Is Doctor Referral to a Low-Energy Total Diet Replacement Program Cost-Effective for the Routine Treatment of Obesity?

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Objective: The study objective was to estimate the cost-effectiveness of a commercially provided low-energy total diet replacement (TDR) program compared with nurse-led behavioral support.

Methods: A multistate life table model and the weight reduction observed in a randomized controlled trial were used to evaluate the quality-adjusted life-years and direct health care costs (in United Kingdom 2017 prices) over a lifetime with TDR versus nurse-led support in adults who had obesity, assuming that (i) weight returns to baseline over 5 years and (ii) a 1-kg weight loss is maintained after 5 years following TDR.

Results: The per-person costs of the TDR and nurse-led programs were £796 and £34, respectively. The incremental cost-effectiveness ratio of TDR was £12,955 (95% CI: £8,082-£17,827) assuming that all weight lost is regained and £3,203 (£2,580-£3,825) assuming that a 1-kg weight loss is maintained after 5 years following TDR.

Conclusions: At current retail prices and with plausible long-term weight regain trajectories, TDR is projected to be cost-effective in adults with obesity and could be considered as an option to treat obesity in routine health care settings.

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Introduction

Obesity is a common condition (1) that is associated with higher risks of type 2 diabetes, vascular disease, osteoarthritis, and some cancers, among other conditions (2). As a consequence, it accounts for a substantial share of health care expenditure. A recent systematic review reported that adults with obesity incurred, on average, a third higher total annual health care expenditures than adults of a healthy weight (3). Weight loss achieved with lifestyle interventions has been shown to reduce all-cause mortality (4), diabetes incidence (5), and cardiovascular risk factors (6).

Multicomponent behavioral interventions have been shown to reduce weight by about 2 kg compared with control at 12 months (7) and have been estimated to be highly cost-effective (8,9). Very-low-energy diets (providing < 800 kcal/d) together with behavioral programs reduce weight by an additional 4 kg at 12 months compared with intensive specialist-delivered behavioral programs alone (10). However, national guidelines do not recommend them for routine treatment of obesity (11,12).

Total diet replacement (TDR) programs involve the replacement of foods with specially formulated, nutritionally complete products. Two recent trials have shown that similar TDR programs, providing 810 to 850 kcal/d, together with behavioral support from a health professional or trained counselor, lead to comparable weight losses in routine health care settings (13,14). Although substantially more effective than behavioral interventions alone, TDR programs are typically more costly, and their cost-effectiveness is not known.
In this study, we evaluate the long-term effects and cost-effectiveness of doctor referral of adults with obesity to a commercially provided low-energy TDR program (Cambridge Weight Plan) using the Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET) study results (14,15).

Methods

The DROPLET trial

A detailed description of the DROPLET trial has been presented elsewhere (15). In brief, 278 adults with BMI > 30 kg/m², identified through primary care registers, were recruited into the study. Participants were randomly allocated to either a behavioral support program delivered by their practice nurse or a low-energy TDR program offered by a commercial provider, with products providing an initial 810 kcal/d for 8 weeks, followed by gradual food reintroduction for 4 weeks and an additional 12-week follow-up, along with regular behavioral support (15 sessions over 24 weeks). Both programs were delivered at no cost to participants.

A total of 272 participants contributed data on clinical outcomes (6 out of 278 participants withdrew their consent for use of data). These participants were predominantly female (61%), were aged from 19 to 78 years with a mean age of 47 years (SD 13) in men and 50 years (SD 13) in women, and had a mean BMI of 37.2 (SD 5.4) (14). At recruitment, 23% had a diagnosis of hypertension, and 15% had type 2 diabetes; 30% were taking medication for diabetes or hypertension.

At 12 months, participants allocated to the nurse-led behavioral support program had lost, on average, 3.1 kg (SD 7.0), while those allocated to TDR lost 10.7 kg (SD 9.6). In an intention-to-treat analysis, adjusting for age, sex, and baseline stratification variables, the mean difference in weight loss at 12 months was 7.2 kg (95% CI: 4.9-9.4), with similar effects observed in subgroups defined by age, sex, or baseline BMI. This weight reduction corresponds to a mean difference in BMI of 2.3 kg/m² in men and 2.7 kg/m² in women. Rates of mild adverse events, defined as those not interfering with normal functioning (constipation, fatigue, headache, and dizziness), were higher among those allocated to TDR, while there was no evidence of a difference in rates of adverse events of moderate or greater severity (i.e., events that interfered with normal functioning) between treatment groups.

The PRIMEtime-Cost-Effectiveness Obesity model

We estimate the accrual of life-years, quality-adjusted life-years (QALYs), and health care costs (in 2017 UK prices) for the UK population by sex and age (in 5-year bands) up to age 100 years using an adapted version of the PRIMEtime Cost-Effectiveness (PRIMEtime-CE) Obesity model (16,17). PRIMEtime-CE Obesity is a population-based, proportional, multistate life table model that links BMI to mortality and noncommunicable disease morbidity (type 2 diabetes, coronary heart disease, stroke, and cancers of the breast, colon, liver, kidney, and pancreas). A fuller description of the model and all data inputs are detailed in online Supporting Information. An R package has been developed to allow easy use of the PRIMEtime-CE Obesity model and is available from https://github.com/seamuskent/PRIMEtime-CE-Obesity.

The PRIMEtime model consists of a life table, which estimates life expectancy, and disease life tables, which estimate the incidence and prevalence of (and mortality from) each modeled condition. Disease and mortality rates depend on age, sex, and BMI. The effects of weight loss are propagated through the model by affecting general mortality and the incidence of each condition. Population impact fractions (PIFs) are calculated for each condition and for mortality using the relative risk shift method (18). Population impact fractions provide an estimate of the proportion by which mortality or disease incidence in the population would be reduced given a change to the BMI distribution, based on the mean weight loss in the target population, the distribution of BMI, and the association between mortality or disease incidence and BMI. They are calculated in each year of the model by sex and age group.

Euroqol (EQ-5D) utilities are calculated for each study year based on the age and sex of participants, as well as the incidence and prevalence of the modeled conditions (19), and are combined with life-years to estimate QALYs. Mean annual National Health Service (NHS) costs per prevalent case of each modeled condition, calculated from 2013-2014 NHS programme budgeting returns (20), were used to estimate the costs of prevalent disease in the PRIMEtime model. Intervention costs were evaluated externally to the model. All costs were converted to UK 2016-2017 prices using the hospital and community services inflation index (21).

Intervention costs

The cost-effectiveness of the TDR program is estimated in comparison to a nurse-led behavioral support program. The nurse-led support program is estimated to cost £34.06 per person in year 1, based on an additional 2 minutes of general practitioner (GP) time in which patients are referred to the nurse-led support program (£8.24), as well as 4 attendances with a nurse practitioner over 12 weeks, each lasting 10 minutes (£25.82). The TDR program is estimated to cost £796.06 per person. This is based on an additional 4 minutes of GP time in which patients are referred to the program and their eligibility is ascertained (£16.49) and on scheduled medication reviews with GPs on 2 occasions (at baseline and 4 weeks) for the 30% of patients taking medication for diabetes or hypertension (£22.69). Finally, based on observed attendances with the counselor (mean 12.3 attendances, with 315 meal replacement products) (see Supporting Information Table S1 for further details), we estimated the cost of the TDR part of the program to be £756.88. This was based on the standard costs of the program when provided directly to the public with an average cost per product of £2.40 (which is priced to incorporate the cost of the behavioral support).

Weight loss beyond 12 months

In the DROPLET trial, participants were followed for 12 months. There is uncertainty about the trajectory of weight in both trial arms beyond 12 months. We model, therefore, 2 main scenarios (Figure 1). First, we assume that, in both treatment arms, weight returns to its baseline level in an approximately linear fashion between 12 months and 5 years following the start of intervention. This is in line with evidence that, on average, individuals tend to regain weight following weight loss (22,23) and with the observed reduction in mean difference in weight loss between 6 and 12 months in DROPLET (14). Second, following the long-term weight change observed in the Diabetes Prevention Program Outcomes Study (5), we assume that a 1-kg weight loss relative to baseline weight is maintained beyond
to estimate the impact of uncertainty in health care costs, quality of life decrements, the associations between BMI and disease incidence and mortality, and the effect of TDR on weight loss at 12 months on cost-effectiveness.

Scenario and sensitivity analysis
We undertake a variety of scenario analyses to explore the impact of different modeling assumptions. In particular, we explore the impact of (1) different combinations of the rate of weight regain and the mean weight loss maintained in the long term; (2) different total TDR program costs, including assuming a fixed fee of £907.20 for the TDR program based on the costs that would be incurred under current retail prices if patients followed the treatment protocol perfectly; (3) discounting health outcomes and costs at 3.5% in line with the NICE guidelines for health technology appraisals (24); (4) adding further health care costs by age and sex (20,26), for health conditions beyond those included in the economic model; (5) modeling a direct effect on weight loss on EQ-5D utility using the observed difference in EQ-5D per kilogram of weight loss at 12 months in DROPLET of 0.02 (14), in addition to the effect on QALYs operating through disease incidence; and (6) applying the treatment to the general UK population of adults with obesity rather than only to participants with characteristics like those enrolled in the DROPLET trial. We also estimate the program cost at which TDR has an ICER equal to £20,000 per QALY, the threshold for cost-effective interventions in the UK.

5 years among participants allocated to TDR, with weight reaching this level from 12 months in an approximately linear fashion.

Base case analysis
Outcomes are simulated up to 100 years of age for a hypothetical population of adults with obesity, with the same age and sex distribution as that of DROPLET study participants, and results are averaged over this hypothetical cohort. We also estimate results within population groups defined by sex, age in 15-year bands (20-34, 35-49, 50-64, and 65-79 years), and BMI (30 to < 35, 35 to < 40, and ≥ 40 kg/m²), assuming a difference in mean weight loss between TDR and the nurse-led behavioral program in each group of 7.2 kg at 12 months.

We compare the life-years, QALYs, and costs accrued with the 2 treatment options and calculate the incremental cost-effectiveness ratio (ICER), which provides an estimate of the additional costs of TDR for every additional QALY gained. The National Institute for Health and Care Excellence (NICE) typically considers interventions as cost-effective if they have an ICER of less than £20,000 per QALY (24). For some analyses, we calculate net monetary benefits (NMBs), which are given as the product of the incremental QALYs and the threshold value (i.e., £20,000 per QALY) minus the incremental costs; a positive NMB indicates that TDR is cost-effective at that threshold.

In the estimation of ICERs and NMBs, future costs and health outcomes are discounted at a rate of 1.5% per annum, based on recommendations by NICE for evaluating preventive programs in which benefits are expected to accrue over a long time period (25). When presented separately, life-years and QALYs are not discounted. We perform probabilistic sensitivity analysis using 500 Monte Carlo simulations to estimate the impact of uncertainty in health care costs, quality of life decrements, the associations between BMI and disease incidence and mortality, and the effect of TDR on weight loss at 12 months on cost-effectiveness.

Results
Compared with the nurse-led behavioral support program, the TDR program is projected to generate an additional 0.069 life-years (95% CI: 0.049-0.089) and 0.065 QALYs (0.047-0.084) at an additional discounted cost of £665 (£635-£696) per person over a person’s lifetime or £12,955 (£8,082-£17,827) per QALY gained, assuming that people return to their baseline weight at 5 years following intervention (Table 1). The higher total costs for TDR reflect an additional £762 in intervention costs, which is only partially offset by £97-lower (£66-£127) NHS costs related to the modeled diseases. For every 100,000 people referred to TDR, it is projected that 50 (34-66) incident coronary heart disease events, 75 (50-100) incident strokes, 899 (688-1,140) cases of type 2 diabetes, and 26 (13-38) cancers would be avoided.

If instead it is assumed that participants following TDR maintain a weight 1 kg lower than their preintervention weight after 5 years, TDR is projected to be even more cost-effective at £3,203 per QALY gained (95% CI: £2,580-£3,825). This reflects higher expected gains in life-years (0.287 life-years; 0.237-0.337) and QALYs (0.245; 0.209-0.281), as well as a reduced net discounted cost difference of £519 (£471-£567), as a result of greater projected NHS cost savings.

The incremental cost per QALY is lower for population groups at higher age, independently of sex, under the assumption of a maintained 1-kg weight loss after 5 years, TDR
TABLE 1 Health benefits and health care costs over 25 years for nurse-led behavioral support and TDR program

| Nurse-led intervention | TDR | Mean difference (95% CI) |
|------------------------|-----|-------------------------|
| **Weight regained by 5 years following intervention** | | (TDR vs. nurse-led intervention) |
| Life-years | 31.31 | 31.38 | 0.069 (0.049 to 0.089) |
| QALYs | 23.19 | 23.26 | 0.065 (0.047 to 0.084) |
| Total costs (£) | 7,425 | 8,090 | 665 (635 to 696) |
| Treatment costs (£) | 34 | 796 | 762 (762 to 762) |
| NHS disease costs (£) | 7,390 | 7,294 | −97 (−127 to −66) |
| ICER (£ per QALY) | | | 12,955 (8,082 to 17,827) |

**Disease incidence (per 100,000 persons)**

| CHD | 10,238 | 10,188 | −50 (−66 to −34) |
| Stroke | 13,947 | 13,872 | −75 (−100 to −50) |
| Type 2 diabetes | 51,142 | 50,243 | −899 (−1,140 to −658) |
| Cancer* | 15,005 | 14,979 | −26 (−38 to −13) |

**Maintained weight loss of 1 kg in TDR arm after 5 years**

| Life-years | 31.31 | 31.60 | 0.287 (0.237 to 0.337) |
| QALYs | 23.19 | 23.44 | 0.245 (0.209 to 0.281) |
| Total costs (£) | 7,425 | 7,944 | 519 (471 to 567) |
| Treatment costs (£) | 34 | 796 | 762 (762 to 762) |
| NHS disease costs (£) | 7,390 | 7,148 | −243 (−291 to −195) |
| ICER (£ per QALY) | | | 3,203 (2,580 to 3,825) |

**Disease incidence (per 100,000 persons)**

| CHD | 10,238 | 10,031 | −206 (−256 to −157) |
| Stroke | 13,947 | 13,704 | −243 (−356 to −130) |
| Type 2 diabetes | 51,142 | 47,020 | −4,122 (−4,651 to −3,592) |
| Cancer* | 15,005 | 14,902 | −102 (−146 to −59) |

Values are means (95% CIs). All reported values are discounted at 1.5% per annum, except life-years and QALYs, which are undiscounted.

*Includes cancers of the breast, colon, liver, kidney, and pancreas.

CHD, coronary heart disease; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; QALY, quality-adjusted life-year; TDR, total diet replacement.

Figure 2 Incremental cost-effectiveness ratios in subgroups by age, sex, and BMI. Error bars show 95% CIs. TDR, total diet replacement.
is cost-effective for all adults. Differences in cost-effectiveness by gender are small. In both scenarios of future weight trajectory, the incremental cost per QALY is highest in adults with class I obesity (BMI 30 to < 35) and lowest (i.e., most cost-effective) in adults with class III obesity (BMI ≥ 40), but the cost is consistently below the standard threshold of £20,000 per QALY for all adults irrespective of their BMI at recruitment.

The longer the duration over which costs and health outcomes are projected, the more cost-effective TDR becomes because the costs of treatment are incurred in year 1 while the health benefits and health care cost savings are accrued in later years. For the total population, TDR becomes cost-effective at £20,000 per QALY when outcomes are projected over time periods longer than 17 years and 13 years in the scenarios of full weight regain and partial maintenance of weight loss, respectively (Figure 3).

The longer weight remains below its preintervention level, and the greater the long-term weight loss maintained, the more cost-effective TDR would be (Figure 4). Assuming a maintained weight loss of at least 1 kg, TDR is cost-effective at £20,000 regardless of how quickly weight is regained to this level following intervention. In the absence of long-term maintenance of weight loss, TDR is cost-effective at £20,000 per QALY so long as it takes more than 3 years until lost weight is completely regained.

Under the assumption of full weight regain at 5 years, the ICER is estimated to be higher than the base case estimate of £12,955 when assuming a fixed fee for the TDR program of £907.20 (ICER = £15,551), discounting costs and health outcomes at 3.5% per year (ICER = £17,673), and including additional health care costs incurred for diseases beyond those modeled in PRIMEtime (ICER = £15,300) (Figure 5). Including an additional direct effect of weight loss on EQ-5D utility reduces the ICER to £6,039. Applying the model to the entire UK population of adults with obesity rather than trial participants produced very similar results. These alternative scenarios had similar directional, but smaller absolute, impacts on the ICERs when assuming partial maintenance of weight loss, with TDR remaining highly cost-effective at £20,000 per QALY in all scenarios.

The cost-effectiveness of TDR decreases linearly with total program costs (Figure 6). For TDR not to be considered cost-effective at £20,000 per QALY, it would have to cost £1,157 or more assuming complete weight regain and £3,518 or more assuming that a 1-kg weight loss is maintained after 5 years.

**Discussion**

The DROPLET trial demonstrated that GP referral to a specific TDR program was a safe and effective treatment for weight loss in adults with obesity (14). Here, we provided evidence that this TDR program is also cost-effective under a range of plausible scenarios regarding weight regain after 12 months. It is most cost-effective in middle-aged and older adults and those at higher levels of BMI, who face higher immediate risks of obesity-related diseases and premature mortality. The cost-effectiveness results are robust to alternative modeling assumptions, including in the discount rate applied to costs and health benefits and the inclusion of further health care costs for diseases beyond those modeled in PRIMEtime.

This is the first study to estimate the cost-effectiveness of TDR for the routine treatment of obesity. Our estimates were informed by effectiveness data from a recent trial (14), and we were able to extrapolate results based on estimates of associations between BMI and the incidence of obesity-related diseases and mortality from leading epidemiological studies. The PRIMEtime model allowed us to model the effect of weight loss on a range of obesity-related conditions and account for multimorbidity (27). We were also able to estimate the
The results presented herein pertain to a specific TDR program, namely GP referral to a commercially provided low-energy diet program with behavioral support delivered over 6 months with gradual food reintroduction after 3 months. The base-case cost estimate for TDR reflects observed attendance rates among participants in the DROPLET study and current recommended retail prices. In practice, it is not clear how this or similar interventions would be organized and financed were the NHS to offer them. There would be some setup costs in procurement of the service, but there may also be opportunities to achieve lower costs of the program itself through competitive tendering. We estimated that a TDR program delivering the weight loss observed in the DROPLET study would be cost-effective at £20,000 per QALY as long as the total program costs were no greater than £1,157, assuming full weight regain at 5 years. However, adherence and, accordingly, effectiveness could also differ under alternative TDR schemes. For example, if the behavioral support was delivered by health care practitioners, or if a copayment scheme in which patients were expected to contribute to the costs was introduced, then adherence to the program, its price, and thus cost-effectiveness might differ.

There are of course a number of important limitations. First, body weight was only measured for 12 months. We made assumptions about the sustainability of weight loss beyond 12 months based on previous evidence, although most studies were short in duration (22,23). In this analysis, we made similar assumptions about weight regain to other studies (8), and the cost-effectiveness of TDR was robust to conservative assumptions about weight regain. Nevertheless, future research would benefit from a better understanding of the durability of weight loss.

Second, we estimated the impact of weight change on disease incidence and mortality from observational studies, which may be subject to bias from residual confounding. Weight loss through surgical or nonsurgical interventions has been associated with reductions in all-cause mortality and diabetes incidence, as well as with diabetes remission (4,5,29,30). Surgical interventions have been associated with reductions in the incidence of fatal and nonfatal cardiovascular events (31) as well as cancer.
in women but not in men (32). Reductions in cardiovascular events and cancer incidence have not been consistently reported in nonsurgical interventions (4,6), but this may relate to low power and insufficient follow-up in these studies, or the extent to which the dietary intervention affects cardiovascular risk factors (33). In DROPLET, TDR was shown to improve cardiovascular risk factors at 12 months (14), and in a similar trial among people with recently diagnosed type 2 diabetes, 45% of people offered a TDR program were in remission at 12 months (13). Future research would benefit from direct randomized evidence on clinical endpoints like disease incidence, remission, and mortality, as well as on health care costs and health-related quality of life.

Third, excess weight has been associated with increased incidence and costs of many health conditions not included in PRIMEtime, including knee osteoarthritis (2,34), and weight loss can promote diabetes remission, which is not included in the model (13,35). Accordingly we may have underestimated the health care savings accruing from weight loss with TDR in adults with obesity. As is the case with most other analyses, the cost-effectiveness analysis was performed from an NHS health care perspective and did not consider wider societal costs. It did not incorporate any costs to the patient of attendance at the behavioral support sessions nor did it consider the cost savings to patients through reduced purchases of their usual food. Finally, we did not model the impact of the higher rates of mild adverse events among those allocated to TDR on health-related quality of life or costs. These events, by definition, do not interfere with normal functioning, are confined to the 12-week weight loss phase of the program, and do not entail large health care expenditures.

Hence, their inclusion would not be expected to materially impact cost-effectiveness.

To our knowledge, there are no cost-effectiveness analyses of TDR programs for the routine treatment of obesity. A number of cost-effectiveness analyses have been undertaken for other surgical, pharmacological, and lifestyle-management interventions. Comparability across studies is difficult because of major methodological differences, including the comparator(s) chosen, population studied, time horizon, and assumptions about effects of weight loss on quality of life, as well as weight regain. Bariatric surgery is generally found to be cost-effective, with ICERs of £2,000 to £4,000 per QALY gained, in patients who have morbid obesity (36). Although an expensive procedure at around £10,000 (37), it delivers substantial and sustained weight loss and improved health outcomes (29). A systematic review of the cost-effectiveness of pharmacological treatments reported a median ICER of £24,000 per QALY for orlistat (38). Orlistat reduces weight by about 2.6 kg at 12 months compared with placebo (39) at a cost of around £540 per year (40). A number of studies have reported on the cost-effectiveness of behavioral interventions for weight loss (8,9,41-44). Most produce modest reductions in weight at 1 to 2 years, but because they can typically be provided at very low cost, they are often considered cost-effective. For instance, referral to a 52-week community-based weight loss group offered by a commercial provider produced an additional weight loss of 4 kg at an additional cost of £176.34 compared with a brief intervention, giving an ICER of £2,394 per QALY over 25 years (8).

Many previous studies, particularly those of pharmacological interventions, have assumed that weight loss has a direct effect on EQ-5D utility. This is probably a major determinant of the low ICERS reported (38). Indeed, in our analysis, assuming such an effect substantially reduced the incremental cost per QALY of TDR from £12,955 to £6,039 assuming full weight regain at 5 years. However, a systematic review and meta-analysis of weight loss trials did not find consistent evidence of improvements in health-related quality of life following weight loss (45).

Based on the current retail prices for the diet-replacement products, the TDR program used in the DROPLET trial is a cost-effective treatment for reducing weight in adults with obesity. Low-energy TDR programs are not currently recommended for the routine treatment of obesity (11,12). In view of growing clinical and economic evidence, the use of, and funding for, such programs should be reconsidered.

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