BMJ Open

Intensive weight loss intervention versus usual care in adults with obesity: a protocol for the LightCARE randomised clinical trial

Sofus C Larsen ,[1,2] Berit Lilienthal Heitmann ,[1,2] Sarah Wane ,[3] Sabrina Wielsøe,[4] Jane Lindschou,[5] Janus C Jakobsen,[5,6] Janus Engstrøm,[5] I O Specht ,[1,2] Ann-Kathrin Lindahl Christiansen ,[1] Aksel Karl Georg Jensen,[7] Kirstine Nyvold Bojsen-Møller,[4,8] Thomas Bandholm ,[8,9,10,11] Gritt Overbeck,[1] Marius Brostrom Kousgaard,[1] Charlotte Albury,[3] Susanne Reventlow ,[1] Kim Rose Olsen,[12] Line Planck Kongstad ,[12] Sten Madsbad,[4] Susan A Jebb ,[3] Carsten Dirksen,[4,8] Paul Aveyard,[3] Frans Boch Waldorff,[1] on behalf of the LightCOM team

To cite: Larsen SC, Heitmann BL, Wane S, *et al*. Intensive weight loss intervention versus usual care in adults with obesity: a protocol for the LightCARE randomised clinical trial. *BMJ Open* 2025;**15**:e107155. doi:10.1136/bmjopen-2025-107155

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-107155).

PA and FBW contributed equally.

Received 27 June 2025
Accepted 21 September 2025

For numbered affiliations see end of article.

Correspondence to
Dr Sofus C Larsen;
sofus.larsen@regionh.dk

ABSTRACT

Introduction Total diet replacements (TDRs) and weight loss medications (WLMs) have proven effective in producing substantial weight loss for individuals with obesity. Evidence is lacking on whether combining these treatments is effective and cost-effective in primary care for adults with obesity class I (body mass index (BMI) 30–34.9) or uncomplicated obesity class II or higher (BMI≥35 without obesity-related disease).

Methods and analysis LightCARE is a 2-year 1:1 randomised, parallel-group, clinical superiority trial with blinded outcome assessment evaluating the benefits and harms of an intensive weight loss (IWL) intervention compared with usual care for adults with obesity in Denmark and the UK. The trial will include 400 participants aged 18–60 years with obesity class I or uncomplicated obesity class II or higher. The IWL programme aims to achieve and maintain a weight loss of ≥20% through a flexible and individualised combination of TDR, behavioural support, including physical activity and sleep guidance, and WLM if needed and will continue for 2 years. The control group will receive usual care offered in each country, typically consisting of brief behavioural support for weight loss. The primary outcome is body weight 2 years after randomisation. Secondary outcomes will include the proportion of participants achieving ≥20% weight loss, Short-Form-36 Mental Component Score, 4-m gait speed and Metabolic Syndrome Severity-Z score. Serious adverse events, the incidence of eating disorders and bone mineral density will be evaluated as safety outcomes. We will also examine the cost-effectiveness of the intervention, within the trial and in the longer term through modelling. We will conduct a process evaluation to inform any future implementation.

Ethics and dissemination Ethical approval was granted in Denmark (December 2023, H-23051332) and the UK (August 2024, 24/SC/0210). Findings from the trial will be disseminated through peer-reviewed journals and scientific conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The intensive weight loss intervention incorporates total diet replacements, weight loss medications and behavioural strategies hypothesised to deliver substantial weight loss, and we have developed two models to deliver it in primary care in Denmark and the UK, respectively.

⇒ By comparing the intensive weight loss intervention with usual care in two countries, we can learn lessons for implementation in different healthcare systems with varied models for the delivery of care.

⇒ Due to the nature of the intervention, blinding of participants to group allocation was not possible. However, outcomes will be assessed blinded, and the statistical analyses and conclusions will be written blinded.

Trial registration number NCT06321432.

INTRODUCTION

In recent decades, the prevalence of obesity has been rising worldwide. As body mass index (BMI) increases, so does the risk of morbidity and mortality,[1 2] including the risk of obesity-related diseases such as type 2 diabetes, ischaemic heart disease, stroke, sleep apnoea, polycystic ovary syndrome, metabolic dysfunction-associated steatohepatitis, osteoarthrosis and several cancers.[3–7]

As shown in 0.5 million people from a UK primary care database, there are strong associations between the magnitude of weight loss and improvements in obesity-related diseases, with the most significant benefits observed for established cardiovascular risk factors,

type 2 diabetes, hypertension and dyslipidaemia.[8] Thus, guidelines urge general practitioners (GPs) and other clinicians to intervene opportunistically to offer obesity treatment.[9–11] In practice, this often involves referring to simple, low-cost group-based behavioural weight management programmes, which typically lead to a mean weight loss of 5 kg or less in 1 year.[12 13]

Recent obesity treatment programmes have demonstrated the safety, efficacy and scalability of using total diet replacements (TDRs)[14–16] and weight loss medications (WLMs)[17–19] to deliver substantial weight loss. However, there is a lack of evidence on how these therapies can be combined within primary care for adults with obesity to give greater benefits than either alone. These newer treatments for obesity are being introduced by a combination of public and private healthcare providers and are mainly driven by patient demand.[20] This leads to disparities in access to obesity management services,[21] alongside a lack of evidence of the effectiveness and cost-effectiveness of these treatments in routine care. Furthermore, the introduction of new effective pharmaceutical treatments for obesity may add to the already demanding workload for GPs. Consequently, new delivery models that support GPs in integrating intensive obesity management within primary care may offer an attractive solution.

The aim of the LightCARE trial is to assess the benefits and harms, as well as the cost-effectiveness of an intensive weight loss (IWL) intervention that includes TDR, behavioural support, plus WLM if predefined goals for weight loss progress are not met. This will be compared with usual care within primary care for adults with obesity class I (BMI 30–34.9) or uncomplicated obesity class II or higher (BMI≥35 without obesity-related disease).

METHODS AND ANALYSIS

Trial design

The protocol has been developed in accordance with the updated Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines,[22] including the use of the SPIRIT checklist, which is provided in online supplemental table 1. Trial reporting will adhere to the Consolidated Standards of Reporting Trials statement and relevant extensions.

LightCARE is an investigator-initiated, 1:1 randomised, parallel-group, clinical superiority trial with blinded outcome assessment assessing the benefits, harms and cost-effectiveness of a 2-year IWL intervention on body weight at 2 years compared with usual care in adults with obesity in Denmark and the UK. The first participant was included in June 2024.

The LightCARE trial is conducted under the Lighthouse Consortium on Obesity Management (LightCOM) consortium,[23] which also includes the LightWAY (NCT06321458) and LightBAR (NCT06309238) trials. All three trials investigate the effectiveness of an identical IWL intervention compared with standard obesity management across different healthcare settings and different patient populations. While LightCARE focuses on individuals with obesity class I (BMI 30–34.9) or uncomplicated obesity class II or higher (BMI≥35 without obesity-related disease), LightWAY targets individuals with more severe and complex obesity in primary or secondary care, and LightBAR compares the IWL intervention with bariatric surgery in secondary care among individuals eligible for surgical treatment.

Participants and recruitment

In Denmark, participants are recruited from the Capital Region of Denmark, with priority given to citizens from the municipalities of Gladsaxe, Frederiksberg and Hvidovre. Recruitment will take place through advertisements, or participants may be identified by their GP or local municipal health centres. In the UK, participants are recruited through approximately 20 GP practices in the Midlands, East Anglia and the North of England. Electronic medical records at sites will be searched using a study-specific algorithm aligned to the inclusion/exclusion criteria to identify potentially eligible patients. Sites will screen these lists and remove any patients they deem ineligible. The final list of patients will be invited to participate in the study via text messages, letters, phone calls or during clinical appointments.

In Denmark, initial eligibility is assessed via an online questionnaire followed by a pre-screening telephone call. In the UK, eligibility is assessed through a telephone call. Potentially eligible participants in both countries then attend a face-to-face appointment where verbal information is provided, informed consent is obtained and formal eligibility screening is completed. Those meeting all criteria may then proceed directly to baseline assessments prior to randomisation.

Inclusion criteria

An individual will be eligible to participate if they

1. Are aged between 18 years and 60 years at screening.
2. Have BMI≥30 kg/m^2 or ≥27.5 kg/m^2 for individuals of South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds.
3. Provide informed consent.

Exclusion criteria

A participant will not be eligible for the trial if they

1. Have clinical obesity class II or higher, defined as BMI≥35 kg/m^2 for white or 32.5 kg/m^2 for non-white participants, with one or more adiposity-related diseases: cardiovascular disease, type 2 diabetes, hypertension, metabolic dysfunction-associated steatohepatitis or sleep apnoea.
2. Are pregnant, breastfeeding or planning to become pregnant within the next 2 years.
3. Have used WLM (including GLP-1 receptor agonists) within the previous 3 months.
4. Are undergoing cancer treatment, except for oestrogen antagonist or treatment for non-melanoma skin cancer.

5. Have a history of bariatric surgery (except for reversible procedures performed more than one 1 year ago).
6. Are diagnosed with or treated for severe eating disorders within the last 6 months.
7. Have any condition likely to impair adherence to the treatment plan or significantly affect quality of life.
8. Have conditions complicating treatment with TDR products (eg, type 1 diabetes, insulin therapy).
9. Participate in another obesity-related research programme that could interfere with the trial.
10. Have conditions that are contraindicating current GLP-1 treatments (eg, history of severe intolerance or recent pancreatitis).
11. Have another member of the same household enrolled in the trial.

Ensuring increased diversity

The recruitment process will prioritise diversity and inclusivity. We will seek to recruit both men and women with various ethnicities and socioeconomic backgrounds by continuously monitoring these data during the recruitment phase and, when possible, prioritise specific groups, for example, men, for inclusion. This data monitoring is performed with no knowledge of allocated intervention group.

Randomisation

Participants will be randomised centrally at the allocation ratio 1:1. Copenhagen Trial Unit (CTU) will create a computer-generated allocation sequence stratified by intervention site. The allocation sequence is generated using permuted blocks with varying sizes concealed from investigators. The allocation is performed within the electronic case report form (eCRF); see 'Data management and data monitoring'.

Blinding

Due to the nature of the interventions, it will not be possible to blind the participants or the healthcare providers administering the interventions. Outcome assessors will be blinded to allocated intervention group. This is possible because outcome assessments are conducted at different locations and by different staff members than those involved in the treatment visits. Participants will be asked not to disclose their allocation when outcomes are assessed.

Statisticians and investigators concluding will be fully blinded. We will conduct the statistical analyses with the intervention groups coded as, for example, 'A' and 'B'. The trial management group will write two abstracts while the blinding is intact; one assuming the IWL is 'A' and usual care is 'B', and one assuming the opposite. After these two abstracts are agreed upon, the code will be broken.

IWL intervention

The IWL programme aims to achieve and maintain ≥20% weight loss through a flexible and individualised combination of TDR, behavioural support, including physical activity and sleep guidance, and WLM if needed and will continue for 2 years.

The intervention is designed as a stepwise algorithm for obtaining weight loss introducing WLM only if lifestyle interventions do not achieve the predefined weight loss targets. This reflects that the intervention focuses on weight loss rather than other treatment goals such as organ protection as now recommended in some guidelines. This approach aligns well with a practical and targeted delivery in primary care.

The intervention in Denmark will be delivered by a clinic (termed hub) in Gladsaxe, Frederiksberg and Hvidovre municipalities in the Capital Region of Denmark. Participants will receive initial consultations with an IWL-trained GP, regular follow-up consultations with a coach trained as dietitians and additional support from a nurse on injection technique if WLM is given.

In the UK, participants will receive care from Liva Healthcare,[24] a weight management provider that currently delivers TDR programmes to the English National Health Service (NHS). We will use this structure to deliver the IWL intervention. Participants will receive regular support through trained coaches, remotely via phone, video conferencing and an app. These coaches have been trained to provide weight management programmes and medication and provide health coaching in NHS programmes and have received additional training on the LightCOM intervention, but may not be health professionals. Prescribing clinicians (medical doctors employed by Liva) will discuss, prescribe and support participants' use of WLM when necessary. The medication will be delivered to their home address via a contracted pharmacy, and the clinician will instruct the participant on the use of the medication. Liva will have two-way communication with the participants throughout.

Each consultation lasts approximately 15–30 min, and follow-up consultations may be conducted.

Phases of the IWL intervention

The IWL consists of three phases: (1) weight loss induction, (2) weight loss continuation and (3) weight loss maintenance (figure 1).

Weight loss induction phase (weeks 1–12)

The goal is rapid weight loss (≥1% per week) using TDR and behavioural support. Participants will follow a nutritionally complete, low-energy formula food plan (800–850 kcal/day) provided to the participant, and low-energy vegetables may be supplemented. They will be encouraged to drink 2–2.5 L of non-caloric beverages daily. If TDR is poorly tolerated, participants may progress to a partial TDR, including one low-energy, high-protein food-based meal (<300 kcal/day) or a low-energy, low-carbohydrate food-based diet (1200 kcal/day). Behavioural support will be provided through biweekly consultations with a coach, either physical or virtual, to support adherence, healthy eating habits, physical activity

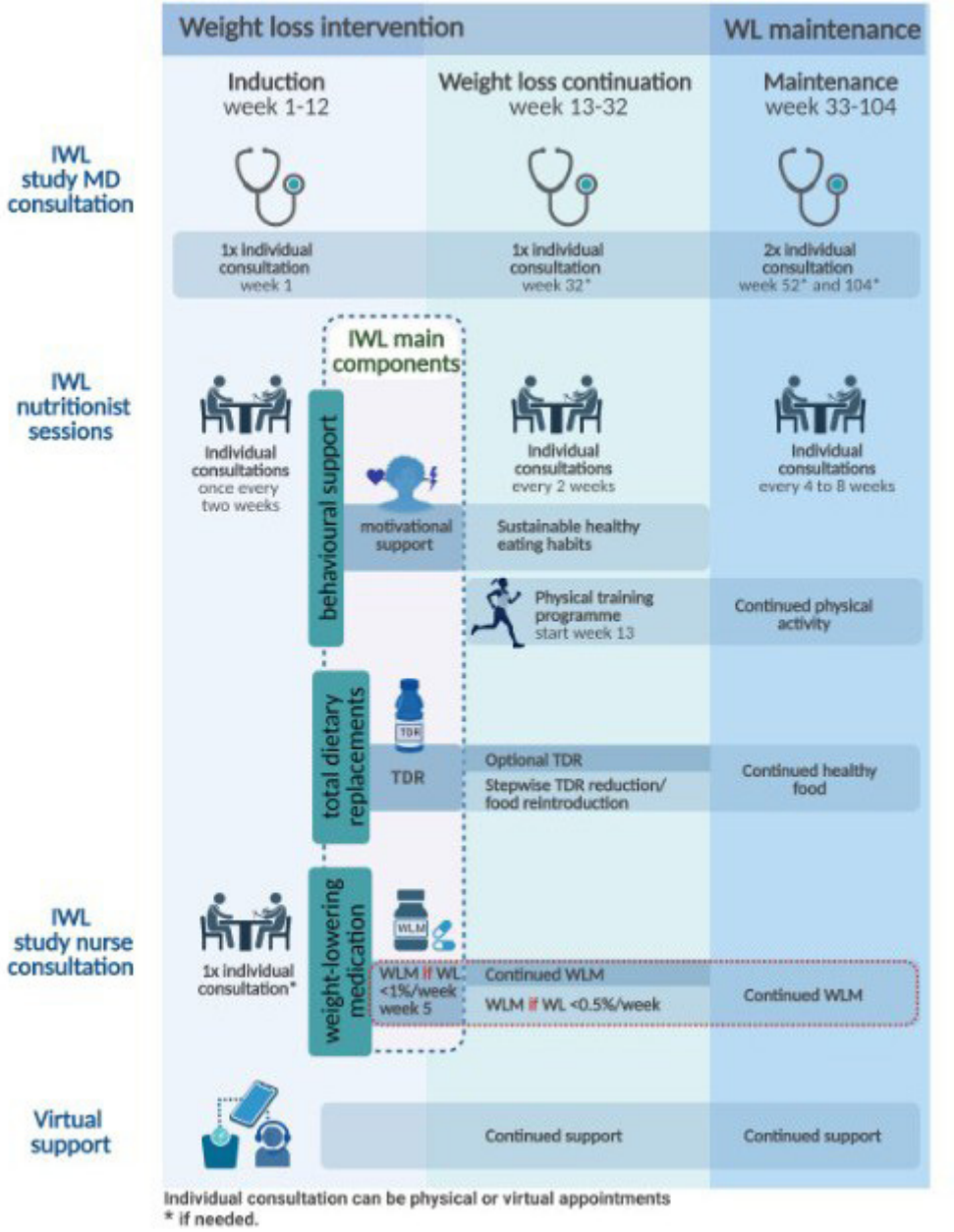

Figure 1 Treatment phases for intensive weight loss (IWL) intervention. TDR, total diet replacement; WL, weight loss; WLM, weight loss medication. Created with BioRender.com.

(eg, walking) and guidance on sleep hygiene. No single therapeutic theory is prescribed as the foundation of the coaching. In practice, it is up to the coach to handle the consultation using their professional knowledge and expertise, within the boundaries of a standard operating procedure (SOP). This allows for flexibility to adapt the approach to the individual participant's needs, while maintaining a standardised overall framework. If weight loss progress is insufficient (eg, <4% by week 4), WLM will be offered and prescribed according to national guidelines. The choice of WLM follows a SOP that is regularly updated. This SOP emphasises that initiation depends on an individual assessment by the prescribing physician, considering efficacy, safety and tolerability, weight loss-independent drug effects, route of administration and the participant's preferences. In general, initiation aligns with current guidance from Danish and British authorities, although local availability and cost may also influence the choice of WLM. WLMs are provided free of charge to participants during the trial.

Weight loss continuation phase (weeks 13–32)

The focus is on supporting ongoing weight loss towards the overall target of ≥20% weight loss from baseline or achieving a BMI≤25 kg/m². Food will be reintroduced gradually. If the participant wishes to continue TDR, it can be extended by a further 8 weeks. Food reintroduction involves the transition to healthy, energy-reduced food one meal at a time, focusing on high-protein, high-fibre foods and slowly absorbed carbohydrates, to maintain

a balanced macronutrient intake (20–25% protein, 40–45% carbohydrates, 30–35% fat). This phase typically lasts 4–8 weeks but may be individualised. During this phase, participants will continue receiving biweekly behavioural support to manage eating behaviours, stress-related eating and cravings, and to develop long-term strategies for weight management. The coach will also help participants to increase physical activity, following WHO's guidelines of 150–300 min of moderate activity per week, including additional resistance exercises,[25] and will explain the associated health benefits. If weight loss is insufficient (eg, <2% in 4 weeks), WLM will be offered or adjusted.

Weight loss maintenance phase (weeks 33–104)

The focus shifts to helping participants to maintain their reduced body weight. Participants may continue to lose weight, but once the 20% target is achieved, the primary objective is to maintain their weight. Participants may continue using a diet replacement product once daily or return to full TDR if weight regain occurs. Behavioural support during this phase will continue, with consultations every 4 weeks until week 52 and every 8 weeks thereafter, focusing on sustaining healthy eating, physical activity and behavioural strategies. WLM medications, if started, will continue.

Response to weight regain

Weight regain is common. To address this, all participants in the IWL intervention will weekly monitor their weight at home. If a participant regains ≥3 kg or is concerned about gaining weight, the coach will discuss return to TDR, intensifying behavioural support, increasing physical activity and adjusting WLM.

Use of medications

Concomitant use of >1 type of WLM will not be allowed. Using TDR will significantly reduce the need for glucose-lowering medication and will lower blood pressure, such that for patient safety it will be necessary to reduce or stop these medications. Participants with reasonable glucose control (HbA1c<70 mmol/mol) and on two non-insulin glucose-lowering medications or less will be asked to stop these medications but continue metformin. Participants on three or more medications will stop two and only continue medications that do not cause hypoglycaemia or ketoacidosis. Participants with poor glucose control (HbA1c≥70 mmol/mol) will continue medications that do not cause hypoglycaemia or ketoacidosis according to an individual treatment plan. If glucose control is good (HbA1c<58 mmol/mol) on treatment with two medications or less, routine self-monitoring of blood glucose at home may not be needed, but everyone else with diabetes will be asked to monitor their blood glucose at least twice a week with guidelines for participants on how to adjust and when to contact the team providing IWL. Likewise, participants with hypertension will reduce medication, in particular diuretic medication. Safety will be ensured by self-monitoring of blood pressure at least once weekly with guidelines for participants on how to adjust and when to contact the team providing IWL.

Usual care for obesity management in primary care

In Denmark, participants randomised to standard obesity management in primary care will receive a pamphlet on current obesity management guidelines from the Danish National Board of Health. They will be advised to contact their GP for referral to local obesity management programmes if available. The trial team will notify the participant's GP to encourage referral. The availability and structure of current obesity programmes vary between municipalities. Still, if available, they usually consist of individual, or group sessions focusing on healthy eating and regular exercise and are typically limited to 12–16 weeks. Some programmes are limited to people with specific obesity-related comorbidities, for example, diabetes. Structured TDR is generally not included. Additionally, GPs may choose to prescribe approved WLM in accordance with current national guidelines. Currently, WLM costs are usually not covered by Danish healthcare.

In the UK, a range of weight management services are available in primary care, although the nature of this and referral routes slightly varies from place to place. These include typically 12-week community-based weight management programmes offering guidance on diet, nutrition and physical activity, 12-week 'digital' programmes for people with hypertension or diabetes. GPs can prescribe WLM that has been approved for use in primary care to their patients, usually orlistat, but currently not GLP-1 receptor agonists, though this may change. The costs of services and medication are covered by the NHS. The trial team will ensure the intervention site has up-to-date information about available, local weight loss programmes and will encourage the participant and the GP to discuss referral to a suitable programme.

For participants allocated to usual care, we will collect information about attendance to weight management programmes and any treatment with weight loss medications.

Assessments

For each trial participant, participation is for 104 weeks with clinical assessments at baseline and after 32, 52 and 104 weeks. Thereafter participants will be followed through national registers to track health outcomes after 5, 10 and 20 years. The trial schedule and information on all trial measures are included in online supplemental table 2. Assessments are conducted in person, except for the self-reported questionnaires, which are completed on site during the baseline visit and may be completed at home or on site for subsequent follow-up assessments, according to the participant's preference. Detailed information on methods used to assess outcomes during clinical visits can be found in online supplemental table 3.

Primary outcome

- Body weight (kg) at 104 weeks after randomisation. Body weight (±0.1 kg) will be measured using a digital scale in participants wearing light clothing.

Secondary outcomes

- Proportion of participants with weight loss ≥20% at 104 weeks after randomisation.
- Short Form 36 (SF-36) Mental Component Score at 104 weeks after randomisation. SF-36 is a generic, short-form health status questionnaire composed of 36 questions within eight multi-item domains assessing role limitations due to physical functioning, role limitations due to physical health problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems and mental health. These will be combined into two summary scores (physical and mental health component scores).[26]
- 4-m gait speed test at 104 weeks after randomisation. The 4-m gait speed test evaluates walking speed. Participants walk 4 m at their usual pace, and this is timed.[27]
- Metabolic Syndrome Severity-Z score (MetS-Z) at 104 weeks after randomisation. MetS-Z score is a composite continuous measure of components of the metabolic syndrome that includes waist circumference, systolic blood pressure, fasting glucose, triglycerides and high-density lipoprotein cholesterol concentrations. Waist circumference will be measured in duplicate at the midpoint between the last palpable rib and the top of the iliac crest following a standardised protocol. If the first two measurements differ by more than 1 cm, a third measurement will be taken and recorded. Blood pressure will be measured seated using a calibrated electronic sphygmomanometer. Three measurements will be taken within a 5 min window, with the arm supported at heart level, and all readings will be recorded. MetS-Z will be calculated as the sum of the five factors with weighted loadings according to sex and ethnicity.[28]

Other outcomes

All prespecified explorative outcomes can be found in online supplemental table 4.

To assess safety, the following outcomes will be evaluated:

- Proportion of participants who experience at least one serious adverse event (International Council for Harmonisation - Good Clinical Practice [ICH-GCP]) during 104 weeks of follow-up. A serious adverse event is defined as any untoward medical occurrence in a trial participant which results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.[29]
- Proportion of participants with incident eating disorders during 104 weeks of follow-up.
- Bone mineral density (BMD) measured with dual-energy X-ray absorptiometry (DXA) at 104 weeks of follow-up.[30]
  (a) BMD (g/cm²) of the hip (total hip and femoral neck).
  (b) BMD (g/cm²) of the lumbar region.

Body composition will be assessed by DXA. Physical functioning will be evaluated through physical activity and sleep using accelerometers (SENS motion) worn continuously for seven consecutive days and installed in accordance with the manufacturer's procedure,[31] the SF-36 Physical Component Score[26] and the 30-Second Sit-to-Stand test, which measures lower body strength by counting how many times a participant can stand up from a chair and sit down in 30 s.[32]

Medication use during the intervention will be assessed, including prescriptions for control of glucose, cholesterol, blood pressure, pain relief and psychiatric conditions. Metabolic health will be assessed through blood pressure, glucose and insulin concentrations, cholesterol profile, biochemical markers of liver and kidney function, and inflammation.

Blood and urine will be sampled for later analysis of additional biomarkers and genetic profiles. Several additional biological outcomes will be measured to provide more insights into the weight loss responses.

Mental health will be evaluated using the Major Depression Inventory,[33] the Weight Bias Internalization Scale[34] and the Eating Disorder Examination Questionnaire.[35] Work-related outcomes include measures of productivity[36] and sick leave days. We will also investigate within-trial cost-effectiveness by assessing health-related quality of life, 2-year costs and incremental cost per quality-adjusted life-year (QALY). Further, we will investigate model-based cost-effectiveness assessing predicted lifetime QALYs gained, predicted lifetime healthcare costs and long-term incremental cost-effectiveness ratios. Moreover, long-term outcomes over 5, 10 and 20 years will track mortality, major cardiovascular events, cancer diagnoses (especially those linked to obesity), fracture risks and employment status, including time off work due to illness.

Concurrent weight management efforts

Participants' use of other weight management programmes and weight loss interventions will be recorded.

Limiting missing data

Dropouts and missing data pose a threat to trial validity, particularly in trials with longer follow-up periods. For primary and secondary outcomes, we therefore plan to extend our efforts to obtain outcome data for participants who fail to have their outcomes recorded at the 104-week follow-up clinical visit. We will do so by conducting home visits, allowing for self-reported data and expanding the period for data collection, if needed.

Trial governance

The overall LightCOM project is overseen by a Project Management Group, a Project Steering Committee and an Advisory Board. CD serves as the sponsor of the LightCARE trial, which operates under the same governance structure as the other trials within the LightCOM project. Moreover, the LightCARE Trial Committee is responsible for the day-to-day management and coordination of the trial, including trial conduct, data collection and communication between sites. This committee ensures that the trial adheres to the approved protocol and regulatory requirements.

Sample size and power considerations

With 200 participants in each intervention group and an estimated dropout of 25%, we will have a power of 82% to detect a 5 kg difference in mean body weight between the IWL and usual care groups with a significance level of 0.05 and an assumed SD for both groups of 15 kg.[14 18]

For the secondary outcomes, with an estimated dropout proportion of 25%, the trial will also allow us to detect differences (significance level 0.05) between intervention groups in the MetS-Z score of 0.3 points with a power of 74% (SD 1.0 points)[37–39]; in the SF-36 mental component score of 4 points with a power of 82% (SD 12 points)[18 40] and in 4-m gait speed test of 0.2 m/s with a power of 93% (SD 0.5 m/s).[41] Finally, we will have a power of 83% to detect a fourfold increase in the proportion of individuals with a weight loss ≥20%, with a significance level equal to 0.05, provided that the proportion of individuals with a weight reduction ≥20% is equal to 2% in the usual care group.[18] Notably, a fourfold increase thus corresponds to a proportion with a weight loss ≥20% equal to 8% in the intervention arm.

Statistical analysis

A detailed statistical analysis plan will be published before the last participant's last visit. Descriptive data will be presented according to trial arms and country using appropriate summary measures. Group differences will be assessed using regression models with intervention group, stratification variables and baseline measurements (when relevant for follow-up measurements) as covariates. Primary conclusions will be based on the intention-to-treat (ITT) population using α=0.05 as significance level. Depending on the degree of protocol violations, secondary analyses will be undertaken in the per-protocol population defined as patients with a baseline measurement, at least one outcome measure at week 104 and no major protocol violations (both groups), in addition to adherence to TDR for at least 4 weeks, and more than 60% contact with IWL providing team, for the intervention group. Exploratory subgroup analyses will examine the interactions between intervention and baseline participant characteristics of country, sex, age (tertiles), socioeconomic status, ethnicity and BMI categories split at the median BMI. None of these findings will be reported individually, and none will be discussed as conclusive, only as hypothesis generating. Considering the small trial population and a recruitment period that is shorter than primary follow-up, we will not perform any interim analyses. Because this is a superiority study aimed at showing differences between intervention groups, tests will be two-sided and missing data will generally be addressed using (conservative) likelihood-based regression models such as linear mixed models.

Process evaluation

A mixed-methods process evaluation will be conducted alongside the trial to explore intervention delivery; contextual influences; participants' and health professionals' experiences of, responses to and interaction with the intervention. The evaluation is guided by the UK Medical Research Council's framework for process evaluations of complex interventions.[42]

Key domains that will be explored include

- **Fidelity**: the extent to which the intervention consultations are delivered as intended across different intervention sites and settings, including assessing the number, timing and content of participant contacts with health professionals.[43]
- **Engagement**: including participant uptake, retention, adherence to TDR, behavioural components and use of WLM.[43 44]
- **Participants' and health professionals' responses to and interactions with the intervention**: including participants' experiences, motivation and perceptions of support, as well as health professionals' reflections on barriers and facilitators.[42 44]
- **Context**: such as organisational, social and cultural factors that may influence perceptions and experiences across the Danish and UK settings.[42 44 45]

Data sources will include intervention logs, attendance records, structured observations, recordings of intervention consultations and semi-structured interviews with participants and staff. In Denmark, approximately 30 consultations will be audio-recorded and analysed, stratified by participant sex and BMI, and in the UK up to 100 consultation recordings will be analysed. We will also conduct around 40 semi-structured interviews in Denmark and around 30 in the UK with participants, health professionals and coaches to identify perceived barriers, facilitators and contextual factors relevant for implementation.

Initial sampling will be designed to ensure variation across demographics and intervention sites, to capture a broad range of experiences. As the trial progresses, sampling will be iterative and responsive to ongoing learning.[46] Qualitative data from interviews and observations will be analysed thematically and informed by relevant theory[47 48]; intervention recordings will be analysed using a fidelity checklist (Denmark) and conversation analysis (UK); and quantitative data on fidelity and engagement will be summarised descriptively. Integration of qualitative and quantitative data will provide a comprehensive understanding of how the intervention

functions in practice.[43 44] Where possible, we will triangulate findings across countries and methods to provide a holistic picture of intervention delivery and reception, and generate learning for implementation.

Findings from the process evaluation will support the interpretation of trial outcomes and provide insight into the potential for scaling and sustaining the intervention within routine primary care.

Economic evaluation

We will perform economic evaluations in the three LightCOM trials using the same methodology.

A within-trial cost–utility analysis from a National Health Payer perspective will be conducted alongside the clinical trial and will adopt a 2-year time horizon (follow-up period). The costs of the LightCARE intervention will be determined separately for the UK and Denmark, reflecting the differences in the organisation and implementation of the intervention in each country. Broader resource utilisation will be captured in a resource use questionnaire included in the eCRF collected at the clinical assessment days at weeks 0, 32, 52 and 104. Unit costs for health resources will be derived from relevant sources and estimated in line with best practice. The five-level EQ-5D health-related quality-of-life questionnaire will be administered at each clinical visit. The EQ-5D-5L responses will be converted into utility scores, for the purposes of QALY estimation, using recommended national algorithms. QALYs will be calculated as the area under the baseline-adjusted utility curve and will be calculated using linear interpolation between baseline and follow-up utility scores.

The statistical analyses will be performed based on the intention-to-treat principle, and appropriate methods will be applied to handle missing data. Multilevel modelling will be employed to reflect the hierarchical structure of the data, with patients nested within countries and sites. This approach allows us to account for variations at different levels and address the complexities inherent in the multinational nature of the trial. Appropriate statistical methods will be used to account for the potential skewness of the outcomes. A number of sensitivity analyses will be conducted, including re-estimation of cost-effectiveness assuming different study perspectives, among these (1) a national health payer and personal social service perspective, (2) a healthcare sector perspective (all healthcare cost regardless payer, including out-of-pocket) and (3) a limited societal perspective (healthcare sector, patient time, patient transportation and productivity loss).[49] Furthermore, sensitivity analyses will include complete case analysis and different methods to address the challenges associated with the multinational nature of the trial. The results of the economic evaluation will be expressed in terms of incremental cost per QALY gained. Cost-effectiveness acceptability curves, generated via non-parametric bootstrapping, will be used to show the probability of cost-effectiveness of the intervention at alternative cost-effectiveness thresholds.

Separate decision-analytic modelling will extrapolate the time horizon of the economic evaluation and express cost-effectiveness in terms of incremental cost per QALY gained over a lifetime horizon. We will use the Sheffield Diabetes Prevention model, which is a microsimulation model that links cardiometabolic risk factors (BMI, HbA1c, systolic blood pressure, cholesterol) to non-communicable disease morbidity (type 2 diabetes, cardiovascular disease, heart failure, microvascular complications of diabetes, osteoarthritis, dementia and cancers of the breast and colon).[42 43] In each model cycle, individual characteristics, medical history and treatment influence the updating of cardiovascular risk factors. Disease incidence and mortality are simulated using established risk equations from diverse evidence sources. Costs and health-related quality of life are calculated per cycle based on healthcare utilisation and health status. Costs and QALYs will be discounted at 3.5% in line with national guidance. The analyses will assess the cost-effectiveness of the IWL intervention compared with usual care from a National Health Payer perspective for the UK and Denmark. A number of sensitivity analyses will be conducted.

The reporting of the results will follow the Consolidated Health Economic Evaluation Reporting Standards 2022 checklist and adhere to the recommendations of the National Institute for Health and Care Excellence and the Danish National Evaluation Agencies.

In addition to the cost–utility analyses, the health economic analyses will include an evaluation of the long-term labour market effect of the LightCARE intervention. To assess the long-term labour market effects, we will apply the Surrogate Index as introduced by Athey *et al*.[44] The method links short-term outcomes with the long-term labour market effects using a retrospective sample of individuals undergoing different weight loss initiatives similar to the intervention. From the retrospective sample, the link between short-term and long-term outcomes is estimated and the precision is established together with the minimum required follow-up years needed to predict the long-term effects.

The Health Economic Evaluation will be prospectively planned and detailed within a ‘Health Economic Analysis Plan’.

ETHICS AND DISSEMINATION

Ethical approval was granted by the Danish Research Ethics Committee of the Capital Region in Denmark on 21 December 2023 (H-23051332) and the South Central—Oxford B NHS Research Ethics Committee in the UK on 15 August 2024 (24/SC/0210). Any substantial amendments to the protocol will be submitted for review and approval by the relevant ethics committees and communicated. All participants provide written informed consent for participation. Participants receive DKK 450 (or GB£ 50) for each completed assessment day, excluding the baseline visit. All personal data will be

handled in accordance with the General Data Protection Regulation and local data protection legislation. Trial data will be handled using OpenClinica, an electronic database managed by the CTU. This incorporates audit trails, data separation between intervention sites and data validation. During the trial, we will employ blinded central data monitoring, initiated after one-third of the participants have been recruited and carried out monthly by the investigators. This aims to enhance data completeness and quality and minimise protocol deviations through blinded evaluation of the data.[45] Findings from the trial will be disseminated through peer-reviewed journals and scientific conferences, enabling real-time dialogue with researchers and practitioners in the field. Development of publications from the trial will be coordinated by the LightCOM Project Management Group following the project's publication rules. Authorship for publications will concur with and be based on the International Committee of Medical Journal Editors recommended criteria. Participants will receive a written summary of the results after the trial has concluded.

Patient and public involvement

We engaged members of the public to discuss the trial design and help improve clarity of the trial documents. We also consulted on the process for recruiting.

In the UK, a Patient and Public Involvement (PPI) panel was convened in Summer 2024. This panel meets every 6 months and will continue to do so for the duration of the project, as well as providing feedback on an ad hoc basis. For example, this panel reviewed the UK participant information sheet, as well as questionnaires used in the trial, and provided input into the initial phone call script to outline the study to potential participants. In addition, they have been involved in the development of the health economics questionnaire.

PPI contributors will also be involved in helping disseminate the research when it is published.

DISCUSSION

We aim to evaluate the benefits, harms and cost-effectiveness of an IWL intervention, incorporating TDR, behavioural support and WLM, compared with standard weight management programmes in primary care for adults with obesity class I or uncomplicated obesity class II or higher. The randomised design with blinded outcome assessment, analyses and conclusion-drawing ensures a high level of methodological rigour and helps reduce bias when evaluating the effects of the intervention. The IWL intervention combines several well-established strategies for weight loss, including TDR,[14–16] behavioural support[46] and WLM,[17–19] offered in a way that allows for individual tailoring.

The LightCARE trial occurs at a time when WLM is starting to take on a larger role in primary care.[47] It will evaluate how such medications might be used with other strategies in a real-world context, whether this leads to better outcomes and is cost-effective compared with current standard care. The intervention is embedded in existing healthcare structures in two healthcare systems. In Denmark, this involves establishing a new municipal 'Hub' infrastructure tailored to the trial, while in the UK, delivery is through an already commissioned remote service. Comparing these two approaches to usual care in each country will help us understand what is feasible and effective across different settings. The trial also includes elements that can support later implementation, including process evaluation and cost-effectiveness analysis. These will provide insight into whether the intervention works and how and at what cost. Being part of the wider LightCOM consortium strengthens the trial further as results will contribute to a broader knowledge base on obesity care.

However, there are also limitations. The minimal clinically relevant difference of approximately 5% weight loss used to power the study is a commonly accepted but somewhat arbitrary threshold. We chose it based on prior evidence linking modest weight loss to improved health outcomes and practical considerations of feasibility and statistical power.[48] Moreover, due to the nature of the intervention, participants cannot be blinded to group allocation, which may influence their behaviour and their willingness to engage in follow-up. In addition, the definition of 'usual care' varies both within Denmark and across countries, and it may not remain consistent throughout the intervention period, which complicates the interpretation of the results.

Author affiliations
[1]Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[2]Research Unit for Diet and Health at The Parker Institute, Frederiksberg and Bispebjerg Hospital, Part of the Copenhagen University Hospital, Frederiksberg, Denmark
[3]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford University Hospitals Biomedical Research Centre, Oxford, UK
[4]Department of Respiratory Diseases and Endocrinology, Amager and Hvidovre Hospital, Part of the Copenhagen University Hospital, Hvidovre, Denmark
[5]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[6]Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Denmark, Odense, Region Syddanmark, Denmark
[7]Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[8]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[9]Physical Medicine & Rehabilitation Research - Copenhagen (PMR-C), Department of Physical and Occupational Therapy, Amager and Hvidovre Hospital, Part of the Copenhagen University Hospital, Hvidovre, Denmark
[10]Department of Clinical Research, Amager and Hvidovre Hospital, Part of the Copenhagen University Hospital, Hvidovre, Denmark
[11]Department of Orthopedic Surgery, Amager and Hvidovre Hospital, Part of the Copenhagen University Hospital, Hvidovre, Denmark
[12]DaCHE - Danish Centre for Health Economics, University of Southern Denmark Department of Public Health, Odense, Denmark

Acknowledgements Camilla Verdich is the administrative project lead on LightCOM and has thereby contributed to the development of the trial protocol. Nils B Jørgensen and Jakob Kragstrup contributed to the early development of the LightCOM project and were part of the group that obtained funding but later left the

project. We would like to acknowledge the clinical staff and research assistants for their valuable contributions to the development of study procedures, data collection and delivery of the intervention.

Contributors CD, BLH, SR, KRO, PA, SAJ, SM and FBW conceived the LightCOM project and secured funding. CD is the trial sponsor and guarantor for the study. SCL and SWa are the trial managers. AKGJ performed the power calculations and was responsible for the overall statistical strategy. SCL prepared the first draft of the manuscript. All authors made substantial contributions to the conceptualisation of the study design and conduct of the protocol.

Funding The LightCARE trial is part of the Lighthouse Consortium on Obesity Management (LightCOM) supported by the Novo Nordisk Foundation under grant agreement number NNF22SA0080921.

Disclaimer The funder had no role in the design of the study, data collection, analysis, interpretation, or decision to submit the manuscript for publication.

Competing interests CD has received research funding from the Novo Nordisk Foundation and others, and served in various roles (investigator, consultant, lecturer, chairperson) for Novo Nordisk, Amgen, Amylyx, AstraZeneca and Eli Lilly, over the past 3 years. SM has served on advisory boards for AstraZeneca, Boehringer Ingelheim, Intarcia Therapeutics, Novo Nordisk, Sanofi, Abbott Laboratories, Bayer and Amgen. He has received lecture fees from AstraZeneca, Novo Nordisk and MSD. He has received research grants from Novo Nordisk, the Novo Nordisk Foundation and Boehringer Ingelheim. These grants were paid to his institution, Hvidovre Hospital, University of Copenhagen, and not to him personally. None of the grants are related to the work presented in this article. He has received support for attending meetings and/or travel from Novo Nordisk, Boehringer Ingelheim and Bayer. SM has also served as principal investigator in the development of drugs for type 2 diabetes and obesity in collaboration with Novo Nordisk and Bayer, with all funds paid to his institution (no personal fees). He is also a consultant for Netdoktor, a Danish health information website that provides medical content and advice to the general public. TB declares that his spouse is employed at Novo Nordisk, and they own shares in Novo Nordisk. JE owns shares in Novo Nordisk. PA and SAJ were investigators on two trials in which total diet replacement products were donated by Nestle. BLH, KNB-M and FBW have, on behalf of their institutions, received research funding from the Novo Nordisk Foundation and other private and public foundations. CA has worked as an independent consultant for the Behavioural Insights team, Wildfowl Wetlands Trust, Adelphi Real World, Oxford Health BRC and Linney Create for which she was paid personally. She was an academic advisor for NESTA and did not receive personal payment. PA and SAJ are funded by NIHR Oxford Health Biomedical Research Centre, NIHR Oxford Biomedical Research Centre, NIHR Oxford and Thames Valley Applied Research Collaboration. PA is an NIHR senior investigator. The remaining authors have no disclosures to declare.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Sofus C Larsen http://orcid.org/0000-0002-0838-9378
Berit Lilienthal Heitmann http://orcid.org/0000-0002-6809-4504
Sarah Wane http://orcid.org/0000-0002-1766-882X
I O Specht http://orcid.org/0000-0002-3114-4715
Ann-Kathrin Lindahl Christiansen http://orcid.org/0000-0003-3917-9151
Thomas Bandholm http://orcid.org/0000-0001-6884-1971
Susanne Reventlow http://orcid.org/0000-0002-4990-142X
Line Planck Kongstad http://orcid.org/0000-0002-9625-5870
Susan A Jebb http://orcid.org/0000-0001-9190-2920

REFERENCES

1 Afzal S, Tybjærg-Hansen A, Jensen GB, *et al*. Change in Body Mass Index Associated With Lowest Mortality in Denmark, 1976-2013. *JAMA* 2016;315:1989–96.
2 Di Angelantonio E, Bhupathiraju SN, Wormser D, *et al*. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *The Lancet* 2016;388:776–86.
3 Riaz H, Khan MS, Siddiqi TJ, *et al*. Association Between Obesity and Cardiovascular Outcomes: A Systematic Review and Meta-analysis of Mendelian Randomization Studies. *JAMA Netw Open* 2018;1:e183788.
4 Dong Z, Xu X, Wang C, *et al*. Association of overweight and obesity with obstructive sleep apnoea: A systematic review and meta-analysis. *Obesity Medicine* 2020;17:100185.
5 Amiri M, Hatoum S, Hopkins D, *et al*. The Association Between Obesity and Polycystic Ovary Syndrome: An Epidemiologic Study of Observational Data. *The Journal of Clinical Endocrinology & Metabolism* 2024;109:2640–57.
6 Zheng H, Chen C. Body mass index and risk of knee osteoarthritis: systematic review and meta-analysis of prospective studies. *BMJ Open* 2015;5:e007568.
7 Mahamat-saleh Y, Aune D, Freisling H, *et al*. Association of metabolic obesity phenotypes with risk of overall and site-specific cancers: a systematic review and meta-analysis of cohort studies. *Br J Cancer* 2024;131:1480–95.
8 Haase CL, Lopes S, Olsen AH, *et al*. Weight loss and risk reduction of obesity-related outcomes in 0.5 million people: evidence from a UK primary care database. *Int J Obes (Lond)* 2021;45:1249–58.
9 Force UPST. Behavioral Weight Loss Interventions to Prevent Obesity-Related Morbidity and Mortality in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA* 2018;320:1163–71.
10 The national institute for health and care excellence (nice). Weight management: lifestyle services for overweight or obese adults. 2014.
11 Livsstilsintervention ved svær overvægt. Anbefalinger for tilbud til børn og voksne. 2021.
12 Aveyard P, Lewis A, Tearne S, *et al*. Screening and brief intervention for obesity in primary care: a parallel, two-arm, randomised trial. *The Lancet* 2016;388:2492–500.
13 Ahern AL, Wheeler GM, Aveyard P, *et al*. Extended and standard duration weight-loss programme referrals for adults in primary care (WRAP): a randomised controlled trial. *Lancet* 2017;389:2214–25.
14 Astbury NM, Aveyard P, Nickless A, *et al*. Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET): pragmatic randomised controlled trial. *BMJ* 2018;362:k3760.
15 Lean MEJ, Leslie WS, Barnes AC, *et al*. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019;7:344–55.
16 Taheri S, Zaghloul H, Chagoury O, *et al*. Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial. *Lancet Diabetes Endocrinol* 2020;8:477–89.
17 Khera R, Murad MH, Chandar AK, *et al*. Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: A Systematic Review and Meta-analysis. *Jama* 2016;315:2424–34.
18 Wilding JPH, Batterham RL, Calanna S, *et al*. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med* 2021;384:989–1002.
19 Wadden TA, Bailey TS, Billings LK, *et al*. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. *JAMA* 2021;325:1403–13.
20 Sørensen MS, Pottegård A, Andersen NE, *et al*. Survey among adult users of semaglutide for weight loss in Denmark: User characteristics, treatment expectations and experienced effects. *Diabetes Obes Metab* 2025;27:2214–22.
21 B. Jensen DD. Det er desværre mere økonomien end overvægten, der er afgørende for, om patienterne får Wegovy. *Ugeskrift for Læger* 2023.

22 Chan A-W, Boutron I, Hopewell S, *et al*. SPIRIT 2025 statement: updated guideline for protocols of randomised trials. *BMJ* 2025;389:e081477.
23 The lightcom project. Available: https://www.regionh.dk/lightcom/uk/pages/for_researchers_and_health_-professionals.aspx
24 Liva healthcare. Available: https://www.livahealthcare.com/ [Accessed 6 May 2025].
25 Bull FC, Al-Ansari SS, Biddle S, *et al*. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med* 2020;54:1451–62.
26 Ware J, Ma K, Keller SD. SF-36 Physical and Mental Health Summary Scales: a User's Manual. 1993;8:23–8.
27 Kim H-J, Park I, Lee HJ, *et al*. The reliability and validity of gait speed with different walking pace and distances against general health, physical function, and chronic disease in aged adults. *J Exerc Nutrition Biochem* 2016;20:46–50.
28 Gurka MJ, Lilly CL, Oliver MN, *et al*. An examination of sex and racial/ethnic differences in the metabolic syndrome among adults: a confirmatory factor analysis and a resulting continuous severity score. *Metab Clin Exp* 2014;63:218–25.
29 European medicines agenct. ich e6 good clinical practice - scientific guideline. 2025.
30 Seimon RV, Wild-Taylor AL, Keating SE, *et al*. Effect of Weight Loss via Severe vs Moderate Energy Restriction on Lean Mass and Body Composition Among Postmenopausal Women With Obesity: The TEMPO Diet Randomized Clinical Trial. *JAMA Netw Open* 2019;2:e1913733–e33.
31 Pedersen BS, Kristensen MT, Josefsen CO, *et al*. Validation of Two Activity Monitors in Slow and Fast Walking Hospitalized Patients. *Rehabil Res Pract* 2022;2022:9230081.
32 Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport* 1999;70:113–9.
33 Bech P, Rasmussen N-A, Olsen LR, *et al*. The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. *J Affect Disord* 2001;66:159–64.
34 Durso LE, Latner JD. Understanding Self-directed Stigma: Development of the Weight Bias Internalization Scale. *Obesity (Silver Spring)* 2008;16:S80–6.
35 Fairburn CG, Beglin SJ. Assessment of eating disorders: Interview or self-report questionnaire? *Intl J Eating Disorders* 1994;16:363–70.
36 Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353–65.
37 Gurka MJ, Filipp SL, Pearson TA, *et al*. Assessing Baseline and Temporal Changes in Cardiometabolic Risk Using Metabolic Syndrome Severity and Common Risk Scores. *J Am Heart Assoc* 2018;7:e009754.
38 Haufe S, Kerling A, Protte G, *et al*. Telemonitoring-supported exercise training, metabolic syndrome severity, and work ability in company employees: a randomised controlled trial. *Lancet Public Health* 2019;4:e343–52.
39 Sandsdal RM, Juhl CR, Jensen SBK, *et al*. Combination of exercise and GLP-1 receptor agonist treatment reduces severity of metabolic syndrome, abdominal obesity, and inflammation: a randomized controlled trial. *Cardiovasc Diabetol* 2023;22:41.
40 Fløjo TN, Tell GS, Kolotkin RL, *et al*. Changes in quality of life 5 years after sleeve gastrectomy: a prospective cohort study. *BMJ Open* 2019;9:e031170.
41 Tabue-Teguo M, Perès K, Simo N, *et al*. Gait speed and body mass index: Results from the AMI study. *PLoS One* 2020;15:e0229979.
42 Breeze P, Thomas C, Thokala P, *et al*. The Impact of Including Costs and Outcomes of Dementia in a Health Economic Model to Evaluate Lifestyle Interventions to Prevent Diabetes and Cardiovascular Disease. *Med Decis Making* 2020;40:912–23.
43 Breeze PR, Thomas C, Squires H, *et al*. The impact of Type 2 diabetes prevention programmes based on risk-identification and lifestyle intervention intensity strategies: a cost-effectiveness analysis. *Diabet Med* 2017;34:632–40.
44 Athey S, Chetty R, Imbens GW, *et al*. *The Surrogate Index: Combining Short-Term Proxies to Estimate Long-Term Treatment Effects More Rapidly and Precisely*. National Bureau of Economic Research, 2019.
45 Olsen MH, Hansen ML, Safi S, *et al*. Central data monitoring in the multicentre randomised SafeBoosC-III trial - a pragmatic approach. *BMC Med Res Methodol* 2021;21:160.
46 Madigan CD, Graham HE, Sturgiss E, *et al*. Effectiveness of weight management interventions for adults delivered in primary care: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2022;377:e069719.
47 Yanovski SZ, Yanovski JA. Approach to Obesity Treatment in Primary Care: A Review. *JAMA Intern Med* 2024;184:818–29.
48 The Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: The look AHEAD study. *Obesity (Silver Spring)* 2014;22:5–13.
49 Kim DD, Silver MC, Kunst N, *et al*. Perspective and Costing in Cost-Effectiveness Analysis, 1974-2018. *Pharmacoeconomics* 2020;38:1135–45.