

Final Topic Refinement Document
Therapeutic Options for Obesity in the Medicare Population
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AHRQ Technology Assessment Program
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Key Questions

KQ1. In patients who are obese and who would be eligible for Medicare, what is the comparative effectiveness of interventions that are intended to improve outcomes by reducing obesity?

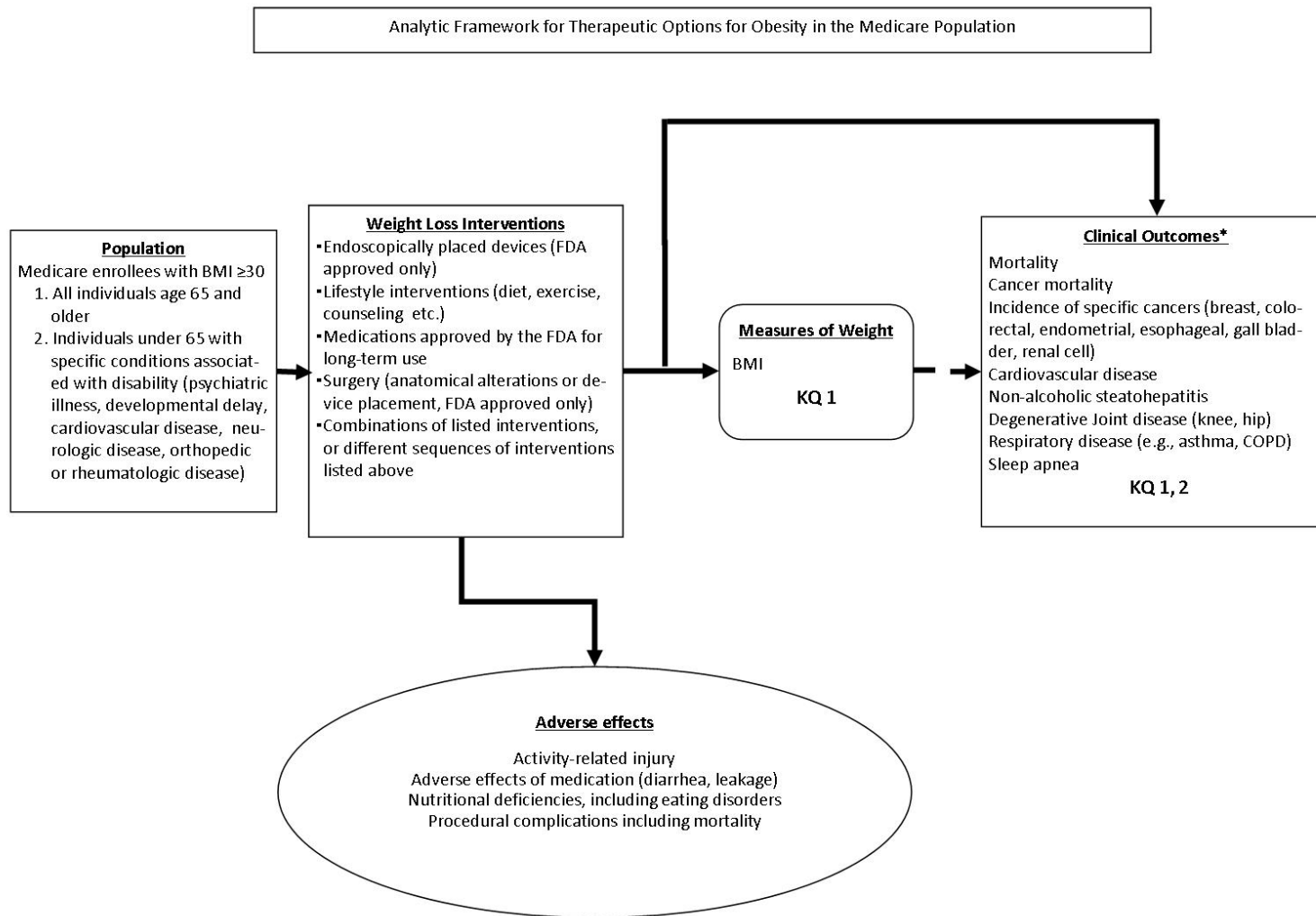
The outcomes of interest include:

- a. BMI
- b. Clinical outcomes
 - Mortality
 - Cancer mortality (any cause)
 - Incidence of specific cancers: breast, colorectal cancer, endometrial cancer, esophageal adenocarcinoma, gall bladder cancer, and renal cell cancer
 - Cardiovascular disease
 - Non-alcoholic steatohepatitis (NASH)
 - Degenerative joint disease (*i.e.*, knee, hip)
 - Respiratory disease (*i.e.*, asthma, COPD)
 - Sleep apnea
- c. Adverse effects of interventions
 - Activity-related injury
 - Adverse effects of medication (diarrhea, leakage)
 - Nutritional deficiencies (including eating disorders)
 - Procedural complications (including death).

KQ2. In patients who are obese and who would be eligible for Medicare, how well does treatment-induced reduction in BMI predict obesity-related outcomes?

- a. The outcomes of interest include the clinical outcomes
 - Mortality
 - Cancer mortality (any cause),
 - Incidence of specific cancers: breast, colorectal cancer, endometrial cancer, esophageal adenocarcinoma, gall bladder cancer, and renal cell cancer
 - Cardiovascular disease
 - Non-alcoholic steatohepatitis (NASH)
 - Degenerative joint disease (*i.e.*, knee, hip)
 - Respiratory disease (*i.e.*, asthma, COPD)
 - Sleep apnea

Figure 1. Analytic Framework



*Includes obesity-related clinical outcomes and conditions exacerbated by obesity

Background

Burden of Disease. Obesity is defined as a Body Mass Index (BMI) greater than or equal to 30 kg/m².¹ Obesity prevalence is increasing in the US and worldwide. Increased longevity is also prevalent. By 2030-2035, over 20% of the adult US population will be aged 65 years and older. For older adults (age ≥ 60 years),² the prevalence of obesity is about 37% among men and 34% among women based upon recent data from the National Health and Nutrition Examination Survey (NHANES).² Morbidity and mortality are increased at a BMI above 30 kg/m² in all age groups, including those over 65 years of age. In older adults above 65, overweight and obesity are associated with new or progressive impairments in activities of daily living (ADLs) instrumental activities of daily living (IADLs).

Population. The Medicare population includes individuals aged 65 years and older and those with qualifying disabilities of all ages. We will focus on a population of 65 years or older with a BMI greater than 30 kg/m². Disability, defined by the Social Security Administration includes an inability to engage in any substantial gainful activity (SGA) by reason of any medically determinable physical or mental impairment(s) which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months.³ A person must receive Social Security Disability Insurance for 2 years or be in the ESRD program in order to be considered “disabled” by Medicare.

Interventions to reduce obesity. The interventions available for obesity include obesity surgery, pharmacologic options, lifestyle interventions, and combination of interventions.

Obesity surgery has been approved for those with severe obesity (BMI ≥ 40 kg/m²) or those with BMI at or above 35 with comorbid conditions. More recently, the Food and Drug Administration (FDA) approved the LAPBAND[®] for those with BMI at or above 30 with a comorbid condition. Obesity surgery is not indicated in those with a reversible cause of obesity, those with serious psychiatric illness, or those who cannot understand the risks and benefits of surgery. We expect to consider several options for obesity surgery, including laparoscopic gastric bypass, gastric banding, vertical sleeve gastrectomy and some new devices (if approved by the FDA) such as intragastric balloons.

The pharmacologic interventions include: orlistat which decreases fat absorption; lorcaserin which is a selective serotonin receptor agonist approved for weight loss ; and phentermine-topiramate combination, benzphetamine, diethylpropion, phentermine, and phendimetrazine, all appetite suppressants.

The lifestyle interventions comprise of caloric restriction, physical activity and behavioral modifications, which could include interventions delivered by application of consumer health informatics. The comprehensive lifestyle approach combines monitoring caloric intake and increasing physical activity with behavior modification. Physical activity also contributes to weight loss, decreases abdominal fat, and improves cardiorespiratory fitness.⁴ A recent European guideline recommended that the first steps to obesity reduction are lifestyle interventions.⁴ Some of the lifestyle interventions recommended include diets with 500 Kcal energy deficits, adequate intake of protein, vitamin D, and calcium, and multi-component exercise. This type of exercise includes flexibility training, balance training, aerobic exercise, and resistance training. The adherence rate is only 75% among the short-term studies that were evaluated.

Choice of interventions. The choice of specific interventions for the elderly and disabled will depend on the specific context and the benefits and risks of interventions. The interventions we

will evaluate are shown in the PICOTS Table. We will focus on interventions that are primarily designed to reduce weight.

Need for Evidence Review. Although numerous guidelines and reviews have been published on the treatment of obesity in general, few consider obesity treatments among individuals older than 65 years of age and individuals with Medicare-qualifying disabilities. A joint position statement from the American Society for Nutrition and the North American Association for the Study of Obesity specifically targets strategies to treat obesity in older persons and states that weight-loss therapy improves physical function, quality of life, and the medical complications associated with obesity in older persons.⁵ Weight-loss therapy that minimizes muscle and bone losses is recommended for older persons who are obese and who have functional impairments or medical complications that can benefit from weight loss.

Previous evidence reviews have not explored the full range of medical databases available for identifying clinical studies. They have not provided enough details to evaluate their methodological rigor. They have only examined a limited set of interventions and have not assessed the full range of obesity-related clinical outcomes.⁶ None of the previous reviews have evaluated the extent to which reduction in BMI mediates clinical outcomes.

Relevance to Clinical Decision Making or Policymaking. It would be beneficial to know which interventions for obesity improve long-term clinical outcomes among the elderly and disabled population. This would allow policy makers to inform relevant guidelines for this population. This topic is of interest to the Centers for Medicare and Medicaid Services (CMS) in making decisions as evidence on various interventions may inform future coverage of interventions for this population. A recent policy decision outlined the specific types of bariatric surgery for which evidence on effectiveness was available that would be covered for the Medicare population.¹

Availability of Evidence. A recent systematic review of interventions on the topic suggested that the medical consequences of obesity in the elderly are alleviated by modest weight loss (5-10 kg) through evidence-based management strategies.⁷ The review recommended weight management, modest exercise, and moderate caloric restriction with reduction of polypharmacy, and suggested that the risks of bariatric surgery may outweigh the benefits.⁷ However, the review did not address a number of important issues. Several pharmacologic options are available for obesity in the United States including lorcaserin, orlistat and Qysmia (phentermine and topiramate combination). Although they are efficacious among adults, the effectiveness and safety of these options for the people above age 65 are unknown. The effectiveness and safety of obesity surgery, intragastric devices and other applications in the elderly is unknown, because the elderly have largely been excluded from clinical trials.⁷ Whether weight loss also exacerbates sarcopenic obesity in the elderly and leads to loss of bone density is unknown.

A recent systematic review reported that behavioral strategies are effective in producing statistically significant weight loss without significant risk to obese older adults.⁶ The review identified 10 trials longer than one year for behavioral interventions among the elderly and noted some improvement in clinical outcomes. Only 4 of 10 studies were longer than 2 years. It did not identify any studies of pharmacologic options among the elderly or any trials of bariatric surgery among the elderly. None of the studies was assessed for bias. Only one database was searched to identify relevant evidence. A more comprehensive search may yield more evidence, especially related to surgical and pharmacologic interventions.

Assessment of Other Ongoing Work. A search of clinicaltrials.gov yielded 71 studies on the Medicare population (any intervention). A separate search on obesity treatment (any

population) showed 2072 on-going studies. We did not find any studies listed in ClinicalTrials.gov on obesity treatment in the Medicare population.

Potential Audiences. This topic is of interest to CMS. It is also of interest to internists, endocrinologists, surgeons, nutritionists, pharmaceutical benefit managers, and other policy makers. A current comprehensive review would be particularly valuable to organizations interested in having clinical practice guidelines on the management of obesity.

Objectives. The main aim of this project is to synthesize the evidence on the comparative effectiveness of non-invasive and invasive therapeutic options for obesity in two priority populations covered by Medicare.

PICOTS

Population(s)

Population

- Studies with population age 65 or older will be included
- Studies with populations under age 65 and disabled due to psychiatric illness, developmental delay, cardiovascular disease, neurologic disease, orthopedic or rheumatologic disease will be included

Interventions

- Surgical procedures including anatomic alteration, FDA-approved device placements, open surgery procedures, as well as laparoscopic and endoscopic procedures
- Medications for obesity approved by the FDA for long-term use
- Lifestyle interventions, including diet, physical activity and, self-management interventions, including those delivered by consumer health informatics
- Combinations of the interventions or different sequences of interventions listed above

Comparators

- Comparison to placebo, usual care, or another intervention

Outcomes

- Clinical outcomes*
 - Mortality
 - Cancer mortality (any cause)
 - Incidence of specific cancers: breast, colorectal cancer, endometrial cancer, esophageal adenocarcinoma, gall bladder cancer, and renal cell cancer
 - Cardiovascular disease
 - Non-alcoholic steatohepatitis (NASH)
 - Degenerative joint disease (*i.e.*, knee, hip)
 - Respiratory disease (*i.e.*, asthma, COPD)
 - Sleep apnea
- BMI
- Adverse effects
 - Activity-related injuries, including fracture
 - Adverse effects of medications (e.g., diarrhea or leakage)
 - Nutritional deficiencies, including eating disorders
 - Procedural complications including mortality

Timing

- Only studies published in 1990 or later are eligible
- Studies must report at least one clinical outcome of interest that includes follow-up of participants at least 18 months after the commencement of the intervention
- Follow-up duration will be considered in the analysis
 - For obesity-related clinical outcomes, outcomes will be reported at 18 months of follow-up and later
 - Among trials that report on clinical outcomes, for BMI, health-related quality of life, and adverse effects, additional time points of interest include the first reported time and 3, 6, 12, 18 months and later times after the commencement of the intervention

Setting

- All settings

*Includes obesity-related clinical outcomes and conditions exacerbated by obesity

Preliminary Literature Scan

Databases Searched. For this preliminary portion of the literature scan, we searched Medline (PubMed) for articles with titles/abstracts and medical subject (MeSH) headings containing terms relevant to obesity and a variety of treatments (See Appendix A for full PubMed search strategy). Future searches will include Embase and The Cochrane Collaboration library.

Relevant Guidelines. Based on the above search, we found 53 guidelines and position statements on the over 65 year-old population. Of these, there were 3 relevant guidelines (all by American societies) that addressed weight loss therapy and its impact on physical function, quality of life, co-morbidity, secondary prevention of heart disease, and osteoarthritis.^{5,8,9} None of the guidelines or position statements addressed the disabled population.

Recent Systematic Reviews and Meta-analyses. We identified 285 potentially eligible meta-analyses that investigated therapeutic options for obesity in an over 65 year old population (or some other population that included this group). Of these, 11 were potentially applicable and addressed the use of lifestyle interventions or surgical options for treating obesity. An additional 49 meta-analyses were identified that could be applicable to the under 65 age group and medically disabled population. Of these, we did not find any meta-analysis that applied specifically to this population. We did identify some meta-analyses that included populations that had conditions common amongst the medically disabled. We believe these are not directly applicable.

Feasibility of New Review. We did not find any other systematic review or meta-analysis that looked at both domains of the Medicare population (over 65 years old, or under 65 years old and disabled), but we found approximately 640 potentially relevant randomized trials based on the initial search strategy. We reviewed 100 of these potentially relevant randomized trials and found eight that were applicable. We estimate that approximately 50 will be identified that apply to this topic. We anticipate that further searching will also identify a number of non-randomized studies.

Definition of Terms

Medicare population: The Medicare population includes individuals aged 65 years and older and those with qualifying disabilities of all ages. ¹

Obesity: Obesity is defined as a BMI greater than or equal to 30 kg/m². ¹

Disability: "Disability" under Social Security is based on your inability to work. We (CMS) consider you disabled under Social Security rules if: You cannot do work that you did before; We (CMS) decide that you cannot adjust to other work because of your medical condition(s); and your disability has lasted or is expected to last for at least one year or to result in death. (<http://www.ssa.gov/dibplan/dqualify4.htm>)

Lifestyle interventions: *Any intervention that included an exercise component, a dietary component or behavior modification element.*¹⁰

References:

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Table 1: Changes between Draft and Final Topic Refinement Document

Original Element	Source	Comment	Decision and change	Rationale
Key Question 1a: multiple measures of weight	CMS	Multiple measures of weight	We are including BMI as the only measure of weight instead of BMI, weight in pounds or kilograms, skinfold thickness and waist circumference	At the request of CMS due to their needs
Key Question 1b	CMS	Intermediate outcomes	We are excluding all intermediate outcomes (adherence, blood pressure, glucose levels, inflammatory markers and lipid levels)	At the request of CMS due to their needs
Key Question 1c, 1d	CMS	Clinical outcomes of interest	We are including a different list of clinical outcomes and deleting dementia, depression, diabetes, metabolic syndrome, other forms of liver disease, and other musculoskeletal disease such as sarcopenia) and including only health-related quality of life instead of a list of patient-reported outcomes (activities of daily living, pain, physical function measures, and satisfaction with care)	At the request of CMS due to their needs
Background	Public	Negative effects of lorcaserin in the background	The negative effects have been removed from the background	There was no rationale for including text on negative effects of one drug.
PICOTS/ Population	CMS	Minimum population age of 60	The minimum age of inclusion was changed to 65	The Medicare population of interest is 65
PICOTS/ outcomes	CMS	Multiple measures of weight	We are including BMI as the only measure of weight instead of BMI, weight in pounds or kilograms, skinfold thickness and waist circumference	At the request of CMS due to their needs
PICOTS/ outcomes	CMS	Intermediate outcomes	We are excluding all intermediate outcomes (adherence, blood pressure, glucose levels, inflammatory markers and lipid levels)	At the request of CMS due to their needs
PICOTS/ outcomes	CMS	Clinical outcomes of interest	We are including a different list of clinical outcomes and deleting dementia, depression, diabetes, metabolic syndrome, other forms of liver disease, and other musculoskeletal disease such as sarcopenia) and including only health-related quality of life instead of a list of patient-reported outcomes (activities of daily living, pain, physical function measures, and satisfaction with care)	At the request of CMS due to their needs

Summary of Changes between Draft and Final Topic Refinement Document:

The JHU EPC felt that the public comments were useful and helpful. A number of comments made by the public were considered for addition to the topic refinement document. For example:

sleep apnea, degenerative joint disease, glucose control were believed to be of interest to the general public and were considered for addition to the final topic refinement. However, CMS did not feel that these endpoints were of sufficient interest and priority at the long-term timepoint outlined in the topic refinement. After considering the input received during the review, CMS chose the final set of outcomes listed on page 1 as being the most relevant to their needs.

Several items included in the draft framework and items suggested by the stakeholders and public commenters were edited or removed at the request of CMS to meet CMS' specific needs. These revisions included: including studies of individuals aged 65 years and older instead of 60 years and older; including individuals with specific conditions associated with disability instead of individuals disabled for any reason; including only medications approved by the FDA for long-term use (time point for long-term use to be determined) instead of a specific list of available medications for weight loss (benzphetamine, diethylpropion, lorcaserin, orlistat, phentermine, topiramate, phentermine-topiramate, and phendimetrazine); including BMI as the only measure of weight instead of BMI, weight in pounds or kilograms, skinfold thickness and waist circumference; excluding all intermediate outcomes (adherence, blood pressure, glucose levels, inflammatory markers and lipid levels); including a different list of clinical outcomes and deleting dementia, depression, diabetes, metabolic syndrome, other forms of liver disease, and other musculoskeletal disease such as sarcopenia) and including only health-related quality of life instead of a list of patient-reported outcomes (activities of daily living, pain, physical function measures, and satisfaction with care). This final revised document reflects the edits requested by CMS.

Appendix A. Preliminary Search Strategy (PubMed)

PubMed Search String	(management[tiab] OR manage[tiab] OR "Therapeutics"[Mesh] OR "therapy"[Subheading] OR "surgery"[Subheading] OR "drug therapy"[Subheading] OR diet[mh] OR diet[tiab] OR "energy intake"[tiab] OR nutrition[tiab] OR exercise[mh] OR exercise[tiab] OR walking[mh] OR walking[tiab] OR walk[tiab] OR running[mh] OR running[tiab] OR run[tiab] OR jogging[tiab] OR jog[tiab] OR biking[tiab] OR bike[tiab] OR aerobics[tiab] OR "resistance training"[mh] OR training[tiab] OR "physical activity"[tiab] OR pharmaceutical[tiab] OR drug[tiab] OR medication[tiab] OR prescription[tiab] OR "orlistat"[Supplementary Concept] OR "orlistat"[tiab] OR behavior[tiab] OR behavioral[tiab] OR surgery[tiab] OR surgical[tiab] OR "Anastomosis, Roux-en-Y"[Mesh] OR "Bariatric Surgery"[Mesh] OR "roux-en-y"[tiab] OR "bariatric surgery"[tiab] OR "adjustable gastric band"[tiab] OR "laparoscopic gastric banding"[tiab] OR "vertical sleeve gastrectomy"[tiab] OR "sleeve gastrectomy"[tiab]) AND (obesity[mh] OR obesity[tiab] OR obese[tiab])
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Additional Recommendations for a Future Systematic Review

1. We are including all settings, but recommend that the final protocol detail that settings where behavioral interventions take place will be considered.
2. The final protocol should consider looking for and reporting on outcomes based on intervention and level of obesity.
3. Regarding the issue of studies that reported on older age groups in stratified analyses, the team should seek to identify studies conducted among persons of all ages that performed stratified analyses or tests for interaction by age. From such studies, it will be important to report on the results of any analysis of stratification or interaction by age.
4. Regarding the 18-month follow-up limit, we considered the input from the Key Informants, and note that the AJCN editorial board agreed a few years ago that 18 months was the minimum amount of follow-up that they require to consider a weight loss trial for publication.
5. Regarding the BMI threshold for obesity, the team should consider using a threshold of 27 instead of 30 for selected subgroups such as people with significant comorbidity.