mean corpuscular haemoglobin concentration, creatinine, leucocytes, CRP, albumin, sodium, potassium, calcium (albumin corrected and ionised, if possible), basic phosphatase, parathyroid hormone, thyroid-stimulating hormone, zinc, magnesium, B-12-vitamin, folate and 25-OH vitamin D.

- Urine
    - Creatinine and albumin for estimation of urine albumin/creatinine ratio.

7.2 SHAPe research biobank

We will establish a SHAPe research biobank to store biomaterials.Blood samples (20 ml) and urine samples (10 ml) will be handled and stored in a local research biobank located at Hvidovre Hospital. All biological material will be pseudo-anonymised and stored in freezers (-20 or -80 degrees Celsius) as required for the subsequent analyses. These samples will be analysed in batches after last patient last visit, searching for potential biomarkes/proteomics-signatures associated to obesity and treatment responses. The proteomics will be analysed by performing deep-coverage quantitative proteomics on archived EDTA plasma using a state-of-the-art MS-based workflow. Using an Orbitrap Astral mass spectrometer with data-independent acquisition (DIA), we will quantify over 1,200 proteins to identify signatures associated with weight loss response. The samples will be stored for up to 10 years after last patient last visit. If a participant withdraws their consent, all samples from that participant will be identified and destroyed.

7.3 Biobank for future research

We will also establish a SHAPe biobank for future research to store any excess original biomaterials from the SHAPe research biobank that remain after the protocolised analysis. Biological material in the biobank for future use cannot be analysed as part of a future research project without approval from the relevant regional ethics committee.

Blood and urine samples will be handled and stored in a local research biobank located at Hvidovre Hospital. All biological material will be pseudo-anonymised and stored in freezers (-20 or -80 degrees Celsius) as required for the subsequent analyses. After the last participants last visit and before the final date for the project, samples will be transferred to the biobank for future research. The samples will be stored for 10 years. If a participant withdraws their consent, all samples from that participant will be identified and destroyed.

8.0 Ethics

8.1 Safety

The study does not include an intervention treatment, and the proposed investigations are thought to pose little to no safety-risk for the participants. The bioimpedance use a small electrical current, and we will therefore not perform bioimpedance on patients with implanted ICD-units or pacemaker.

8.2 Collaboration Statement

Subproject B and D will be performed in collaboration with health economist Line Planck Kongstad, DaCHE, Department of Publich Health, SDU. Therefore, the personal identification number (CPR) of the participants will be shared with study personal at SDU in order to perform the health economics analysis and combine clinical data with data from the national health registries as described under 6.1. Sub-project C will be conducted in collaboration with anthropologist Bodil Just Christensen, Department of Biomedical Science, KU.

8.3 Trial conduct

The trial will be conducted in compliance with the present protocol, and The Helsinki Declaration. The trial meets the requirements of the Regional Ethics Committee for the Capital Region, and the GDPR ('databeskyttelsesforordningen' and 'databeskyttelsesloven'). We will ensure the required approvals regarding data security through the Capital Regions system Privacy. Before any data will be shared with either KU or SDU they will enter into a collaboration agreement and data processing agreement. The protocol will be registered on www.clinicaltrials.gov prior to the inclusion of the first participant. Any substantial deviation from the protocol will only be implemented after review and approval from relevant regulatory authorities. Any deviation, however minor, will be documented and made available with the protocol.

8.4 Insurance

The participants are insured by the Danish Patient Insurance Association

8.5 Finance

The study has been initiated by primary investigator Olivia Duun and. Ass. Professor Kirstine Nyvold Bojsen-Møller. Salary for the primary investigator is partly funded by the Clinical Academic Group SHIFT supported by Greater Copenhagen Health Science Partners (500.000 dkk) of which Kirstine Nyvold Bojsen-Møller is vice chair. We are in the process of seeking funding for running costs. The funding will be placed in a "forskningskonto" administered by Hvidovre Hospital. Neither Olivia Duun nor Kirstine Bojsen-Møller has any financial interest in the project.

8.6 Reimbursement

In recognition of the lack of benefit for attending the assessment visit, participants will receive DKK 450 for the follow-up visit. Furthermore, we will reimburse the participants for their travel-expenses to Hvidovre hospital.

We do not believe the reimbursement will influence the patients' choice of consent for participation, as the amount is relatively small and only given after the completion of the follow-up assessment, where no treatment is provided. Participants are advised that the reimbursement is taxable.

9.0 Timeline

The study is scheduled to run from fourth quartile of 2025 until 2036. Patients have been enrolled in the clinical treatment program since 2022 and will be recruited for the study until end of 2027.

10.0 Dissemination plan

We plan to publish the findings from this study both written and verbally through oral and poster presentations at academic conferences and symposia, and social media. Additionally, we will publish our findings in peer-revied journals and will ensure open-access. We expect to publish at least one article from study B. Authorship is granted according to the Vancouver guidelines.

In accordance with the principles of the Helsinki declaration, all outcomes of this study as listed in the protocol, positive as well as negative and inconclusive, will be published.

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