Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
This study examined the long-term cost-effectiveness of orlistat with lifestyle intervention to reduce the risk of metabolic disorders in obese patients aged 35 years or more. The authors concluded that orlistat could be a cost-effective addition to lifestyle intervention and was better value-for-money in the sub-group of patients with impaired glucose tolerance, identified through a screening programme. The study was well conducted and the extensive sensitivity analysis enhances the validity of the authors’ conclusions.

Type of economic evaluation
Cost-utility analysis

Study objective
This study examined the long-term cost-effectiveness of orlistat with lifestyle intervention to reduce the risk of metabolic disorders in obese patients, with a body mass index (BMI) of over 30, aged 35 years or more.

Interventions
A four-year treatment with orlistat in combination with lifestyle intervention was compared with lifestyle intervention alone. The lifestyle intervention was a reduced-calorie diet and exercise. Orlistat was given at a dosage of 120mg three times per day.

Location/setting
Italy/secondary care.

Methods
Analytical approach:
This economic analysis was based on a Bayesian Markov model with a time horizon of 10 years. The authors stated that the analysis was carried out from the perspective of society.

Effectiveness data:
The bulk of the evidence came from a double-blind, randomised controlled trial (RCT), namely the XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) trial, which enrolled 3,305 obese patients, with non-diabetic glucose tolerance at oral glucose tolerance testing, who received either orlistat or placebo, with the lifestyle intervention. Further data came from Italian mortality tables and other studies, including a large US population study. Cardiovascular disease (CVD) mortality was calculated using the Framingham Heart Study approach. Epidemiological data on the obese cohort came from official national registries. The key clinical endpoint was the probability of transition from the obese condition to diabetes.

Monetary benefit and utility valuations:
The utility valuations were derived from various published studies, including the 1998 US National Health Information Survey and the Italian sub-sample of the Cost of Diabetes in Europe (CODE-2) study.

Measure of benefit:
Quality-adjusted life-years (QALYs) were the summary benefit measure and were discounted at an annual rate of 3.5%. Other model outputs such as life expectancy and CVD events were also reported.

Cost data:
The economic analysis included the costs of orlistat, glucose tolerance test for impaired glucose tolerance (IGT), treatment of diabetes (primary and specialist care, examinations and analyses, hospitalisation, emergency room admissions, and drugs), and treatment of obesity. The cost of orlistat was borne by the patient since it was not reimbursed by the Italian National Health Service (NHS) at the time of the study. The treatment costs were borne by the NHS and included the direct medical costs. The drug cost was based on the public price, recommended dosage, and compliance or persistence reported in the RCT. Diabetes-related costs came from the Italian sub-sample of the CODE-2 study. The cost of obesity was based on a large American study. The additional cost of the main CVD events was from average diagnosis-related groups data. Costs were in Euros (EUR) and were discounted at an annual rate of 3.5%. The price year was not explicitly reported.

Analysis of uncertainty:
A probabilistic sensitivity analysis based on a Monte Carlo simulation with 30,000 iterations was undertaken to generate cost-effectiveness acceptability curves. In an alternative scenario, a hypothetical Italian NHS reimbursement price for orlistat was considered (66.65% of the public price). Sub-group analyses were carried out for IGT status, gender, and age (under or over 60 years). Two alternative hypotheses were also explored. In scenario one, the Italian NHS provided orlistat to every obese patient and, in scenario two, the drug was given only to obese patients with IGT, which was defined by an initial screening programme for every obese patient.

Results
Orlistat led to a QALY gain of 0.046 (95% credibility interval, CI: 0.017 to 0.076) and a cost increase of EUR 2,948 (95% CI: EUR 369 to EUR 3,353) per patient. Thus, under base-case conditions, the incremental cost per QALY gained with orlistat over placebo was EUR 75,310.

The subgroup analysis showed that similar findings were achieved in all subgroups, except for IGT patients, whose incremental cost per QALY gained was EUR 21,230 (95% CI: -EUR 49,820 to EUR 62,050).

In scenario one, the incremental cost per QALY gained was EUR 42,300 and Italian NHS costs were expected to increase by about EUR 6,800 million in 10 years. In scenario two the incremental cost per QALY was EUR 10,160 and the expected increase in costs was about EUR 300 million.

The probabilistic sensitivity analysis showed a great degree of variability in the model outputs, which was also indicated by their wide CIs. In scenario two, the probability of the incremental cost per QALY gained with orlistat being below the threshold of EUR 45,000 was 99.2%. This relatively high figure shows the cost-effectiveness of treatment restricted to obese patients with IGT, identified through a screening programme.

Authors' conclusions
The authors concluded that orlistat could be a cost-effective addition to lifestyle intervention, but was best value-for-money in the sub-group of obese patients with IGT, identified through a screening programme.

CRD commentary
Interventions:
The study comparators appear to have been appropriately selected. They were the two strategies in the primary trials, which were the main sources of evidence.

Effectiveness/benefits:
The clinical data came from a selection of known, relevant studies. Most of the evidence came from a large RCT, the design of which should have ensured the validity of the clinical inputs, due to its double-blind and randomised approach. Supplementary data came from other published sources, including national registries, and were used to extrapolate the short-term trial data to the 10-year time horizon. Little information on the sources of the utility valuations was provided. For instance, the authors did not report the instrument used to elicit preferences for health conditions. However, all clinical inputs were tested in the sensitivity analysis. QALYs are a validated and appropriate benefit measure, which capture the impact of treatment on patients' quality of life and survival. They also allow cross-disease comparisons to be made.
Costs:
The authors stated that a societal perspective was adopted, but indirect costs were not considered. It appears that the analysis included only those costs borne by the Italian NHS and the patients. The authors justified the exclusion of the costs associated with the lifestyle intervention, as these were the same in both treatment arms. Most costs were presented as macro-categories and were not broken down in individual items. The authors acknowledged that the main limitation of the economic analysis was the use of an aggregate estimate of the cost of diabetes, with no breakdown of cost items. They did point out that item estimation would have required a lot of assumptions and further modelling, which was beyond the scope of this study, which did not focus on diabetes treatment. The sensitivity analysis investigated the issue of uncertainty around all inputs to the model.

Analysis and results:
The costs and benefits were appropriately synthesised and the findings were clearly presented. The issue of uncertainty was extensively addressed by means of a probabilistic sensitivity analysis, which has the advantage of considering multiple aspects of uncertainty in a comprehensive and simultaneous approach. In general, the use of a Bayesian Markov model was the main strength of the analysis. The authors noted that a potential drawback was the inadequate analysis of the relationship between weight reduction and cardiovascular risk.

Concluding remarks:
The study was well conducted and the potential limitations of the analysis were addressed in the sensitivity analysis, which enhances the validity of the authors' conclusions.

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