Systematic review of clinical and cost-effectiveness of endoscopic treatments for obesity to inform a model-based cost-effectiveness analysis

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1. Summary of the research

Background: Obesity has negative impacts on health, the NHS and the wider economy. Bariatric surgery (BS) is currently the most effective obesity treatment resulting in sustained long-term weight loss and improvements in obesity complications and quality of life. NICE clinical guidance 189 recommended the use of BS as a treatment option in patients with body mass index ≥ 35 kg/m^2 who fulfil certain criteria. However, the number of BS performed in the UK is one of the lowest in Europe. This is due to multiple factors including limited resources leading to reduced commissioning and a post code lottery in service provision, among others. Endoscopic bariatric treatments have been increasingly available worldwide but not in the UK. These treatments are cheaper than BS, require shorter hospital stay and do not require full anaesthesia, which makes them a bridge, or a potential alternative, to BS and could address some of the barriers to accessing treatment in the NHS. The research brief details the need for an overarching evidence synthesis to establish the clinical and cost-effectiveness of endoscopic obesity treatments.

Research question: What is the current evidence for the clinical and cost-effectiveness of endoscopic treatments for obesity?

Objectives and methods: We will answer the research question by conducting evidence synthesis including clinical and cost effectiveness using the following approaches:

Study design:

- *Systematic review (SR) of clinical effectiveness:*
  - Based on randomised, non-randomised controlled and uncontrolled studies
  - Meta-analyses and sub-group analyses (e.g. based on Type 2 Diabetes status, age groups, ethnicities) will be performed if possible
  - Network meta-analysis (NMA) may be performed if the assumptions of the NMA model are met.
  - Outputs will include an evidence map and identify unmet research needs. Outputs will also be used where possible to inform the economic model.
- *SR of cost-effectiveness and model based economic evaluations.*
- *Model-based cost effectiveness analysis comparing endoscopic treatments with other alternative treatments:*
  - Development of new model or adaption of existing published model
  - Analysis from the UK NHS perspective and informed by the SRs of clinical and cost-effectiveness studies
  - Deterministic and probabilistic sensitivity analysis to explore the robustness of the results

Timelines for delivery: 15 months

Anticipated impact and dissemination: The evidence reviews, and economic analyses will influence clinical guidelines and commissioning of endoscopic treatments for obesity. The project outputs will

be disseminated to health care practitioners, patients and commissioners to enable them to make informed decisions regarding endoscopic treatments for obesity.

2. Background and Rationale:

2.1. What is the problem being addressed?

The proposed research is in response to a NIHR HTA commissioned workstream call(1). Obesity is an ongoing research priority for all NIHR programmes(2).

Obesity is very common in England affecting 26% of men and 29% of women(3). This is a steep increase from 1993 and was accompanied by an increase in the prevalence of severe obesity (BMI ≥ 40 kg/m^2) form 1% in 1993 to 3% in 2018(3). The high prevalence of obesity affects all ethnicities and age groups, with a peak in men and women aged 45-64 years(3;4).

Obesity is associated with poorer quality of life (QoL) and an increased risk of Type 2 diabetes (T2D), cancers, and cardiovascular disease (CVD) amongst others(5-8). In addition, obesity is associated with increased mortality and reduced survival of between 3 and 14 years. Obesity and being overweight contribute to at least 1 in every 13 deaths in Europe(5-7;9). More recently obesity was associated with an increased risk of severe COVID-19(10).

The NHS spent £6.1 billion on overweight or obesity related ill-health in 2014-2015 with an estimated cost to the wider society of £27 billion(11). These annual costs are projected to reach £9.7 billion for the NHS, and £49.9 billion for society by 2050(11).

Hence, it is of major interest and importance to patients, the NHS and wider society to provide effective treatments to reduce the negative impacts of obesity. Treating obesity (via lifestyle behavioural interventions (LSI), pharmacotherapy, or bariatric surgery (BS)) offers an opportunity to improve the health and QoL of people living with obesity and reduce the burden of obesity complications. Treating obesity also has economic benefits to the individual, the NHS, and the wider economy.

2.2. Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health and care services?

Weight loss (WL) via LSI (including dietary restrictions) is difficult to maintain in the majority of patients; even 5% WL is regained within 2 and 5 years in 50% and 80% of patients respectively(12-18). This weight regain is driven by complex neurohormonal metabolic adaptations(14;15;17;18). Hence there is a need for treatment strategies that can maximise WL and WL maintenance. Some of the above-mentioned metabolic adaptations are addressed by pharmacotherapy or BS (such as increasing satiety hormone levels) which results in sustained long-term weight loss(19;20).

Several RCTs, observational controlled studies and systematic reviews (SRs) (including from our group) have shown the superiority of BS in terms of WL, metabolic outcomes (such as hypertension, hyperglycaemia, hyperlipidaemia), cardiovascular disease (CVD), microvascular complications and mortality compared to routine care, LSI or intensive medical management in people with and without T2D(21-32). BS is also associated with improved QoL, particularly physical well-being(33). In people with T2D, several RCTs have shown the superiority of BS to medical treatment in achieving T2D remission or improvement in glycaemic control with fewer medications(21;22).

BS (especially gastric bypass) has been shown to be the most cost-effective procedure compared to weight management programmes and very low calorie diets in the HTA funded REBALANCE mixed-methods SR and economic evaluation(34). NICE guideline CG189 also recommended BS as a treatment option for patients who fulfil certain criteria(35). These criteria include:

1. BMI ≥ 40 kg/m^2, or between ≥ 35 kg/m^2 with obesity-related comorbidities (for example, T2D or high blood pressure);
2. All appropriate non-surgical measures have been tried without sufficient effect;
3. The person is under the intensive management of a specialist service;
4. The person is deemed fit for anaesthesia and surgery;
5. The person commits to the need for long-term follow-up.

NICE CG189 also recommended that BS should be considered as a treatment option in people with Type 2 diabetes and a BMI of 30-34.9 kg/m^2 (35).

However, despite the above-mentioned guidelines, access to BS is limited in the UK with around 4000-5000 primary BS per year (https://nbsr.e-dendrite.com/). This is one of the lowest number of BS in Europe, which is surprising considering that the UK obesity prevalence is one of the highest in Europe(36). The limited access to BS is driven by lack of financial resources and variation in the provision and commissioning of weight management services across the country and worsened by obesity stigma(37;38).

Endoscopic obesity treatments have emerged as a possible alternative to BS(39;40). These endoscopic treatments are expected to be more affordable than BS and are less invasive requiring less time in hospital (41). Hence, endoscopic treatments might address some of the barriers of access to BS and could be a treatment option in patients with contraindications to BS. The number of endoscopic obesity treatments performed is still low in the NHS, but most bariatric surgeons anticipate these procedures will become a bridge, or a possible alternative, to surgery(1).

The need for the SR and cost-effectiveness analysis for endoscopic obesity treatments was detailed in the research brief. We propose in this application to conduct this SR and economic evaluation in order to clarify the evidence base around endoscopic treatments for obesity and to provide timely evidence to guide patients, doctors, funders, commissioners and the NHS, and to inform future clinical guidance and services provision.

If these procedures were shown to be clinically effective and/or cost-effective, then this could transform the life of people living with obesity who need bariatric surgery considering that an endoscopic approach can be easier, safer and more accessible. There is a continuous need to improve obesity care as the prevalence of obesity and its complications continue to rise and hence the findings of this project will be relevant and important for a long time.

2.3. Review of existing evidence - How does the existing literature support this proposal?

The commissioning brief and the additional background information for this call provides a brief overview of endoscopic treatments for obesity(1). Endoscopic treatments can be broadly classified as (Figure 1)(40;42;43):

- Gastric occupying devices: multiple types of intra gastric balloons (IGB); the TransPyloric shuttle (TPS) and the Full Sense device.

- Restrictive procedures: endoscopic sleeve gastrectomy/gastroplasty (ESG) which can be performed using multiple techniques, the Primary Obesity Surgery Endolumenal (POSE), and the transoral anterior-to-posterior greater curvature plication with the Endomina® suturing device.
- Aspiration devices: such as AspireAssist
- Small bowel interventions (including liner procedures): these include the EndoBarrier (which is Duodenal-jejunal bypass liner DJBL), Gastroduodenojejunal bypass sleeve, duodenal mucosal resurfacing, and entero-enteral dual-path bypass using self-assembling magnets (Figure 2).

The commissioning brief specifically mentions IGB, ESG, bypass liners, and aspiration therapy but it also highlighted other recognised procedures.

Figure 1: Examples of endoscopic treatments for obesity(40;42).

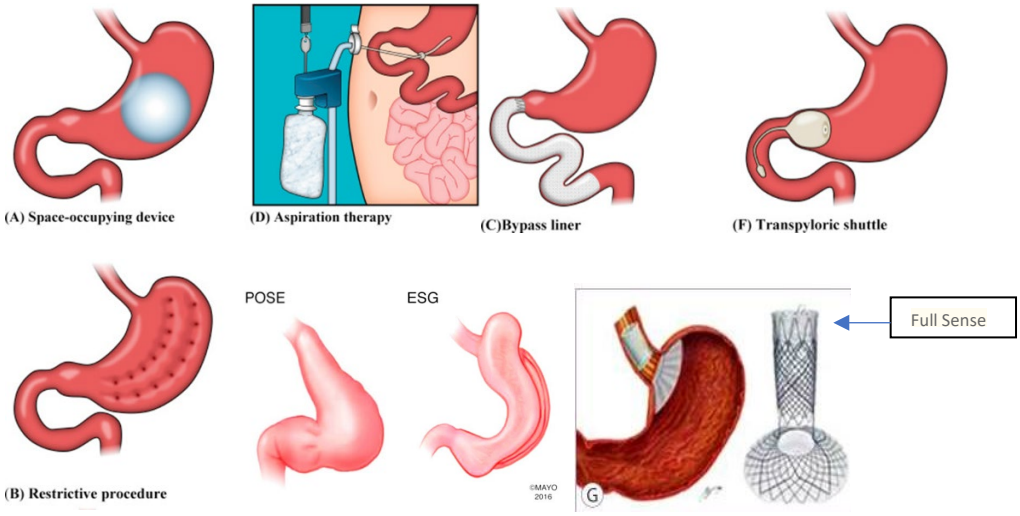
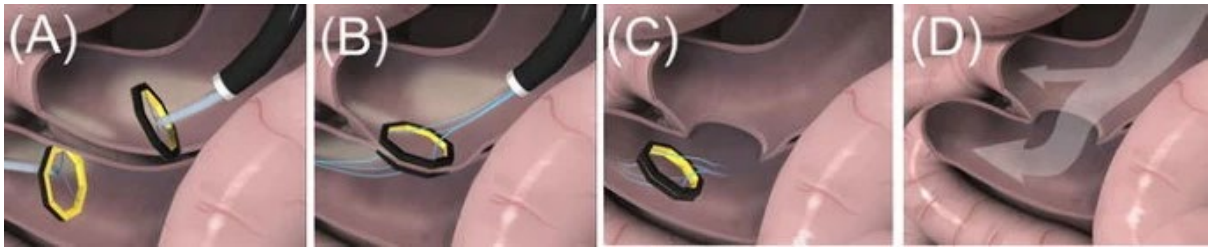


Figure 2: entero-enteral dual-path bypass using self-assembling magnets(43)



As indicated in the research brief, there are several SRs addressing endoscopic treatments: which broadly indicate that endoscopic treatments are effective, but the conclusions are limited by heterogeneity, a lack of randomised studies and restrictive study eligibility criteria. Our own initial scoping has identified a further seven SRs not included in the research brief (44-50): 3 included IGB, 2 ESG, 1 aspiration therapy, 1 comparing multiple procedures and 1 focussed on endoscopic treatments and QoL.

Gadd et al(45) SR (20 studies, 876 patients) examined the impact of endoscopic bariatric procedures on QoL. 18/20 studies showed improvement in QoL following the endoscopic procedures and 1/20 showed no impact over a follow up of 4-12 months. The remainder of the SRs (summarised below in Table 1) showed results consistent with the other SRs mentioned in the brief in that IGB, ESG, Aspiration therapy, DJBL and POSE all resulted in significant WL; with ESG showing greater WL when compared to IGB. The SRs included a variety of study designs including RCTs where available. One of the SRs reported on metabolic outcomes other than WL.

Table 1: Summary of Systematic reviews not included in the research brief. %TWL: percentage total weight loss; %EWL: percentage Excess Weight Loss; LSI: Life Style Interventions; LSG: Laparoscopic Sleeve Gastrectomy; IGB: Intra Gastric Balloon; SAE: Serious Adverse Events; AE: Adverse Events

Study	Intervention	Results	Comments
Vantanasiri et al(44)	Elipse (a swallowable IGB). 6 studies (2013 patients)	The pooled %TWL at 12 months: 10.9% (95% CI 5.0–16.9, I^2 98%)	SAE: small bowel obstruction (3 patients), gastric perforation (1 patient). Early expulsion by emesis (3 patients), Early deflation (9 patients)
Singh et al(46)	ESG and IGB. 28 studies (1 directly compared ESG to IGB, 9 ESG alone, 18 IGB)	ESG: %TWL: 17.51 (95% CI 16.44–18.58) %EWL: 60.51 (95% CI 54.39–66.64) IGB: %TWL: 10.35 (95% CI 8.38–12.32) %EWL 29.65 (95% CI 25.40–33.91) ESG achieved superior %TWL vs. IGB (mean difference 7.33, 95%CI 5.22–9.44, p<0.001) at 12 months	Mean %TWL and %EWL after IGB significantly decreased at 18 or 24 months compared to 6 months indicating weight regain after IGB removal.
Kotinda et al(47)	IGB. 13 RCTs IGB vs. sham or LSI (1523 patients)	Mean difference %EWL 17.98% & %TWL 4.40%in favour of IGB	6.12 kg absolute weight loss difference
de Miranda Neto et al(48)	11 ESG studies (2170 patients)	mean %TWL and %EWL from 2 studies that had 18 months follow-up of 16.8% and 73% respectively.	Similar results at earlier timepoints (with more studies).
Jirapinyo et al (49)	Aspiration therapy 5 Studies (590 patients).	%TWL at 1 (n=218), 2 (n=125), 3 (n=46), and 4 (n=27) years: 17.8, 18.3, 19.1, and 18.6% respectively	At 1 year: improvements in blood pressure, Triglycerides and HbA1c (-1.3%, 95%CI -1.8 to -0.8).

		%EWL at 1,2,3 and 4 years: 46.3, 46.2, 48.0, and 48.7% respectively	In the 2 RCTs the %TWL and HbA1c improvements were greater in the intervention vs. controls (%TWL: 11.6 (6.5–16.7)%, A1c: 1.3 (0.8–1.8)%).
Due-Ptersson et al (50)	ESG. 23 studies: ESG vs IGB, high intensity LSI, or LSG	ESG vs IGB: %TWL at 12 months 21.3 ± 6.6 vs 13.9 ± 9.0% ESG vs LSI: %TWL at 12 months 20.6 ± 8.3 vs 14.3 ± 10.2%. ESG vs LSG: %TWL at 6 months 17.1 ± 6.5 vs. 23.6 ± 7.6%	ESG had a significantly lower rate of adverse events than both LSG and IGB.

There are also more recent published primary studies (e.g.(51) and (52)) that have not yet been included in the review evidence. A multicentre retrospective study showed that ESG following weight gain post laparoscopic sleeve gastrectomy resulted in %TWL of 18.3 % (5.5) at 12 months(51). In addition, there are several ongoing systematic reviews and primary studies likely to be published in the timeframe of this project.

There are also existing cost-effectiveness studies(53-55). These studies concluded that aspiration therapy was not cost-effective relative to bariatric surgery but cost-effective for treatment of patients who lack access to bariatric surgery(53); ESG was not cost-effective relative to laparoscopic sleeve gastrectomy(54); and EndoBarrier was cost effective in combination with Liraglutide treatment in patients with Type 2 diabetes(55).

Hence, up-to-date SRs of clinical and cost-effectiveness studies and an economic model encompassing all endoscopic treatments are required.

2.3.1. Network meta-analysis (NMA):

Our scoping review identified 2 NMAs(56;57). The NMA by Jung et al (56) compared different endoscopic procedures in 22 studies (2141 patients) and found a mean difference (95% CI) in %TWL vs. controls: aspiration therapy 10.4 [7.0 to 13.7]; fluid-filled balloon 5.3 [3.4 to 7.2]; POSE 4.9 [1.7 to 8.2]; and DJBL 4.5 [1.4 to 7.7]). The corresponding %EWL were 27.3 [15.3 to 39.3]; 22.4 [15.4 to 29.4]; 15.3 [2.5 to 28.0]; and 13.0 [4.9 to 21.2], respectively. In a NMA of 15 RCTs, Bazerbachi et al (57) found that certain IGBs resulted in significant %TWL compared to control at 6 months (Orbera, 6.72% (95% CI, 5.55, 7.89); ReShape Duo 4% (95% CI 2.69, 5.31); Obalon 3.3% (95% CI 2.30, 4.30)) but not at 12 months. In addition, the study found that fluid filled IGBs were more likely to achieve greater weight loss compared to gas filled IGBs.

This data suggests that a NMA may be possible. However, the most recent NMA by Jung et al (64) found evidence of global inconsistency in the network and the inconsistency was not investigated in the paper. The results of this analysis are difficult to interpret as little detail was provided on the statistical methods used and no network evidence diagram was included. Therefore, we may perform an NMA if the assumptions of the NMA model are met.

2.3.2. Evidence in paediatrics and adolescents:

We have also performed scoping searches for SRs, primary studies and ongoing studies for the use of endoscopic bariatric treatments in children, adolescence and young adults. We found one SR examining all obesity treatments in young people (defined < 21 years old), including 7 studies IGB (mean age 13.9-18.5 years) and 1 study for Endobarrier (mean age 18.2 years) (58). The IGB studies showed conflicting results but 1 study showed that 48.8% of patients (11-21 years old) maintained weight loss 24 months post IGB(59). The Endobarrier study that was included in this SR was based on an abstract that showed at 6 months after insertion, all patients experienced significant weight loss with a mean weight reduction of 20.8%.

We have also identified several studies examining endoscopic bariatric treatments in children and adolescents that were published since the above-mentioned SR. (60-66). In an open label prospective uncontrolled clinical trial in adolescents (mean age 17.2 years), DJBL resulted in %TWL (mean (95%CI)) 11.4 (7.4-15.3) % at DJBL removal and 4.1 (- 2.6-10.8)% at 12 months follow up post removal(61). DJBL was also associated with improvements in insulin resistance and lipids profile.

In another uncontrolled study of children and adolescents (10-20 years old), the mean % TWL at 6, 12, 18, and 24 months was 14.4% ± 6.5%, 16.2% ± 8.3%, 15.4% ± 9.2%, and 13.7% ± 8.0%, respectively(62). In an uncontrolled study in adolescents, IGB for 6 months resulted in clinically relevant improvements in blood pressure, insulin: glucose metabolism, liver function and sleep apnoea at 6 months but these changes were not sustained at 2 years(66). The remaining studies used IGB and showed significant short term weight loss in adolescents and paediatrics with severe obesity.

In addition, we have also identified several ongoing studies:

Aspiration Therapy for Obese Adolescents

https://www.clinicaltrials.gov/ct2/show/NCT03598920?cond=Obesity&intr=endoscopic&age=0&draw=2&rank=5

Effectiveness Gastric Balloon in Obese Adolescents

https://www.clinicaltrials.gov/ct2/show/NCT04209842?cond=Obesity&intr=endoscopic&age=0&draw=2&rank=7

Treatment of Morbidly Obese Adolescent With a Duodena-jejunal Liner

https://www.clinicaltrials.gov/ct2/show/NCT02183935?term=adolescent&cond=Obesity&intr=endobarrier&age=0&draw=2&rank=1

Intragastric Balloon in Obese Adolescents With Comorbidities (IGB)

https://www.clinicaltrials.gov/ct2/show/NCT03233048?term=adolescent&cond=Obesity&intr=balloon&age=0&draw=2&rank=1

Due to the increasing number of studies examining endoscopic obesity treatments in children and adolescents we will include such studies in our proposal. We defined paediatrics < 12 years old and adolescence from 12 to 21 years old, in this proposal which is mostly consistent with definitions used in some of the above studies.

3. Aims and Objectives:

We aim to undertake the following:

Study design:

- *Systematic review (SR) of clinical effectiveness:*

❖ Based on randomised, non-randomised controlled and uncontrolled studies

❖ Meta-analyses and sub-group analyses (e.g. based on T2D status, age groups, ethnicities) will be performed if possible

❖ Network meta-analysis (NMA) may be performed if the assumptions of the NMA model are met.

❖ Outputs will include an evidence map and identify unmet research needs. Outputs will also be used where possible to inform the economic model.

- *SR of cost-effectiveness and model based economic evaluations.*
- *Model-based cost-effectiveness analysis comparing endoscopic treatments with alternative treatments:*

❖ Development of new model or adaption of existing published model

❖ Analysis from the UK NHS perspective and informed by the SRs of clinical and cost-effectiveness studies.

❖ Deterministic and probabilistic sensitivity analysis to explore the robustness of the results

The scope of the research will be as detailed in the commissioning brief:

❖ **Research question:** What is the current state of the evidence for endoscopic treatments for obesity, and are they cost-effective?

❖ **Population:** People of any age (including children <12 and adolescents 12-21 and adults >21 years old) with obesity and with or without obesity complications

❖ **Intervention:** Any endoscopic treatments for obesity (not restricted to UK use).

❖ **Control/Comparator:** Any suitable control/comparator (alternative endoscopic treatment, sham, BS, LSI, or medical management), including comparison of interventions against each other.

4. Outcomes

4.1. Clinical effectiveness:

Weight; changes in diabetes status or treatment and/or CVD risk; adverse events; reintervention/revisional surgery; any obesity-related morbidity; mortality (all cause, CVD-related and cancer-related); quality-of-life assessed by any tool; micronutrient status.

4.2. Cost-effectiveness:

Costs, quality-adjusted life years, disability adjusted life years, life years gained, measures of cost effectiveness (e.g. incremental cost effectiveness ratios, net monetary benefit).

There are no core outcome sets defined specifically for endoscopic procedures for obesity treatment, but the choice of outcomes has been informed by the outcome sets for benefits and adverse events of bariatric and metabolic surgery.

5. Research Plan and Methods

5.1. Clinical effectiveness review:

Standard SR methodology will be followed, with study selection and risk of bias assessment undertaken in duplicate, and data extraction checked by a second reviewer to minimise bias and errors. Disagreements will be resolved through discussion with a third reviewer or the wider team. Reporting of the SR will be according to PRISMA guidelines(67).

Primary studies will be sought from MEDLINE, Embase and Cochrane CENTRAL. Searches will be developed by an information specialist and include combinations of free text and index terms as appropriate. There will be no restriction by date, language or publication status. Scoping searches identified several relevant SRs which will be used as an additional source for primary studies. Ongoing primary studies will be sought from clincialtrials.gov and the WHO ICTRP portal. PROSPERO will be checked for ongoing SRs, and authors contacted where published versions of these cannot be identified. Existing reviews indicate that the combined patient number across relevant studies is large (n>4,000), therefore additional registry data will not be sought. Grey literature (e.g. institutional reports) will be sought from key organisations (including the American Society for Metabolic and Bariatric Surgery ASMBS, American Society for Gastrointestinal Endoscopy ASGE, and international federation for the Surgery of Obesity IFSO). Conference abstracts will not be excluded. For example of search strategy please see Appendix 1.

Inclusion criteria will be broad to capture any endoscopic treatments for obesity. There will be no limitations by type of treatment, place in the treatment pathway (e.g. stand-alone or bridge to BS) or study design. The population, intervention, control, and outcomes are detailed in the previous heading. There will be no restriction on length of follow-up. The study screening process, including reasons for exclusion will be documented in a PRISMA flow diagram. For a full list of inclusion and exclusion criteria please see Appendix 2.

For risk of bias assessment, we will use tools appropriate to the study design. The Cochrane risk of bias tool -2 (68)will be used for RCTs, whilst recognising that blinding may not be possible for endoscopic interventions or for comparator LSIs. Risk of bias assessment of non-randomised interventional studies and single arm (before-and-after) studies will be informed by the ROBINS-I tool(69). Adjustment for confounders will be important in non-randomised studies. Risk of bias tools may be supplemented by items from the McHarms checklist(70) as adverse events are a key outcome.

A predefined and piloted data extraction form will be used. Authors will be contacted for missing outcome data if required.

In considering and reporting the evidence we will take a hierarchical approach. Randomised controlled trials (RCTs) will be considered in the first instance, with evidence from controlled non-randomised studies, and finally uncontrolled studies being used to supplement findings where there are gaps, for example regarding specific outcomes. Full analysis of uncontrolled studies may not be undertaken where there is more robust evidence available from (randomised) controlled studies. However, all studies and findings will be reported.

All results will be tabulated and narratively described. Results will be reported by type of endoscopic treatment and type of comparator where applicable; within these groups, results will be reported on an outcome-by-outcome basis. Meta-analysis within these groupings will be considered where there is reasonable clinical and methodological homogeneity (e.g. in terms of study design, population, type of intervention and comparator, outcome/outcome metric and length of follow-up). For single arm studies, it may be possible to pool rates, whilst for comparative studies a pooled relative risk (e.g. for mortality) or mean difference (e.g. for weight) may be calculable. A random effects model will be more appropriate given likely residual heterogeneity. STATA (version 15) will be used for all meta-analyses, and the Chi^2 and I^2 statistics used to assess statistical heterogeneity(71). Where studies are deemed too dissimilar to pool, visual representation in forest plots without pooling will be considered to show variability.

Important sub-groups will be T2D or CVD status, BMI (> or <50 Kg/m^2), age (<12, <21, >21 and > 60 years) and ethnicities. We will report any such sub-group analyses within the included primary studies. We will also consider between-study sub-group analysis where study populations fall into different categories; this may be hampered by studies including mixed populations or a low number/no studies within a certain category. If possible, differences between subgroups will be explored using random-effects meta-regression.

Network meta-analyses (NMA) will be considered where there are RCTs assessing different interventions within the same connected network. This will be contingent on epidemiological assessment of the transitivity assumption being met, i.e., the sets of RCTs being similar in important patient and clinical characteristics other than the treatment comparison. This may only be appropriate for some comparisons. As far as possible we will assess evidence of both global and local inconsistency. However, scoping indicates limited direct comparisons of different types of endoscopic treatments. Any inconsistencies in the network will be assessed using subgroup analysis as described in the paragraph above as well as sensitivity analysis excluding studies at high risk of bias. Analysis will be performed in STATA (version 16) using the 'network' suite of commands.

All findings will be reported in the context of study risk of bias. The GRADE criteria(72) will be used to guide an assessment of the overall quality of the body of evidence in terms of risk of bias, imprecision, inconsistency, indirectness, and publication bias. Where meta-analyses include 10 or more studies, we will explore the presence of small study effects (funnel plot asymmetry), which may indicate publication or other bias(73).

Outputs from the SR will be effectiveness estimates (with indication of uncertainty) which will feed into the economic model. We will produce an evidence map, which will detail the findings (including any pooled estimated from meta-analyses) according to population, different intervention-comparator combinations, outcome and study design (PICOS). Findings from the NMA will be incorporated where direct evidence for relative effectiveness of different endoscopic treatments is

not available. The certainty and robustness of findings (likelihood of bias) will be indicated for all findings. Ongoing studies will also be included, and the map will indicate when updating with new evidence will likely be required. An excel spreadsheet will be used to enable filtering by parameters of interest (e.g. by outcome, population or type of endoscopic treatment against a certain comparator). We plan to make this map available to researchers, who may in the future be interested in updating it as more evidence becomes available. The existing structure will enable new evidence to be added to relevant categories. It will also aid in identifying current gaps in the evidence, which will inform future research priorities thereby reducing unmet need.

5.2. Cost effectiveness review:

The economic model will guide commissioning decisions and priority setting. It will combine data from several sources to estimate the cost-effectiveness of endoscopic obesity treatments when compared to BS or LSIs for patients with obesity. This will estimate the costs and benefits from increasing access to endoscopic treatments.

We will follow the same review protocol as the clinical effectiveness review for search strategies, with additional filters for economic studies and searching of economic databases such as EconLit, CEA registry and NHSEED (noting that some of these are no longer updated). We will select for review all studies that report economic evaluations and any cost studies or quality of life studies. We will assess the quality of economic evaluations using appropriate checklists(74;75).

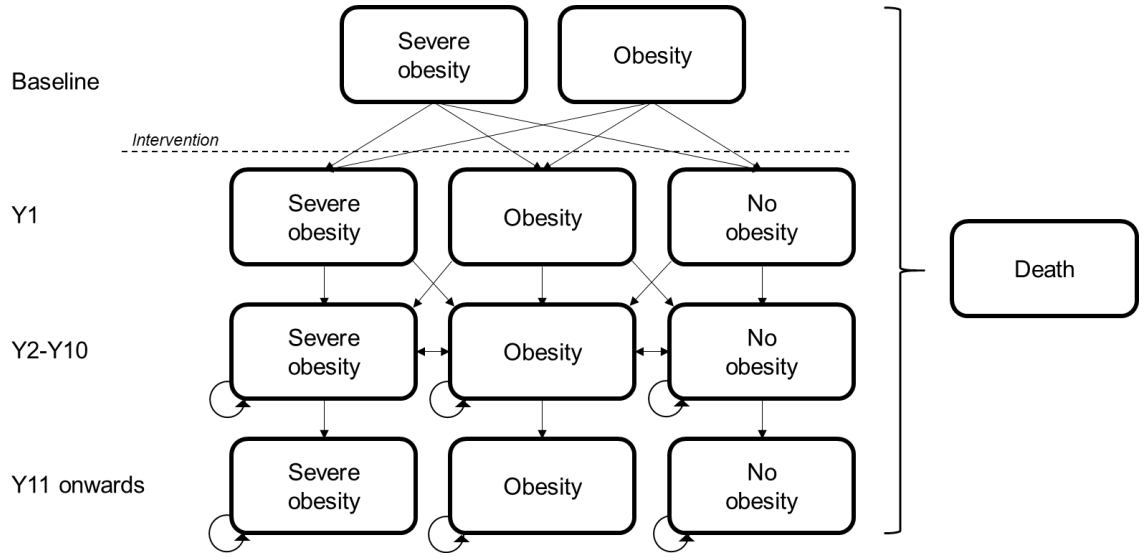
All relevant studies found in the review of economic evaluations will be considered as potential sources for the economic modelling. Most importantly, we will be looking for the types of model used, and especially the range of health states used in any model. We will be identifying inputs for the three types of model parameters including patient transitions, resource use, and quality of life values. Our expectation is that since endoscopic treatments are not routinely used within the NHS, there will be limited information on resource use in the literature and we will apply a 'bottom-up' costing approach using clinical expert opinion and unit cost data from national sources(76;77). We will not carry out any formal synthesis of the results of the economic evaluations, but rather we will consult the original sources of any data used and synthesise data at that level to inform the model.

5.3. Cost effectiveness economic modelling:

We will develop an economic model (or adapt an existing model) to estimate the long-term cost-effectiveness of endoscopic treatments compared to other alternative treatments for obesity, including BS and LSIs and weight management programmes, for treatment of patients with obesity. This is likely to be a state-transition model such as a probabilistic Markov model as this reflects a lifetime horizon, potential progression of obesity, long term implications of being overweight/living with obesity, and recurrence of weight gain. Health states are likely to reflect BMI categories incorporating obesity-related co-morbidities (morbidity, T2D, CVD, stroke and cancer) and associated cost and QoL. Effectiveness will be measured in quality adjusted life years (QALYs). Figure 3 provides an example of a model structure and has been sourced from a previous (as yet unpublished) project that estimated the cost-effectiveness of surgery versus weight management for

treatment of patients with obesity. The final model structure will be informed by the economics literature review and also consulting clinical experts within the team.

Figure 3: Example Markov model structure. The structure is identical for endoscopic treatments and the comparator treatment options. Arrows indicate transition probabilities between the states. The dashed line indicates the intervention (treatment taking place). Death is included as an absorbing state.



The model will assume a patient cohort for which the age range will be determined by both the clinical and economic SR. The scoping review found data in children and adolescence, so we will include all age groups where possible. Subgroup analysis will include restricting the population to patients who are only eligible for endoscopic treatment where BS is contraindicated or inappropriate – in this case the comparator will be weight management service or LSIs; and also, if data allows, estimating the cost-effectiveness for subgroups as detailed in the clinical effectiveness section. The model will run with an effective lifetime horizon, costs and outcomes will be discounted at 3.5%. Model inputs will be taken from a variety of sources with the main source being the economic SR, supplemented by access to available data sets such as the Swedish Obese Subjects (SOS) study (78), a prospective patient cohort study of patients who underwent BS, and clinical expert opinion from within the team and the steering committee. We expect that a number of assumptions will be required to build the model and therefore deterministic and probabilistic sensitivity analysis will be conducted to explore the robustness of the results to plausible variations in the analytical methods used. Cost-effectiveness acceptability curves will be used to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. All methods and analyses will be reported as recommended by the CHEERS reporting guidelines(79).

6. Data selection and study extraction

6.1. Study selection (clinical and cost-effectiveness)

Two reviewers will independently screen records using pre-specified and piloted screening criteria. Full texts will be screened where a decision cannot be made on the basis of title and abstract. Disagreements will be resolved through discussion, with involvement of a third reviewer if necessary. EndNote 2020 (Clarivate Analytics) reference management software will be used to record decisions. The study selection process will be documented using a PRISMA flow diagram. Reasons for exclusion at the full text stage will be recorded.

6.2. Data extraction

Data will be extracted by one reviewer using a pre-designed and piloted data extraction form, and checked by a second. Disagreements will be resolved through discussion, with involvement of a third reviewer if necessary.

6.3. Information extracted will include:

6.3.1. Clinical effectiveness

- Details on population (e.g. age/sex, ethnicity, T2D status, other co-morbidities, socioeconomic status, country)
- Type of intervention (e.g. gastric occupying device, restrictive procedure, aspiration device or small bowel intervention)
- Type of comparator (e.g. a different endoscopic procedure for obesity treatment, BS, LSI)
- Outcomes (changes in weight, T2D status and/or CVD risk; adverse events; reintervention/revisional surgery; morbidity (obesity complications); mortality; quality-of-life; methods of outcome assessment)
- Study (study design, e.g. randomised or not, controlled or not, prospective or retrospective, length of follow-up, timing of outcome assessments, sample size)

6.3.2. Cost-effectiveness

Further to the relevant data above, from cost effectiveness studies we will also extract data including types of model used, range of health states utilised in any models and types of inputs used in the models relating to patient transitions, resource use and quality of life measures as well as cost-effectiveness findings and indicators of aspects of modelling to which cost-effectiveness findings are particularly sensitive.

7. Timing and effect measures

There will be no restriction on length of follow-up or effect measures included. Effect measures will include mean difference for continuous data (or standardised mean difference when pooling from studies using different tools measuring the same outcome), relative risks for dichotomous data, hazard ratios for survival, or % of patients for adverse events.

8. Risk of bias assessment

8.1. Clinical effectiveness

For risk of bias assessment, we will use tools appropriate to the study design. The Cochrane risk of bias tool -2 will be used for RCTs, whilst recognising that blinding may not be possible for endoscopic interventions or for comparator LSIs. Risk of bias assessment of non-randomised interventional

studies and single arm (before-and-after) studies will be informed by the ROBINS-I tool. Adjustment for confounders will be important in nonrandomised studies. Risk of bias tools may be supplemented by items from the McHarms checklist as adverse events are a key outcome.

8.2. Cost-effectiveness

The Consensus on Health Economic Criteria (CHEC) tool for economic evaluation will be used to assess the quality of cost effectiveness studies. For any model-based studies that are found the Philips checklist will be utilised

Risk of bias assessment will be undertaken by one reviewer and checked by a second independent reviewer. Disagreements will be resolved through discussion, with involvement of a third reviewer if necessary. Tools will be piloted before use and amended where necessary

9. Dissemination:

9.1. Public and Patients:

The patient co-investigator (KC) and the two people living with obesity on the steering committee (SLB and AV) are members of Obesity UK and the Obesity Empowerment Network, which are the two largest and leading organisations/ charities for people living with obesity. They conduct regular online and in-person (pre COVID-19) events and they produce regular newsletters; members of these charities often represent the patient voice on a variety of committees (including NICE) and at conferences. Hence, our patient co-investigator and the people living with obesity on the steering committee will disseminate the results among patients and policymakers, and at relevant conferences via the above-mentioned activities.

9.2. Health care professionals:

In addition to an HTA monograph we will publish academic papers in peer reviewed journals. JD, EF, DM, RS and AT will disseminate the findings in their respective disciplinary and professional networks (including health economists, systematic reviewers, bariatric surgeons, obesity physicians, endocrinologists, and diabetologists) via conference presentations and webinars. AT will also disseminate the results via the Association for the Study of Obesity (ASO) UK as he is a trustee of the ASO and the chair of the clinical practice committee. AT is also a member of the obesity management task force and the Centre for Obesity Management (COM) from the European Association for the Study of Obesity (EASO) and this will aid dissemination amongst obesity physicians in the UK and Europe. Some of the steering committee members have leading positions in the British Obesity & Metabolic Surgery Society (BOMSS) and international federation for the Surgery of Obesity (IFSO) and other leading endoscopy societies (please see project management for details) which will aid dissemination of the results to the bariatric surgeons and other HCPs associated with bariatric surgery (such as dietitians, psychologists, radiologists and physiotherapists) and endoscopists.

9.3. Policy makers and commissioners:

Susannah Howard, on the steering committee, is the sustainability and transformation partnership (STP) Programme Director, Suffolk & North East Essex STP with in-depth knowledge of contemporary health and care policy. She will contribute to disseminating the findings among commissioners and policy makers. SH, KC, EF and AT are also members of the Strategic Council of the All-Party

Parliamentary Obesity Group and AT is a member of the Obesity Policy Engagement Network (OPEN) UK and EU and will disseminate the findings among policy makers.

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Appendix 1

EMBASE search strategy

Embase <1974 to 2022 January 25>

1 exp obesity/ or obes*.ti,ab. 683445

2 exp bariatrics/ or bariatric*.ti,ab. 41309

3 exp bariatric surgery/ or weight loss surgery.ti,ab. 50412

4 exp gastric balloon/ 1575

5 (intragastric balloon* or gastric balloon*).ti,ab. 1768

6 (adjustable balloon system or swallowable balloon or fluid-filled balloon or gas-filled balloon).ti,ab. 129

7 transpyloric shuttle.ti,ab. 9

8 POSE.ti,ab. 70871

9 primary obesity surgery endolum*nal.ti,ab. 66

10 ((gastric* or greater curv*) adj3 plicat*).ti,ab. 786

11 ((endoscopic or endolum*nal) adj3 (sutur* or stitch*)).ti,ab. 1569

12 ((endoscopic or gastric or endolum*nal or curv*) adj3 plication).ti,ab. 860

13 gastroplication.ti,ab. 93

14 aspiration device*.ti,ab.370

15 aspiration therap*.ti,ab. 134

16 (bypass adj2 (sleeve* or liner*)).ti,ab. 1952

17 (bypass adj4 magnet*).ti,ab. 98

18 ((endoscop* or endolum*nal) adj3 (gastrectomy or gastroplasty or liner or sleeve)).ti,ab. 1026

19 ESG.ti,ab. 647

20 endoscopic gastric sleeve*.ti,ab. 2

21 ((duodenaljejunal or duodenojejunal or duodenal-jejunal or gastroduodenaljejunal or gastroduodenojejunal or gastroduodenal-jejunal) adj3 (liner or bypass or sleeve)).ti,ab. 633

22 duodenal mucosal resurfac*.ti,ab. 79

23 ((endoscopic or gastric or intragastric) adj3 (botox or botulinum)).ti,ab. 313

24 (gastric electrical stimulation or gastric pacing or implantable gastric stimulation or vagal nerve blockade or vbloc).ti,ab. 856

25 (transoral or trans-oral).ti,ab. 7126

26 gastric volume reduction.ti,ab. 65

27 (TOGA or TRIM or TERIS).ti,ab. 4420

28 (endomina or endobarrier).ti,ab. 205

29 aspireassist.ti,ab. 35

30 full sense.ti,ab. 42

31 (endocinch or overstitch or stomaphyx or endozip or restore sutur*).ti,ab. 374

32 (heliosphere bag or ellipse balloon or elipse balloon or allurion or orbera or obalon).ti,ab. 196

33 (silimed balloon or reshape balloon or endball or spatz or medsil or ullorex or satisphere or endosphere).ti,ab. 912

34 (gelesis or plenity).ti,ab.16

35 magnetic anastomos*.ti,ab. 39

36 (gastric adj3 balloon).ti,ab. 713

37 1 or 2 or 3 699212

38 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 93191

39 37 and 38 7196

Appendix 2

Studies should be marked ***include***, ***exclude*** or ***maybe*** in Rayyan.

Add a **label** for ease of retrieving and cost or health economic studies or systematic reviews ***economic***, ***systematic review***.

Optional: ***Add Note***, e.g. if there is a particular reason something is unclear.

No need to add a **reason** for exclusion at this stage (we'll only do that after the first round of title and abstract screening).

	Include	**Exclude**
Population	People of any age with obesity (as defined by study authors) with or without obesity related co-morbidities.	
Intervention	Any endoscopic treatments for obesity. Studies reporting *swallowable* balloons even though these are not placed by endoscopy. Studies reporting endoscopic procedures as a bridge to weight loss in preparation for bariatric surgery. Studies reporting endoscopic procedures to address weight regain or other obesity-related outcomes after bariatric surgery. Studies reporting balloon removal.	Swallowable pseudobezoars. A revisional or "redo" procedure carried out endoscopically immediately or soon after bariatric surgery e.g. to correct an adverse event such as repairing leaks. NB. Not to be confused with endoscopic treatment for weight regain or plateau after bariatric surgery which could be included. Studies where balloons are used solely as a means of measuring stomach capacity or satiety when the outcomes such as weight change, complications or safety are not included (e.g. used once at start of study and once at end).

		Endoscopy as an exploratory assessment in preparation for bariatric surgery.
Comparator	Any comparator (alternative endoscopic obesity treatment, sham treatment, bariatric surgery, life-style intervention, medical management or no treatment). No comparator also eligible (as we are including single arm studies).	
Outcome	*Any one or more of:* Clinical effectiveness: any weight related outcome (including BMI); changes in diabetes status or treatment and/or CVD risk; adverse events; reintervention/revisional surgery; any obesity-related morbidity; mortality (all cause, CVD-related and cancer-related); quality-of-life assessed by any tool; micronutrient status. Include composite outcomes that may include any of the above. Cost-effectiveness: costs, quality-adjusted life years, disability adjusted life years, life years gained, measures of cost effectiveness (e.g. incremental cost effectiveness ratios, net monetary benefit), utilities.	Any other outcome not listed. Solely qualitative outcomes. *NB unlikely that study would be excluded on outcome only at title and abstract screening stage, as abstract may not list all outcomes but be reported in full text.*
Study design	There will be no limit on study design (studies with n>1). Include ongoing studies, study protocols. Cost-, cost-effectiveness and health economic studies.	Qualitative studies. Single case reports. Commentaries (assume would have picked original

		study up), letters etc with no primary study data. Narrative (non-systematic) reviews. Systematic reviews BUT label as “systematic review”.
Publication status	Any (including fully published or conference abstracts only, and unpublished studies).	

Endoscopic procedures include:

Use a small, flexible scope inserted through the patient’s mouth. It is less invasive and safer than bariatric surgery, and does not require full anaesthesia. Endoscopic treatments can be broadly classified as:

• Gastric occupying devices: multiple types of intra gastric balloons (IGB); the TransPyloric shuttle (TPS) and the Full Sense device.

• Restrictive procedures: endoscopic sleeve gastrectomy/gastroplasty (ESG) which can be performed using multiple techniques, the Primary Obesity Surgery Endolumenal (POSE), and the transoral anterior-to-posterior gastric greater curvature plication with the Endomina® suturing device.

• Aspiration devices: such as AspireAssist.

• Small bowel interventions (including liner procedures): these include the EndoBarrier (which is Duodenal-jejunal bypass liner DJBL), Gastro-duodeno-jejunal bypass sleeve, duodenal mucosal resurfacing, and entero-enteral dual-path bypass using self-assembling magnets, endoscopic sleeve gastroplasty (ESG).