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Intensive weight loss intervention versus usual care for adults with severe and complex obesity: the LightWAY randomised trial protocol

Sarah Wane ,[1] Paul Aveyard ,[1] Sabrina Wielsøe,[2] Sofus Christian Larsen ,[3,4] Jadine Scragg,[1] Jane Lindschou ,[5] Janus Christian Jakobsen,[5,6] Janus Engstrøm,[5] Ina Olmer Specht ,[3,4] Ann-Kathrin Lindahl Christiansen ,[3] Aksel Karl Georg Jensen,[7] Thomas Bandholm ,[8,9,10] Charlotte Albury,[1] Gritt Overbeck,[3] Susanne Reventlow ,[3] Kim Rose Olsen,[11] Patrick Farr,[1] Kirstine Nyvold Bojsen-Møller ,[2,12] Berit Lilienthal Heitmann ,[3,4] Frans Boch Waldorff,[3] Sten Madsbad,[2,12] Carsten Dirksen,[2,12] Susan Ann Jebb [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Susan Ann Jebb;
susan.jebb@phc.ox.ac.uk

ABSTRACT

Introduction Effective treatment for clinical obesity is available but is rarely offered by healthcare systems, which often treat complications without treating the underlying cause. The LightWAY trial will investigate the clinical benefits and harms as well as cost-effectiveness of an intensive weight loss intervention compared with existing weight management programmes for people with clinical obesity.

Methods and analysis LightWAY is an investigator-initiated, international, randomised, parallel-group clinical superiority trial with blinded outcome assessment. Six hundred people seeking treatment for clinical obesity (body mass index ≥35 kg/m^2 with comorbidities) will be recruited in centres in the UK and Denmark and randomised 1:1 to one of two groups. The experimental group will be offered a 2-year intensive weight loss programme providing support and advice to follow a total diet replacement programme, followed by gradual transition to an energy-reduced diet in combination with increased physical activity and if needed, prescription of weight loss medication. The control group will receive usual care, typically comprising brief behavioural support for weight loss and treatment of the complications of obesity or occasionally referral to specialist weight management services. The two co-primary outcomes are cardiometabolic risk, assessed with metabolic syndrome severity Z-score, and body weight assessed at 2 years. The secondary outcomes include the Short Form-36 mental component scale, 4-metre gait speed and proportion of participants achieving ≥20% weight loss. The key adverse effects will be the proportion of participants with at least one serious adverse event, incidence of eating disorders and disproportional loss of bone mass. Incremental cost-effectiveness will be assessed over the trial period and over the lifetime through modelling.

Ethics and dissemination Ethical approval was granted in the UK (August 2024, 24/SC/0211) and Denmark (December 2023, H-23065222). Findings will be disseminated through peer-reviewed journals and scientific conferences and to participants in the trial and clinicians.

Trial registration number NCT06321458.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The intensive weight loss intervention aims to achieve substantial weight loss in patients with clinical obesity compared with current best practice across two different healthcare systems.
⇒ The co-primary outcomes will assess the effects of the intervention on weight and metabolic health, comprehensively describing the effects of the intervention in ways that are meaningful to clinicians and patients.
⇒ Process and health economics evaluations are built into the outcomes and design to allow full exploration of how the intervention would work for patients and healthcare systems and in the wider economic context.
⇒ Although it will not be possible to blind participants to their allocation, primary outcomes will be assessed blinded, and the statistical analyses and conclusions will be conducted with the two coded, for example, 'A' and 'B'.

INTRODUCTION

Obesity has become common worldwide over the past 50 years, and more severe obesity, here defined as body mass index (BMI) ≥35 kg/m^2 and ≥32.5 kg/m^2 in those of white and non-white ethnicities, respectively, has become much more prevalent, with around 1 in 10 adults in high-income countries above this threshold.[1 2] Consequent on the rise of obesity is the increase in prevalence of obesity-related

disease, such as hypertension, type 2 diabetes, metabolic-dysfunction associated steatohepatitis (MASH), impaired mental health and sleep apnoea. The co-occurrence of high BMI and disease caused by excessive adiposity is termed clinical obesity.[3] Until recently, the main option available for clinicians managing patients with clinical obesity was to treat the symptoms and complications. Rarely have clinicians referred patients for treatment of obesity, but doing so is associated with reducing blood pressure, improving lipid profile, reducing liver fat and improving sleep apnoea.[4] Where obesity treatment has been offered, it has typically comprised low-intensity brief support, eg, referral to a commercial weight management programme that is not often intensive enough to lead to significant clinical improvements for patients.[5]

Recently, treatment programmes offering substantial weight loss have become available and shown to be safe, effective and capable of meeting the scale of the need. These include total diet replacement (TDR) programmes and glucagon-like peptide-1 (GLP-1) receptor agonists, both of which can lead to over 10 kg (>10%) of weight loss on average for patients offered these treatments.[6–8] Combining these treatments and continuing them over an extended period may produce weight loss that may put obesity-related disease into remission. However, these weight management options are far more expensive than most other options to support weight loss. Even if these treatment programmes are successful and the treatment effect is additive, it may not prove to be cost-effective relative to standard care or may cause adverse consequences.

In the LightWAY trial, we aim to assess the clinical benefits and harms, as well as cost-effectiveness of an intensive weight loss (IWL) intervention that includes total dietary replacement, behavioural support and weight loss medication (WLM) compared with existing weight management programmes for people with clinical obesity.

METHODS AND ANALYSIS

Trial design

The protocol has been developed in accordance with the updated Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines,[9] including use of the SPIRIT checklist (online supplemental table 1). Trial reporting will adhere to the Consolidated Standards of Reporting Trials (CONSORT) statement and relevant extensions.

The LightWAY trial is an investigator-initiated, international, 1:1 randomised, parallel-group, clinical superiority trial conducted to investigate an IWL intervention compared with usual care for adults with more severe obesity with complications in primary or secondary care in Denmark and the UK. It is one of three trials (LightCARE (NCT06321432) and LightBAR (NCT06309238)). All three trials compare an identical IWL intervention with usual care; however, the trials have different settings and patient populations. LightCARE focuses on a population with less severe obesity and without complications and is often treated in primary care (control). Conversely, LightBAR focuses on patients with severe clinical obesity who are eligible for weight loss (bariatric) surgery, in which surgery will be the comparator, in a non-inferiority design.

Participants and recruitment

In the UK, participants will be recruited from the community in response to invitation from general practitioner (GP) practices or invitation from waiting lists for hospital clinics. In Denmark, potential participants will be recruited from social media, relevant websites, posters in public places like municipality health centres, postal invitation or email, job centres, gyms etc., or through the individual's GP. All advertisements will direct potential participants to the LightCOM website in which they will have access to participant information and a link to a short online eligibility questionnaire. Potentially eligible participants will be contacted by trial staff and assessed for eligibility.

Inclusion criteria

Participants will be included if they met the following:

1. Are between 18 and 60 years at screening (both inclusive).
2. Have clinical obesity, that is, BMI≥35 kg/m^2 (for white individuals) or BMI≥32.5 kg/m^2 (for non-white individuals), and one or more adiposity-related chronic diseases, defined here as cardiovascular disease, type 2 diabetes, hypertension, MASH or sleep apnoea.
3. Provide informed consent.

Exclusion criteria

Participants will be excluded if they met the following:

1. Are pregnant or breastfeeding or planning to become pregnant in the next 2 years.
2. Have used WLMs or GLP-1 agonist treatments within the last 3 months.
3. Currently having cancer treatment, except for oestrogen antagonist therapy or non-melanoma skin cancer.
4. Have had prior bariatric surgery (except reversible procedures that were performed over 1 year ago).
5. Have severe eating disorders diagnosed or treated in the last 6 months.
6. Have any disease that could impair adherence to the treatment plan or significantly affect quality of life.
7. Have any conditions that complicate the use of TDR products (eg, type 1 diabetes and insulin therapy).
8. Have any contraindications for GLP-1 agonist treatment (eg, recent history of pancreatitis).
9. Are participating in other obesity-related research that could interfere with the trial.
10. Have another member of their household enrolled in the trial.

This study aims to enrol a diverse population and monitor recruitment by sex, socio-economic status and

ethnicity and may close recruitment to some groups to increase diversity.

Randomisation

Participants will be stratified by site with random permuted blocks (block sizes concealed to the investigators). The randomisation list (ie, sequence generation) will be computer-generated before participant inclusion by independent data manager from the Copenhagen Trial Unit and concealed by the trial database until after consent and eligibility are confirmed to ensure allocation concealment.

Blinding

Given the nature of the interventions, blinding the participants or the healthcare providers administering the interventions will be impossible. In all other aspects of the trial, blinding will be employed. Outcome assessors will be blinded to treatment (ie, will not have information on the participant's group allocation) and will not be delivering the intervention. Participants will also be requested not to disclose their allocation when outcomes are assessed. All aspects of the intervention programme are available outside of this programme (ie, TDR or GLP-1), which means that participants receiving usual care could receive any of these treatments; therefore, any adverse events would not, in itself, reveal the allocated treatment group.

Statisticians and investigators drawing conclusions will be fully blinded. Statistical analyses will be conducted 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 have both obtained consensus, the blinding will be broken by the data manager at the Copenhagen Trial Unit.[10 11]

Intensive weight loss intervention

The IWL intervention aims to support participants to achieve and maintain a weight loss of at least 20% from baseline or a BMI <25 kg/m^2. To achieve this, the IWL intervention offers regular behavioural support to follow an individualised programme of TDR, followed by a healthy food-based diet and WLM if needed to meet weight loss goals. The IWL has three major phases: (1) weight loss induction, (2) weight loss continuation and (3) weight loss maintenance, and a structured response to weight regain (figure 1). In the UK, support will be provided by a commercial partner that provides TDR programmes contracted to the NHS through telephone and video calls and an app. To deliver the intervention in Denmark, clinic (termed hub) staff in Gladsaxe, Frederiksberg and Hvidovre municipalities in the capital region of Denmark will deliver the intervention. The intervention will be delivered by municipal dieticians via in-person visits and remote consultations. Participants will receive initial consultations with an IWL-trained GP, regular follow-up consultations with a dietitian and additional support from a nurse on injection technique if starting weight loss medication.

Weight loss induction phase (weeks 1–12)

The weight loss induction phase aims to achieve at least 1% weight loss per week using TDR combined with behavioural support. Weight loss progress will be evaluated every week 4. If weight loss is not ≥4% at 4 weeks, WLM may be added. TDR provides nutritionally complete formula food products of 800–850 kcal/day to replace usual foods, but participants will be allowed to add low-energy vegetables or salad for tolerability plus a fibre supplement to reduce constipation. Participants will be advised to drink 2–2.5 L of non-caloric beverages. If TDR is poorly tolerated, participants will be allowed to progress to partial use of dietary replacements with one low-energy, low-carbohydrate food-based meal (<300 kcal/day). If TDR is not tolerated, they will be supported with an individualised low-energy, low-carbohydrate food-based diet (1200 kcal/day, with<30% of daily energy intake from carbohydrates and a minimum of 60 g protein/day).

Consultations with an online health coach in the UK and a municipality dietician in Danish hubs will be scheduled every 2 weeks to guide TDR, improve adherence and provide additional behavioural support. Participants will be advised to maintain or increase physical activity, especially walking, to individual tolerance. Participants will be encouraged to adopt a regular sleep pattern.

Weight loss continuation phase (weeks 13–32)

Weight loss continuation aims for at least 20% weight loss or BMI≤25 kg/m^2 in white people or≤23 kg/m^2 in people in other ethnic groups, whichever comes first. Weight loss progress will be evaluated every fourth week. If weight loss progress does not meet or exceed 2% over 4 weeks, WLM addition will be suggested. TDR food products may be reduced and a healthy low energy food-based diet introduced. Alternatively, TDR may be continued for up to 8 weeks, depending on participant choice, followed by stepwise reduction and reintroduction of a healthy energy-reduced diet. The low-energy diet will focus on foods containing slowly absorbed carbohydrates high in dietary fibre (targeted daily intake of dietary fibre >35 g), with high-quality proteins (targeted macronutrient composition, 20%–25% of total energy from protein, 40%–45% from carbohydrate and 30%–35% from fat, preferably unsaturated), based on a Mediterranean[12] or Nordic[13] dietary pattern. Hub dieticians and coaches will advise participants to limit their intake of free sugars to <5% of total energy intake. Food reintroduction would typically take 4–8 weeks but may vary depending on individual needs. Use of up to one dietary replacement product per day is allowed after food reintroduction to aid weight-loss maintenance.

Consultations with a hub coach will be scheduled at least every 2 weeks during food reintroduction to support behavioural strategies to support this transition and help

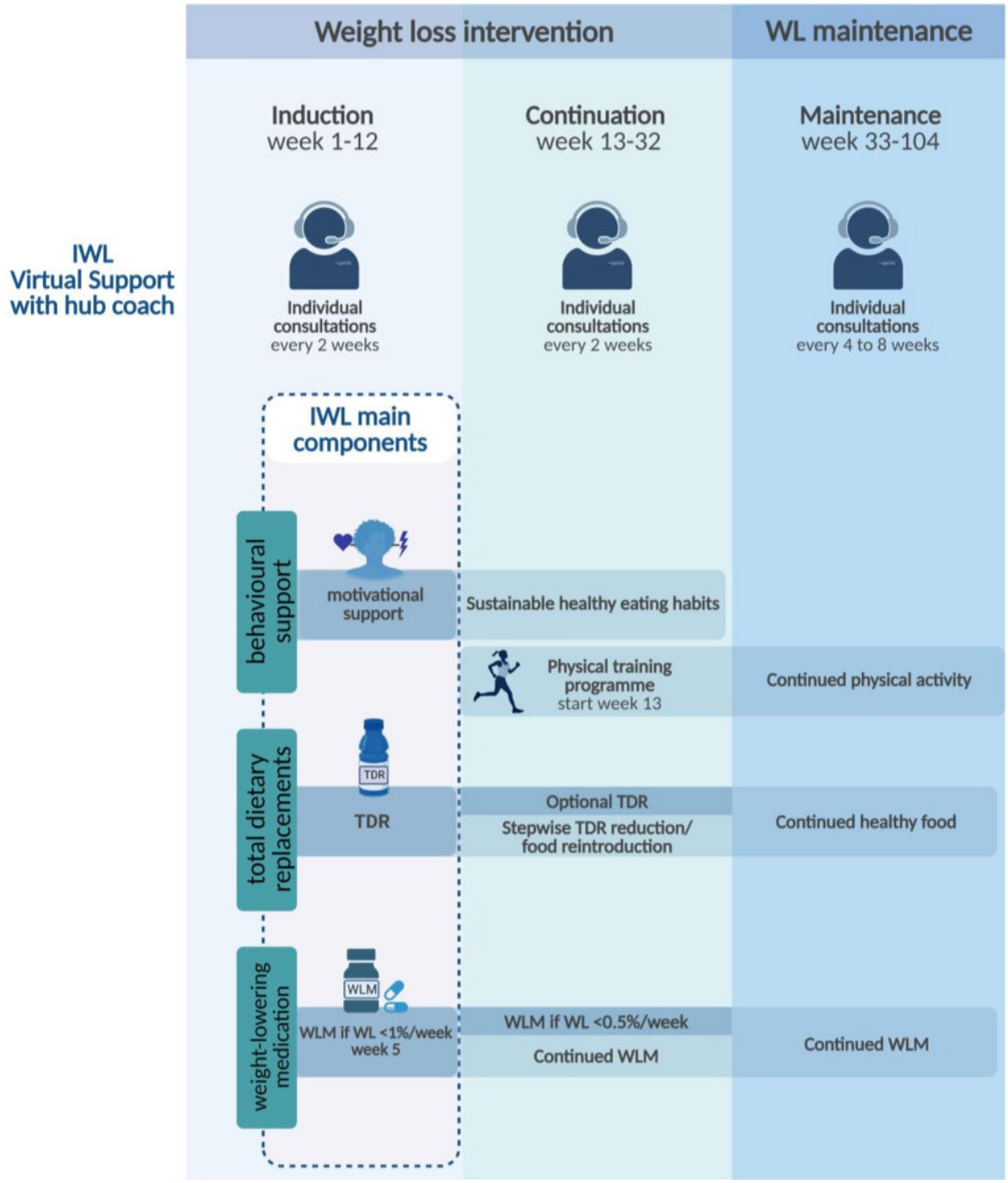

Figure 1 Treatment phases for IWL intervention. Created with BioRender.com. IWL, intensive weight loss

develop long-term healthy eating patterns. Support will include ways to address maladaptive eating behaviours (eg, emotional eating, external eating, binge eating and reactivity to food cravings) and aim to cultivate and enhance self-regulation by improving awareness of emotional and sensory cues, which may be important for altering one's relationship with food.

During the weight loss continuation phase, dieticians and coaches will support participants to incorporate physical activity and exercise into their daily schedule and educate on the benefits to their health. Participants will aim to increase to 150–300 min of moderate physical activity a week, with two strength sessions per week.[14] Participants will be encouraged to use pedometers to track steps taken. They will be taught to use the modified Borg Perceived Exertion scale[15] to understand the activity and the level that they should aim for. They will also be directed to accessible information on ways

to increase their physical activity level by signposting to trusted websites on ways to complete different activities, such as performing resistance exercises or stretching (eg, the UK's National Health Service website, Exercise page https://www.nhs.uk/live-well/exercise/).

Weight loss maintenance phase (weeks 33–104)

The weight loss maintenance phase aims to support participants to follow a food-based low-energy diet and physical activity as described above to maintain weight loss during the weight loss phase with behavioural support offered every 4 weeks. However, TDR products will be offered to replace meals, or a TDR could be reintroduced if weight regain occurs. WLM will continue.

Weight regain response

Early identification of weight regain is essential for successful weight maintenance. Therefore, participants in the intervention will be prompted to weigh themselves weekly for the duration of the intervention; if they do not own scales, a set will be sent for this purpose. If participants regain ≥3 kg or are concerned about regaining weight, they will be invited to a hub session to help identify any potential factors and develop an individualised rescue plan. This may include a period of TDR, increased behavioural support, initiation or review of WLM or a combination.

Use of medications

WLMs include all medications approved by national authorities for weight loss treatment in adults and will be prescribed and titrated according to the standard label. Prescribing clinicians in the hubs will initiate and titrate medication. Concomitant use of >1 type of WLM will not be allowed. Weight loss medication will not be initiated if BMI is <27 kg/m^2. Once initiated, WLM will be continued for the rest of the treatment period.

Severe energy restriction and weight loss reduce blood pressure and blood glucose, so concomitant medications will be adjusted. Participants will continue metformin but stop other glucose medications following a trial-specific instruction, monitoring their blood glucose if indicated. Likewise, treatments for hypertension will be reduced following a trial-specific instruction, and participants will be asked to monitor their blood pressure if indicated.

Usual care

Usual care will be offered to the control group. The availability of treatment differs between Denmark and the UK and among areas within countries. Participants' use of weight management programmes and medication will be recorded at each follow-up visit at 32, 52 and 104 weeks.

In the UK, participants may be eligible for referral to local community weight management programmes (typically 12 weeks of in-person group support), the NHS Digital Weight Management programme (12 weeks of support via an automated app with or without additional in-person coaching by app), NHS diabetes remission programmes (a yearlong programme incorporating 12 weeks of total diet replacement) or tier 3 weight management services (multidisciplinary weight management programmes lasting many months that can incorporate WLM). At baseline, participants randomised to usual care will be offered a referral to the most effective programme available to them. GPs may also prescribe WLM in accordance with national guidelines.

In Denmark, at baseline, participants will be given a self-help pamphlet on how to lose weight, which was produced by the Danish National Board of Health,[16] and advised to contact their GP for referral to local obesity management programmes. These programmes often involve 12 weeks of group sessions focusing on diet and physical activity, often limited to people with specific obesity-related comorbidities, such as type 2 diabetes. The trial team will notify the GP of the participant's involvement in the trial and suggest referral to weight management. GPs may prescribe any approved WLMs in accordance with current national guidelines but currently in Denmark, and this is at the participant's expense.

Assessments

Participants will be assessed at baseline and at 32, 52 and 104 weeks after randomisation. At baseline, potential participants will discuss the trial with the trial staff and, if they agree, sign a consent form, and eligibility will be assessed. The trial team will administer all the assessments outlined above and obtain blood and urine samples for biobanking. Other assessments will take place at general practices or hospitals. Given additional funding is secured, participants will be followed for over 18 years through health service records and other routinely collected data to ascertain the incidence of disease by trial arm. Consent for any substudies will be sought where required.

We will seek to minimise missing data by conducting home visits, allowing for self-reported data and expanding the period for data collection if needed. Data will be entered into the OpenClinica database, which incorporates confidentiality, audit trails and data validation checks. Periodic data monitoring (at least monthly) will be conducted to assess quality and take corrective action if needed.

Outcomes

Both co-primary outcomes are assessed at end of intervention at 2 years:

- Metabolic syndrome severity Z-score (MetS Z)[17]
- Body weight

The secondary outcomes are also assessed at 2 years:

- Quality of life assessed as the SF-36 mental component score[18]
- Mean 4-metre gait speed[19]
- Proportion of participants with weight loss≥20%

Safety outcomes and adverse events (AEs) assessed over 2 years or at 2 years:

- Proportion of participants with≥1 serious AEs (SAEs) during the intervention period. An SAE is defined as any untoward medical occurrence that results in

death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.[20]
- Proportion of participants with a new eating disorder during the intervention period.
- Bone mineral density:

1. Bone mineral density of the hip (total hip and femoral neck)
2. Bone mineral density of lumbar region

Exploratory outcomes

The exploratory outcomes assess body composition via waist circumference and dual-energy X-ray absorptiometry, proportion of participants losing 10% of their weight, physical activity and sleep quality via accelerometer,[21] quality of life, physical function, sleep quality, blood pressure and pulse rate. They will also assess markers for metabolic health, including Homeostatic Model Assessment of Insulin Resistance, glucose control, indicators of liver fibrosis and renal function, medication for cardiovascular and metabolic conditions and genetic profiles associated with weight loss/metabolic health. All will be assessed at 2 years (online supplemental table 3 for more details). In addition, mental health will be assessed using the Major Depression Inventory,[22] Weight Bias Internalisation Scale[23], Eating Disorder Examination Questionnaire,[24] SD-36, as well as work-related productivity[25] and sick leave. The trial will assess the incremental cost-effectiveness ratio. This will be assessed at 2 years by a within-trial cost-effectiveness assessment, including health resource use, and over the lifetime using modelling.

The main aim of obesity treatment is to prevent long-term ill health; this will be assessed through follow-up by health records over the subsequent 18 years. These assessments will be conducted at 5, 10 and 20 years after randomisation. We will assess deaths from any cause, incident cardiovascular disease, use of medications for glucose, blood pressure and lipid regulation, pain relief and psychiatric disorders, incidence of cancer and adiposity-related cancers and incidence of osteoporotic fractures. In Denmark, where suitable registers exist, participation in and contribution to the labour market, including employment status, salary, sick leave and long-term sick leave, will be also assessed.

Sample size

The sample size is estimated separately for the two primary outcomes but using a 0.025 significance level for each outcome such that the reported power corresponds to a familywise error rate of <0.05.

For weight, we determined that a 5 kg difference is likely to lead to clinical improvements in cardiovascular and metabolic risk factors. Assuming a (pooled) SD equal to 15 kg, significance level equal to 0.025 and 25% dropout, with 600 participants, we would have 90% power to detect a 5 kg difference in mean weight between intervention groups.

For the mean MetS Z-score, a sample size of 600 with 25% dropout gives 82% power to detect a difference in the mean Z-score between the intervention and control groups equal to 0.3, assuming an SD equal to 1 and a significance level equal to 0.025. A 0.3 difference in the mean Z-score was deemed clinically relevant because it is associated with an increased risk of fatal or non-fatal cardiovascular disease within 10 years follow-up.[26]

A sample size of 600 participants (including a 25% dropout), will have adequate power to detect plausible effects on the secondary outcomes, at a 0.05 significance level. We will have a power of 94% to detect a difference in mean SF-36 score between the intervention and control group, equal to 4 points (minimal clinically important difference)[27 28] assuming an SD of 12 and a power of 99% to detect a difference in gait speed equal to 0.2 points assuming an SD of 0.5.[21] We assume that around 1% of the control group participants achieve at least a 20% wegith loss, based on data from a trial of TDR with a usual care group.[6] With 600 participants, a 25% dropout and 0.05 significance level, we will have a power of 90% to detect a 6% increase, which translates to 7% of the intervention participants achieving at least a 20% wegith loss. The intervention will only be recommended based on a positive finding on primary outcomes. No multiplicity adjustment is planned for secondary outcomes; power calculations for these endpoints are included primarily to guide interpretation, for example, is it realistic that the study could detect clinically meaningful differences in these outcomes.

Statistical methods

A detailed statistical analysis plan will be written before the last participant's last visit and without knowing any unmasked results. This will include analyses of missing data, which will be addressed using multiple imputation methods or similar; analysis will be described further and published in the analysis plan. 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 for primary and secondary outcomes will be based on the randomised population (including dropout) using α=0.05 as significance level unless specifically stated otherwise. Depending on the degree of protocol violations, supplementary secondary analyses will also be conducted in the per-protocol population defined as patients with a measurement of the primary outcome at baseline and at the 2-year follow-up and without major protocol violations (both groups), in addition to adherence to TDR for at least 4 weeks and engaged in >60% of the behavioural support sessions with the IWL team (for the intervention group). Exploratory subgroup analyses will examine interactions between intervention and baseline participant characteristics in terms of country, sex, age (tertiles), socio-economic 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. Statistical power in subgroups will vary with sample size and will provide plots of detectable effect size versus sample size for reference when appropriate.

Considering the small trial population and a recruitment period that is shorter than the primary follow-up, any interim analyses will not be conducted, or stopping rules will not be applied. In addition, all components of the intervention are already being used within routine care; therefore, this trial is considered relatively safe.

Exploratory (hypothesis generating) subgroup analyses will examine interactions between intervention and baseline participant characteristics, in terms of country, sex, age (tertiles), socio-economic status, ethnicity and BMI categories (split at the median BMI). We recognise that statistical power in subgroups will vary with sample size and provide plots of detectable effect size versus sample size for reference.

Process evaluation

A mixed-methods process evaluation will explore implementation fidelity, contextual influences, participants' and professionals' experiences of responses to and interactions with the intervention. The evaluation will be guided by the UK Medical Research Council's framework for process evaluations of complex interventions.[29]

Key domains that will be explored are described below:

Fidelity

We will assess the extent to which the intervention is delivered as intended across different intervention sites and settings. Quantitative data will include attendance at behavioural support sessions and participants' use of TDR, rescue TDR and WLMs. Summary data will be generated to describe engagement with treatment options.

We will randomly sample a minimum of 100 video-recorded or audio-recorded consultations to examine fidelity of intervention delivery, variation in practice and implementation processes. Conversation analysis will be conducted to explore how delivery relates to patient outcomes such as weight loss and adherence.[30]

Engagement

We will explore participant uptake, retention, adherence to the TDR programme and behavioural components and use of WLMs. Participant experiences of consultations, use of treatments and discussions within their social networks will also be examined, recognising the role of social context in engagement with the intervention.

In Denmark, additional ethnographic observations will be conducted with up to 20 families to understand how family contexts influence (non-)adherence to TDR. These observations will be analysed using the Family Meal Framework, a grounded theory-based model describing the work involved in family mealtimes.[31]

Participants' and professionals' responses to and interactions with the intervention

We will investigate participants' experiences, motivation and perceptions of support, as well as professionals' perspectives on implementation barriers and facilitators. Qualitative data will be generated through semi-structured interviews with participants and healthcare professionals. Interview schedules will be iterative and responsive to emerging insights.[32 33]

Up to 50 participants in the UK and Denmark from the intervention arm will be purposively sampled based on variation in age, location (seeking variation in the index of multiple deprivation), BMI at baseline, ethnicity, use of WLMs, adherence and additional considerations advised by patient and public involvement (PPI) input. Participants will be interviewed up to three times to explore changes over time. Previous research has highlighted the importance of longitudinal sampling, as it can be difficult to recruit individuals who discontinue weight loss efforts, and memories of prior experiences may otherwise be influenced by subsequent events.[34]

Semi-structured interviews with up to 40 healthcare professionals will be conducted, with sampling based on years of experience, location and role. Analysis will be performed thematically and informed by implementation theory.[35–37]

Context

We will explore organisational, social and cultural factors influencing delivery and engagement across the UK and Danish settings. Comparative analyses will examine how similar intervention processes may be experienced differently in distinct national contexts.

Relevant qualitative data will also be analysed using the normalisation process theory[37 38] to understand how the intervention activities, organisational settings and professional collaborations affected implementation. This analysis will identify factors influencing workability, compatibility with existing practices and transferability to other contexts.

Data analysis and integration

Qualitative data (interviews, observations and family ethnographies) will be analysed thematically[39] or using conversation analysis as appropriate. Quantitative data on fidelity and engagement will be summarised descriptively. We will triangulate findings across sources and across country contexts to enhance the reliability and comprehensiveness of the evaluation.

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 evaluations

Economic evaluations in the three LightCOM trials will be performed using the same methods. A within-trial cost-utility analysis from a healthcare system perspective will

be conducted alongside the clinical trial and will adopt a 2-year time horizon (follow-up period). The costs of the LightWAY intervention will be determined separately for the UK and Denmark, reflecting 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 electronic case report form collected at the follow-up visits 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 5-level EQ-5D (EQ-5D-5L) health-related quality of life questionnaire will be administered at each Clinical investigation day (CID). EQ-5D-5L responses will be converted into utility scores, for the purposes of quality-adjusted life year (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. Different sensitivity analyses will be conducted including re-estimation of cost-effectiveness assuming different perspectives, among these, a healthcare and personal social service perspective and a wider societal perspective. 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. The Sheffield Diabetes Prevention model, which is a microsimulation model that links cardiometabolic risk factors (BMI, HbA1c, systolic blood pressure and cholesterol) to noncommunicable disease morbidity (type 2 diabetes, cardiovascular disease, heart failure, microvascular complications of diabetes, osteoarthritis, dementia and cancers of the breast and colon) will be used.[40 41] 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 National Health Payer perspective for the UK and Denmark.

The reporting of the results will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 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 LightWAY intervention. To assess the long-term labour market effects, we will apply the Surrogate Index as introduced by Athey *et al*.[42] 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 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 signed off by the programme management group.

Ethics and dissemination

Ethical approval was granted by the South Central – Oxford B NHS Research Ethics Committee (24/SC/0211) in the UK and by the Regional Ethics Committee for the Capital Region in Denmark (H-23065222, 21 December 2023). All participants provide written, informed consent for participation (online supplemental material).

Findings from the trial will be disseminated through peer-reviewed journals and scientific conferences. In accordance with the principles of the Helsinki declaration, all outcomes of this trial as listed in the trial protocol, positive as well as negative and inconclusive, will be published. Publications will be coordinated by the LightCOM Project Management Group. Authorship for publications will concur with and be based on the International Committee of Medical Journal Editors recommended criteria. In addition, in the UK, participants will be sent a summary of the results when the main findings are published.

Patient and public involvement

Members of the public have been involved in the trial design, and two PPI members sit on the trial advisory board. Furthermore, in the UK, we have set up a PPI panel that meets regularly to discuss any trial challenges, review participant information and provide feedback on different elements of the trial. PPI will be consulted prior to dissemination of the study results.

DISCUSSION

This trial tests a complex intervention comprising behavioural support to enhance adherence to total diet replacement and weight loss medication and change habitual diet and physical activity, each of which have been shown to be effective alone. Clinicians will be free to reintroduce TDR and start any WLM at any point, reflecting the way that these interventions would be used in clinical practice. Likewise, the comparator comprises a mix of treatments to support weight loss because the eligibility for weight loss support depends on where participants live, the nature of local services and the comorbidities that they have that would make them eligible for particular weight loss programmes. This complexity is typical of a pragmatic trial, in which the aim is to assess whether a flexible package combining the most effective weight loss elements is effective and cost-effective for people with clinical obesity compared with best usual care. This package is not, to our knowledge, in use around the world.

The pragmatic nature of this trial will allow clinicians to pursue people who do not attend the programme only to the same extent as would happen in clinical practice. Similarly, our recruitment of people seeking treatment for obesity with minimal exclusions for safety of the intended package of care, setting of the trial, organisations delivering the intervention, nature of the primary outcomes and analysis plan all represent pragmatic elements in the design.[43]

The trial described here tests an intervention to treat clinical obesity, a condition that rarely receives treatment in many health systems and affects a high proportion of the population. The standard medical approach is to treat most of the complications of obesity, namely adverse lipids, high blood pressure and diabetes with medications. Treatments for this condition are, in many cases, very cheap and safe. Given that most of the premature morbidity and mortality cases due to obesity are caused by its adverse consequences on blood pressure, lipids and glucose regulation, one could argue that optimising treatment of these conditions with cheap and widely available treatments could represent better value. This trial, by pitting two treatment strategies against one another, will go some way to answering this. These trial data will be integrated with the other two similar trials that test IWL with different intensity treatments and in different groups of people with obesity. This will allow us to assess effectiveness and cost-effectiveness for people with less severe obesity and without complications and for people prepared to undergo bariatric surgery, who typically have very severe obesity with complications.

Trial status

The first participant was included in Denmark in April 2024. We expect the recruitment to be finalised in April 2026, resulting in the collection of primary outcome data to be finalised in April 2028.

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

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Collaborators LightCOM team.

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. SWa and SWi are the trial managers. AKGJ performed the power calculations and was responsible for the overall statistical strategy. SW prepared the first draft of the manuscript. All authors made substantial contributions to the conceptualisation of the study design and conduct of the protocol.

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Competing interests Carsten Dirksen has received research funding from the Novo Nordisk Foundation on behalf of his institution. Over the past 3 years, he has received personal fees for lecturing, consulting and committee membership from Novo Nordisk, AstraZeneca, Amylyx and Empros. He has served as principal investigator on pharmaceutical trials conducted by Novo Nordisk and Amgen, with payments to his institution. Additionally, he has held various unpaid roles, such as lecturer and chairperson, for Novo Nordisk, Amgen, AstraZeneca and Eli Lilly. Thomas Bandholm: spouse works at Novo Nordisk and owns Novo Nordisk stock. Sten Madsbad: advisory boards: AstraZeneca; Boehringer Ingelheim; Intarcia Therapeutics; Novo Nordisk; Sanofi, Abbott Lab, Bayer, Amgen. Lecture fees: AstraZeneca; Novo Nordisk, MSD. Research Grant Recipient: Novo Nordisk; Novo Nordisk Foundation, Boehringer Ingelheim. Grants were paid to the Hvidovre Hospital, University of Copenhagen (no personal fee). None of the grants have any relation to the work presented in the paper. Support for attending meetings and/or travel: Novo Nordisk, Boehringer-Ingelheim, Bayer. SM has served as PI in relation to development of drugs for treatment of type 2 diabetes and obesity in collaboration with Novo Nordisk and Bayer with funds paid to the institution where he is employed (no personal fee). Consultant for Netdoktor. Paul Aveyard and Susan Jebb were investigators on two trials in which total diet replacement products were donated by Nestlé. Charlotte Albury has worked as an independent consultant

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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.

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ORCID iDs
Sarah Wane https://orcid.org/0000-0002-1766-882X
Paul Aveyard https://orcid.org/0000-0002-1802-4217
Sofus Christian Larsen https://orcid.org/0000-0002-0838-9378
Jane Lindschou https://orcid.org/0000-0002-0891-8129
Ina Olmer Specht https://orcid.org/0000-0002-3114-4715
Ann-Kathrin Lindahl Christiansen https://orcid.org/0000-0003-3917-9151
Thomas Bandholm https://orcid.org/0000-0001-6884-1971
Susanne Reventlow https://orcid.org/0000-0002-4990-142X
Kirstine Nyvold Bojsen-Møller https://orcid.org/0000-0003-1962-5302
Berit Lilienthal Heitmann https://orcid.org/0000-0002-6809-4504
Susan Ann Jebb https://orcid.org/0000-0001-9190-2920

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