REBALANCE

(**RE**view of **B**ehaviour **A**nd **L**ifestyle interventions for severe obesity: **AN** eviden**CE** synthesis)

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PROTOCOL
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1. PROJECT TITLE

SYSTEMATIC REVIEW AND INTEGRATED REPORT ON THE QUANTITATIVE, QUALITATIVE AND ECONOMIC EVIDENCE BASE FOR THE MANAGEMENT OF SEVERE OBESITY [CLASSES II AND III OBESITY (BMI ≥35kg/m^2)]

2. SUMMARY OF RESEARCH

Background: Over BMI 35kg/m^2 obesity-related co-morbidities, and economic consequences greatly increase. Systematic review evidence on the feasibility/acceptability and (cost) effectiveness of weight management for BMI ≥35kg/m^2 is lacking.
Objective: Synthesise the quantitative, qualitative and economic evidence, and develop an economic model to inform weight management programmes for people with BMI ≥35kg/m^2.
Design: 5 systematic reviews (**SRs**) on behavioural interventions, licensed pharmacotherapy and bariatric surgery weight loss/maintenance for adults BMI ≥35kg/m^2 **(1) SR1** – long-term randomised controlled trials (RCTs); **(2) SR2** – long-term randomised and non-randomised studies conducted in UK; **(3) SR3** - qualitative and mixed-methods research on patient/provider experiences with interventions; **(4) SR4** - economic evaluations of interventions; **(5) SR5** – long-term RCTs behavioural and/or drug interventions versus bariatric surgery. **Economic model** (micro-simulation) to estimate long-term costs, outcomes and cost-effectiveness of promising interventions, behavioural and/or drug interventions versus bariatric surgery. Innovative methods utilised to identify effective intervention characteristics and control for variability in support provided to comparator groups.
Search strategy: SRs 1-5 (no language restrictions, study completion 1990 and later): Medline, Embase, Cinahl, CCTR, DARE, Psycinfo, NHS EED, Social Science Citation Index will be consulted. Contact professional, health and commercial organisations for unpublished studies; trial authors for detailed descriptions of intervention and comparator group support, qualitative and process outcomes, and outcome data clarification.
Research strategy: SR1-2,5: Outcomes are weight, cardiometabolic risk factors, disease outcomes, adverse events, quality of life. Study quality using Cochrane risk of bias tool and checklist used for NICE reviews. Intervention and comparator group support coded using the TIDieR classification, BCT (Behaviour Change Technique)-v1 taxonomy, and Campbell and Cochrane Equity Methods Group checklist. Meta-analyses and (bivariate) mixed-effects meta-regression analyses to synthesise evidence and explore study, sample, intervention and comparator group characteristics associated with outcomes. **SR3**: feasibility and acceptability of interventions from perspective of participants and providers. Coding and thematic analysis of qualitative and mixed-methods research. Quality assessment of studies' conceptual clarity and interpretative rigor. Comparison of patterns and associations to give broader narrative and interpretative themes. **SR4:** costs and outcomes for interventions collected. Standard checklists used to assess the quality of the economic evaluation. **Economic model:** data from **SRs 1,2,4,5** used to populate the UK Health Forum "Obesity Micro-simulation Model", estimating cost-effectiveness of most promising interventions, including bariatric surgery, from an NHS perspective. **SRs 1-5** integrated in narrative realist synthesis.
Expected outputs of research: Evidence to inform guidance on weight management for BMI ≥35kg/m^2 and future research. At least 5 research papers; conference presentations; summaries for policy makers, health professionals, patients and public; online videos and podcasts.

Project timetable: Months 0-2: protocol, advisory meeting. Months 2-14: **SR1,SR2,SR5**. Months 9-14: **SR3**. Months 12-17: **SR4**, identification of data and population of health economic model. Months 15-17: complete analyses, synthesis of **SR1-5** and economic model analysis. Months 18-20: advisory meeting, final report, conference submissions, peer-reviewed papers.
Expertise: AA, PA: SRs of obesity treatments. GM, PA, MdB: coding and meta-analysing (behavioural) interventions, including comparator group variability in RCTs. DB, LW: economic modelling and evaluations. ZS, AA: mixed-methods synthesis.

3. BACKGROUND AND RATIONALE
There has been a continued increase in severe obesity [denoted here by BMI, body mass index (weight kg/(height m)^2) ≥35kg/m^2] in the UK. As BMI increases, obesity-related co-morbidities, social, psychological and economic consequences increase, as does the need for greater support for help with weight loss. Current NICE and SIGN guidance on weight management for obesity does not distinguish between obesity (BMI 30 to <35kg/m^2) and severe obesity (BMI ≥35kg/m^2); and public health guidance excludes evidence on weight loss programmes for obese people with co-morbidities (1-3). People with severe obesity are particularly likely to end up being treated in Tier 3 obesity services (clinical services) in the obesity pathway, leading to Tier 4 bariatric surgery (1,4). This implies that Tier 3 services are being created and money is being spent without an appropriate evidence synthesis that clarifies what works for people with severe obesity (and their co-morbidities). This project seeks to address this issue by evaluating the feasibility, acceptability, effectiveness, and cost-effectiveness of interventions for people with severe obesity.

We propose to use state-of-the-art methodology for research syntheses, adopting several methodological innovations to generate the most informative evidence, namely (a) code in detail the intervention and comparator group behaviour change techniques in weight loss and maintenance interventions; (b) incorporate in (bivariate) mixed-effects meta-regression analyses variability in comparator groups to arrive at truer estimates of treatment effects (i.e., as if all interventions had been compared against equal comparator groups); (c) examine process evaluations, qualitative and mixed-methods data from studies to examine the engagement, feasibility, acceptability and appropriateness of interventions; (d) correct for dropouts in intervention and comparison groups to provide better estimates of intention to treat analyses, where not undertaken by the investigators; (e) use micro-simulation disease modelling methods to predict future BMI related disease events, based on the most robust estimates of treatment effect, to generate high quality evidence on cost-effectiveness; (f) integrating findings from quantitative and qualitative evidence in a narrative realist synthesis.

3.1 Burden of disease
Data from the 2013 Health Survey for England (5) show that 5% of women and 6% of men have BMI ≥35kg/m^2 to <40kg/m^2, and, in addition, 1% of men and 4% of women have BMI ≥40kg/m^2. BMI ≥40kg/m^2 is most prevalent in the 55-64y age group. 6% of women in the most deprived group have BMI ≥40kg/m^2, compared to 2% in the least deprived group. For men 1% of both most and least deprived groups have BMI ≥40kg/m^2.

Data from Scotland, Wales and Northern Ireland (6-8) generally confirm this pattern for BMI ≥40kg/m^2 – most prevalent in the 55-64y olds, more common in women than men, particularly women from deprived communities. Similar breakdown data for BMI ≥35kg/m^2 to <40kg/m^2 are not available. Present data from the English National Obesity Observatory do not provide comparable data for severe obesity in ethnic communities, making allowance for the different BMI cut-offs (9).

Increased disease risk from severe obesity
The Prospective Studies Collaboration (10) has shown that each 5kg/m^2 higher BMI above BMI 22.5-25kg/m^2 was associated with 30% higher overall mortality; 40% higher vascular mortality; 60-120% higher diabetic, renal and hepatic mortality; 10% higher cancer mortality; and 20% higher respiratory mortality. For people with BMI 40-45kg/m^2 median survival was reduced by 8-10 years, compared to BMI 22.5-25kg/m^2. Using 2003-2010 National Health and Nutrition Examination Survey data, Grover and colleagues

(11) found that healthy life-years lost were at least 2-4 times greater than years of life lost for each bodyweight category.

The increasing trend of obesity BMI ≥40kg/m^2 in England has significant implications for health services, with the much greater risk of type 2 diabetes. Health service costs in 2010-2011 were already £8.8billion/y with indirect costs of £13billion for type 2 diabetes (12).

In the UK, the Million Women Study found significant increases in the risk of, and length of, hospital admission with increasing BMI (13). Women with BMI ≥35kg/m^2 had the most marked increase in hospital admissions compared to BMI ≤25kg/m^2 (for knee replacement relative risk RR 7, venous thromboembolism RR 3, atrial fibrillation RR 3, gallbladder disease RR 2, hip replacement RR 2). Korda and colleagues reported that BMI 35-50kg/m^2 was associated with twice the risk of hospitalisation compared to that for normal weight men and women aged 45-64y (14).

Compared with people of normal weight (BMI 18.5-24.9kg/m^2), people with BMI ≥35kg/m^2 also have the greatest decrements in health related quality of life, as determined by the Short Form-12 and EuroQol (15). Depressive and anxiety disorders are particularly associated with BMI ≥35kg/m^2, especially in women (16).

Increased costs from severe obesity
The costs of overweight and obesity to the UK economy are very substantial. Costs of overweight and obesity to society and the economy as a whole amounted to almost £16 billion in 2007, representing more than 1% of total gross domestic product in the economy (GDP) (17). Some estimates suggest that if the trend of obesity remains unchecked, economic costs could increase to £50 billion by 2050 (17). Morbid obesity represents a particularly high healthcare and economic cost burden. A 2013 systematic review found that people with BMI ≥40kg/m^2 had 1.5-3.9 times higher direct healthcare costs and 1.7-8.0 times lost productivity costs of people with BMI 18.5-24.9kg/m^2 (18). Costs grew exponentially as the level of obesity increased. The McKinsey Global Institute found that in the UK medical costs were 80% higher in people whose BMI was ≥35kg/m^2 compared to people BMI <25kg/m^2 (19).

Benefits from weight loss
Although having a BMI ≥35kg/m^2 has potential to impact on health and quality of life, is there any evidence that effective weight loss programmes can improve long-term weight, health and quality of life? There is clear systematic review evidence, that the greater the weight loss, the greater the improvement in cardiovascular risk factors in obesity (20,21). The largest, long-term randomised trial of weight loss in people with Type 2 diabetes conducted in the US, The Look AHEAD Study, examined an intensive lifestyle intervention compared to control in a population of over 5000 participants with a mean BMI of 36kg/m^2 (22). Whilst an effect on cardiovascular outcomes was not demonstrated, numerous other beneficial outcomes have been reported. Mean weight loss was still 5% after eight years in the intervention group (23), with no reduction in effectiveness of the intervention in people with BMI ≥40kg/m^2 (24). With the intensive lifestyle intervention the incidence of severe chronic kidney disease (25), non-alcoholic fatty liver disease (26), knee pain and reduced mobility (27,28), depression (29), and urinary incontinence in women (30), was reduced. The lifestyle intervention also reduced the symptoms of incontinence in men (31), erectile dysfunction (32), and sleep apnoea (33).

The intensive lifestyle intervention was more likely to produce remission of type 2 diabetes (34) and preserve physical health related quality of life (29). Over 10 years' follow-up the lifestyle intervention reduced hospital days by 15% compared to the control group (35).

In addition to Look AHEAD, there has been a substantial increase in the number of long-term weight management RCTs evaluating not just weight and risk factor outcomes, but quality of life, adverse events morbidity and mortality.

3.3 Existing reviews

NICE public health and clinical guidance has recently conducted evidence syntheses (including for bariatric surgery), but these do not examine behavioural interventions according to the severity or complexity (presence of co-morbidities) of obesity (1,2,36). The evaluation for public health guidance excluded trials in people who were obese with obesity related co-morbidities, thus that guidance is less likely to be applicable to people with higher BMIs, who are more likely to have co-morbidities (2). The NICE Public Health Guidance 53 economic model does suggest that behavioural interventions were found to be most cost-effective with increasing age, and in groups where initial BMI lies between 30 and 40 kg/m^2 (2).

Our literature search conducted in March 2015 in the Cochrane Library revealed no published umbrella reviews, current or planned systematic reviews, or sub-group analyses, relevant to severe obesity. The PROSPERO register of systematic reviews contains details of three reviews, but with very limited scope:

- A systematic review of systematic reviews by the University of Birmingham (37) registered in July 2014 will examine weight loss and health outcomes from systematic reviews of weight loss interventions in people with BMI ≥40kg/m^2. Reviews of studies with people recruited specifically because of health conditions will be excluded, and the focus is not on long-term outcomes.
- A systematic review of behavioural interventions for people with BMI ≥35kg/m^2 by the US Palo Alto Medical Foundation Research Institute, registered in May 2014 (38). This includes RCTs, non-randomised designs and quasi-experimental studies. Weight outcomes only are being sought and included studies will have a minimum duration of 6 months.
- A systematic review by the University of Birmingham (82) registered in July 2014 will examine weight loss and health outcomes from weight loss RCTs and non-randomised controlled interventions in people with BMI ≥40kg/m^2, compared to usual care or no intervention only, of any duration. Comparisons between different interventions will be excluded. We estimate that the University of Birmingham review will include approximately 10 studies of the more than 130 that we plan to review (see uploaded list of RCTs already identified by us).

A systematic review of long-term RCTs of very low calorie diets (VLCDs) and low calorie diets found on Medline only was published in 2006 by Tsai and Wadden (39). The average BMI of participants in the 6 included trials exceeded 35kg/m^2 and weight loss was 5-6% at 12 months. We know of at least 4 newer trials on the same topic.

A systematic review of VLCDs (85) just published in 2016, included RCTs of VLCDs in people with BMI ≥25kg/m^2 (overweight and above), but did not compare different VLCD regimens. This review contains 10 RCTs that we would include in our review, but does not examine behaviour change techniques in intervention and comparator groups.

Hence, there are a few available and planned reviews that address some elements of the work proposed here, but these are very limited in their scope and relevance because of (a) the exclusion of co-morbidities, or (b) short follow-up, or (c) limited range of outcome measures, or (d) focus on interventions in different BMI categories from our review, or (e) limitations in comparator groups, whereas we will seek to examine all available comparisons, or (f) no comparison with bariatric surgery. Moreover, they do not specifically examine what would work in the UK context, nor do they integrate evidence on effectiveness with evidence on feasibility/ acceptability of weight loss programmes and their cost-effectiveness. Also, the above-mentioned methodological innovations which we will use (such as examining what intervention and comparator group issues are associated with outcomes, and estimating truer treatment effects by adjusting for variability in comparator groups between trials) are not adopted.

3.4 WHY THIS RESEARCH IS NEEDED NOW

In the 2015 series on obesity in the Lancet, it was pointed out that 'policy and environmental changes are unlikely to achieve substantial weight loss in patients with severe obesity'. As 'obesity already poses an enormous clinical burden, innovative treatment and care-delivery strategies are needed. Alignment of the intensity of therapy with the severity of the disease is necessary to improve care for obesity' (40).

There is no current guidance from NICE or SIGN on behavioural interventions specific to people with severe obesity, particularly those people with co-morbidities, with the exception of VLCDs for people who need to lose weight rapidly, e.g. for joint replacement or fertility treatment. Although people with severe obesity are likely to attend Tier 1 and 2 weight management, they may eventually be managed in Tier 3 services in the pathway (see Figure 1 below) (41).

A guide for commissioning Tier 3 services, published in 2014, was accredited by NICE (4, 83). This focussed mainly on pathways for referral (including assessment and onward referral for bariatric surgery) and staffing of services, but provided very little detail on the actual interventions to deliver. It suggested GPs could consider referring patients with BMI of 40 or ≥35kg/m^2 with obesity-related comorbidity to Tier 3 services. The Royal College of Physicians' (42) working party provided guidance on organising hospital based obesity management, but undertook no evidence-based reviews of what interventions to provide. Patients in Tier 3 may not necessarily desire bariatric surgery. Effective Tier 3 services could also reduce the numbers of patients moving on to Tier 4, or contribute to the subsequent effectiveness after bariatric surgery. We have also recently completed a systematic review of behavioural interventions before and after bariatric surgery (43), which found very little research on behaviour change in participants definitely planning to have bariatric surgery.

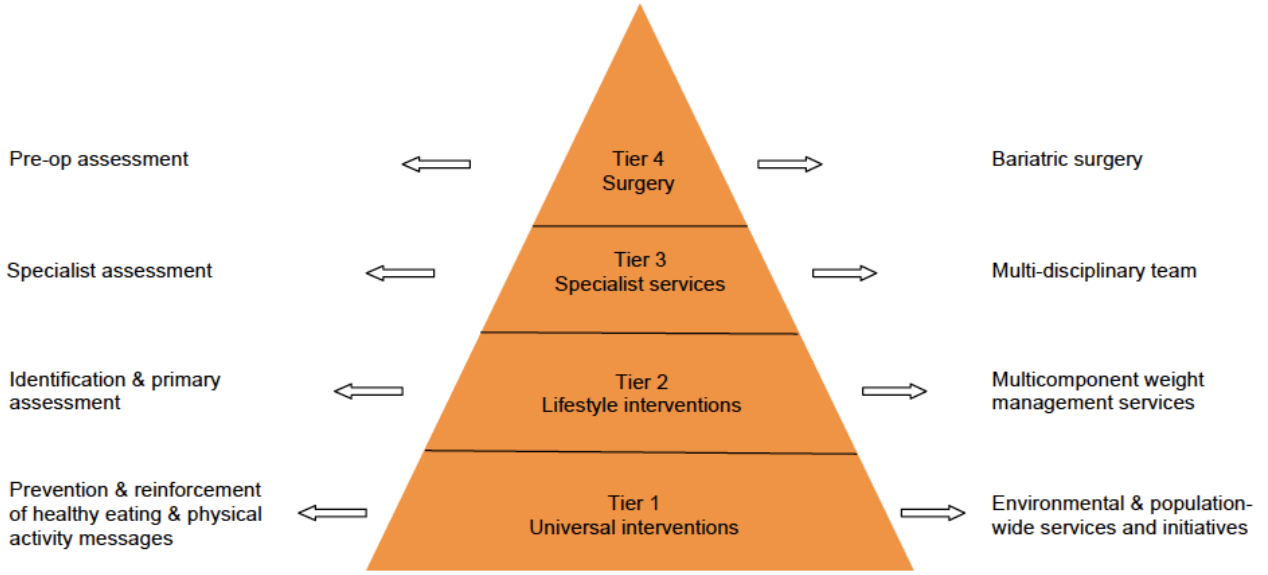


Figure 1 – Tiers of weight management services (4)

There has been confusion on who should fund and provide Tier 3 services. A 2014 working group (44) convened by NHS England and Public Health England concluded that Clinical Commissioning Groups should commission Tier 3 services (with Local Authorities responsible for Tiers 1 and 2). Provision of Tier 3 services remains patchy and the content of programmes is very variable. Professor John Wass highlighted in 2015 to the House of Commons Health Select Committee that only 4 out of 32 Clinical Commissioning Groups in London had a Tier 3 service (45). He stated that 'We are just finishing a survey for the rest of England, Northern Ireland and Wales, but the generality is that there is a hugely missed opportunity because Tier 3 services simply do not exist.' At the end of 2015 a report on mapping of Tiers 2 and 3 weight management services by Public Health England reported on barriers to commissioning services. These barriers were 'evidence and outcomes, national guidance, funding and resource, commissioning, the obesity pathway and service model.' In the same document a survey of endocrinology and diabetes consultants by the Royal College of Physicians found that 40% did not have a Tier 3 service.

In Scotland, a 2014 survey of Tier 2 and 3 services provided by Health Boards, undertaken by Dr Jennifer Logue (personal communication), found most health boards had some form of Tier 3 service, but these were very limited in scope. Referral criteria to Tier 3 ranged from BMI 30 to 40kg/m^2 (with the lower limit

for people with co-morbidities). One health board had an upper age limit of 44y, suggesting that this was a service designed only for people suitable for bariatric surgery. Tier 3 services were often similar to Tier 2 services in duration, and provided very little specialist psychology, dietary, exercise or pharmaco therapy. The comment was made that 'the lack of detailed guidance has created a situation whereby service planning is difficult and has subsequently led to large disparities in service provision between areas'. This would also appear to be the case for the rest of the UK.

Hence, the lack of guidance for what constitutes effective and cost-effective weight loss support for those with a BMI ≥35kg/m^2, may lead to potentially ineffective programmes or simply no programmes for this target group.

Since our initial NIHR funded health technology assessment undertaken in 2001-2002 (20), we have maintained a database of long-term RCTs of weight management indexed on Medline and Embase. From this database our scoping search for this project shows that there are more than 130 long-term (≥1y follow-up) RCTs of weight management in adults with baseline BMI ≥35kg/m^2. Over one third of these trials recruited people specifically because of co-morbidities, e.g. hypertension, risk of or presence of type 2 diabetes, cancer, sleep apnoea, erectile dysfunction, osteoarthritis, and consequently also present health as well as weight loss outcomes. Interventions examined include types of diet (including VLCDs), whether to provide patient preferred reducing diets, remote versus in person care, initial residential course, types of counselling, frequency of contacts, licensed pharmacotherapy, commercial providers, type of healthcare provider. The large number of RCTs also allows greater exploration of data in meta-regression.

Our scoping review has also indicated that there may be around 10 sources of long-term UK data for interventions for BMI ≥35kg/m^2 few of which are RCTs, around 20 studies providing qualitative research of relevance, and around 19 economic evaluations (including four of behavioural interventions compared with surgery) relevant to BMI ≥35kg/m^2. There are now more than sufficient data to undertake an evidence synthesis. We will examine RCT and non-RCT data, qualitative data and health economic evaluations as we did for our evidence synthesis on obesity in men (ROMEO project) (46), where the narrative realist synthesis provided crucial evidence to inform service provision. We will take these methods forward by introducing behaviour change and intervention content coding in both treatment and comparison groups to provide truer estimates of treatment effects; more detailed evaluation of process and qualitative data for the engagement, acceptability and appropriateness of interventions; correction for dropouts in intervention and comparison groups to allow estimation of intention to treat analyses, where not undertaken by the investigators. In addition, we will conduct a new economic evaluation of at least two promising behavioural interventions, and behavioural and/or drug interventions versus bariatric surgery. By populating the economic model with the most robust, accurate estimates of treatment effect and by using UK relevant cost and utility data, we will develop the best possible estimates of cost-effectiveness of the most promising weight loss /maintenance interventions from the perspective of the UK NHS.

4. PLANNED INVESTIGATION

4.1 Aim

The aim is to systematically review the evidence base for bariatric surgery, behavioural and pharmacotherapy interventions for weight loss and weight maintenance for managing obesity BMI ≥35kg/m^2, and evaluate their feasibility, acceptability, effectiveness, and cost-effectiveness.

4.2 Research objectives

The overarching objective is to integrate the quantitative, qualitative and economic evidence base for the management of higher levels of obesity by weight loss and maintenance services, researching concurrently to systematically review:

- The effectiveness of interventions for weight loss and maintenance for people with BMI ≥35kg/m^2
- The qualitative and mixed-methods evidence relating to
    - the acceptability, feasibility and appropriateness of interventions for adults with BMI ≥35kg/m^2

- the feasibility of delivering services
- The cost-effectiveness of interventions for weight loss and maintenance for people with BMI ≥35kg/m^2

4.3 Research plan

4.31 Design

1. **Systematic review 1** Systematic review of RCTs of weight loss or weight maintenance interventions (behavioural and/or licensed pharmacotherapy) for adults who are obese with BMI of ≥35/m^2 with follow up of at least one year, any setting. Classification of behaviour change techniques and theories, and TIDieR (47) components used in intervention and comparison groups in SR1. Metaregression analysis to look for features of more effective interventions.
2. **Systematic review 2** Systematic review of UK only weight loss or weight maintenance interventions with any study design with BMI of ≥35kg/m^2 with follow up of at least one year, any setting.
3. **Systematic review 3** Systematic review of qualitative and mixed-methods research exploring adults' experiences of living with, and receiving weight loss or maintenance interventions for obesity BMI ≥35kg/m^2 (including research exploring the views of professionals involved in their care).
4. **Systematic review 4** Systematic review of economic evaluations of weight loss and maintenance interventions for adult BMI ≥35kg/m^2
5. **Systematic review 5** Systematic review of RCTs of weight loss or weight maintenance interventions (behavioural and/or licensed pharmacotherapy) for adults who are obese with BMI of ≥35/m^2 with follow up of at least one year, any setting, compared with bariatric surgery. Classification of behaviour change techniques and theories, and TIDieR (47) components used in intervention and comparison groups in SR5. Metaregression analysis to look for features of more effective interventions.
6. **Economic evaluation** Use data from SRs 1-5 to populate a micro-simulation model predicting life time costs, outcomes and cost-effectiveness of the most promising effective weight loss and weight maintenance interventions.
7. **Integration of findings** in realist mixed-methods synthesis to produce a detailed summary of the effectiveness, acceptability, appropriateness and cost-effectiveness of weight loss and maintenance interventions for people with BMI ≥35kg/m^2; and to understand how the content and processes of the interventions affect participant behaviour to achieve their outcomes.

4.32 Health technologies being assessed

Technologies to be reviewed are behavioural (e.g. diet, physical activity, behaviour change techniques or combinations of any of these), meal replacements, reducing diets (including very low calorie diets); and licensed pharmacotherapy interventions for the management of obesity. Interventions which include an initial residential course will also be included, as will innovative mechanisms for delivering services, e.g. web-based/email/mobile phone support. Very low calorie diets will be defined as ≤800kcal/d (1).

We will include orlistat for weight loss, which has been estimated by NICE to cost £24431/Quality Adjusted Life Year (QALY), but without details of cost/QALY for severe obesity (36). Other drugs will be included if they have a product licence from the European Medicines Agency, and are prescribed in the UK.

We will include bariatric surgery procedures in current use (gastric bypass, gastric sleeves, gastric bands) for weight loss and include a bariatric comparison within the micro-simulation model.

4.33 Search strategy

The search strategy for RCTs will be similar to that of our previous work on men's obesity (46), whereby we used our existing comprehensive MEDLINE and Embase searches for RCTs of behavioural interventions for weight loss in obese adults with at least 1 year of follow-up, in conjunction with further searches for surgery trials in these databases, and searches conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, PsycINFO, Social Sciences Citation Index and trial registries. We will restrict searching to studies published from 1990 for relevance to current practice.

Highly sensitive electronic searches will also be undertaken to inform the review of UK interventions, using terms appropriate to any intervention study design. Experts in the field, professional and commercial organisations will be contacted for suitable reports.

In our scoping search, we have already identified more than 130 long-term RCTs to evaluate for systematic review 1 and around 15 RCTs for systematic review 5. We will contact all authors of included RCTs by email to request full intervention materials/protocols for active and comparator groups (including treatment-as-usual, or an augmented version thereof), and written reports of any qualitative research, process or economic evaluations. Authors will be contacted for clarification of details within the timeframe of the project. Full details of intervention materials/protocols are required for detailed behaviour change technique coding (48).

It is widely reported that identifying qualitative and mixed-methods studies tends to be more complex than searching for RCTs, often due to suboptimal indexing in bibliographic databases (49). With that in mind, our search strategy for the qualitative evidence synthesis will take an iterative approach and will be focused on supplementary search methods, in addition to comprehensive searches of MEDLINE, Embase, CINAHL and PsycINFO. Rather than simply searching an exhaustive list of bibliographic databases, which has been demonstrated to be ineffective (50), we will search specialist sources for non-journal literature and grey literature in addition to citation searching and contacting weight loss organisations, experts in the field and authors of RCTs and other relevant quantitative studies to seek published and unpublished qualitative data linked to intervention studies.

To identify cost-effectiveness studies and to inform the economic model, we will search the databases outlined above, but in addition the following databases will be searched: NHS Economic Evaluation Databases (NHS EED), Cost-effectiveness Analysis Registry, Health Management Information Consortium (HMIC) and Research Papers in Economics (RePEc).

To avoid unnecessary overlap with our previous work (20), the update search for behavioural RCTs will be limited to studies published since 2001. All other searches will be limited to studies published since 1990 because evidence from before this date is unlikely to be relevant to current practice. There will be no language restrictions imposed on any of the searches.

4.34 Quantitative review methodology – Systematic reviews 1,2 and 5
Inclusion and exclusion criteria
Study design
Systematic reviews 1 and 5 will include only RCTs or quasi-randomised trials (including trials with a cluster design) with a mean or median duration of 52 weeks or over of follow-up. This duration of follow-up for data is to ensure that long-term weight loss and maintenance interventions are evaluated, with their associated effects on obesity-related co-morbidities (20). This was also the minimum duration of studies adopted by NICE for its reviews.

For systematic review 2, reports of UK behavioural interventions of any study design providing follow-up is for 12 months at least, will be considered in order to include and evaluate as much UK relevant research as possible. We are aware of four UK RCTs that would fit this category, that would also be included in systematic review 1, but the majority of studies will not be RCTs. This review will include any published or unpublished service evaluations from the UK for weight management interventions of any provider. This allows us to compare outcomes and intervention content from the UK against that seen and provided in other studies in all our reviews.

Participants
Studies must include adults with a mean or median age of 16 years or over, with no upper age limit. All groups or sub-groups of participants in studies for **systematic reviews 1 and 2** must have a mean or median

BMI of ≥35kg/m^2 (and for weight maintenance interventions a BMI ≥35kg/m^2 at the start of the weight loss phase).

Interventions

For both **systematic reviews 1 and 2** we will include interventions in the form of diet, physical activity, type of counselling, meal replacements (including low calorie and very low calorie diets), settings including short-term residential courses; orlistat (and other weight loss medications providing they have obtained an EMA licence at time of the review and are prescribable across the NHS in the UK); or combinations of any of these. The aim of the interventions must be to assist weight loss or prevent weight regain after weight loss. We will include innovative mechanisms for delivering services, e.g. web-based/email/mobile phone support. Studies examining the type of personnel, frequency of contact, mode of delivery (e.g. group versus individual, use of incentives, will also be included. Comparators will be alternative interventions, or control interventions, recognising that often control interventions also have the potential to change behaviour but vary widely in content and intensity between trials (discussed in more detail later).

For **systematic review 5** we will include interventions eligible for systematic reviews 1 and 2 where compared to bariatric surgery in RCTs. Forms of bariatric surgery to be examined will be gastric banding, gastric bypass and gastric sleeves.

Complementary therapy, e.g. acupuncture, and non-diet products promoted for weight loss available solely over the counter will not be included. Weight loss or weight gain prevention must be explicitly stated as the outcome of the studies.

Setting

All settings for interventions will be reviewed, including hospital, primary care, community (including community pharmacy), commercial organisations, voluntary sector, leisure centres, workplaces, internet and other digital domains, e.g. mobile phone networks.

Outcomes

The quantitative outcomes to be reported in the systematic reviews will include changes in weight, BMI, blood pressure, lipids, glycaemic control, disease specific outcome measures (e.g. development of type 2 diabetes, development of hypertension, reduction in sleep apnoea), changes in medication, adverse events (e.g. musculoskeletal injuries, gallbladder problems which are particularly likely after bariatric surgery), psychological wellbeing, quality of life outcomes. Data on process outcomes, costs and economic evaluations will be collected.

Quantitative review data collection and analysis

The methods we will follow are based on those of our previous reviews (20,46), as detailed below:

Selection of studies

One reviewer will review the titles and abstracts of potentially eligible reports identified in the searches and a second researcher will screen these before full copies are obtained for assessment. Differences in opinion will be resolved by consensus or discussion with a third member of the team, if required. References will be stored using Reference Manager Software.

Data extraction and management

One reviewer will extract details of study design, methods, participants, interventions, settings and outcomes, Behaviour Change Techniques (BCTs) (48) and TIDIER (47), which will be checked by a second member of the team.

Quality assessment

The methods used for assessing quality in studies reporting quantitative data, including RCTs, will be based on those used by the Health Services Research Unit, HSRU (University of Aberdeen), for technology

assessment reviews (TARs) for NICE. The Cochrane risk of bias tool will be used to assess the risk of bias in RCTs (51) and a 17 question checklist for non-randomised comparative studies and case series (46). The development of the latter checklist was led by HSRU in partnership with the Review Body for Interventional Procedures for NICE. This checklist rates bias, generalisability, sample definition and selection, description of the intervention, outcome assessment, adequacy of follow-up, and performance of the analysis. Two reviewers will independently assess the quality of all included full-text primary studies. We will use an adapted version of the Campbell and Cochrane Equity Methods Group checklist (52) to assess the effect of interventions on disadvantaged groups and/or their impact on reducing socioeconomic inequalities. Differences in opinion will be resolved by consensus or discussion with a third member of the team, if required.

Coding interventions and comparison group support

We will use the TIDieR 12 item checklist to guide data collection on the content, context and intensity of the interventions delivered (47). TIDieR is a general taxonomy for reporting and coding the characteristics of any type of interventions (e.g., behavioural, surgical, pharmacotherapy), and therefore well-suited for the current SRs. TIDieR includes collection of information on materials used in interventions and the active ingredients of the intervention; details of the provider delivering the intervention; modes of delivery (e.g. face-to-face, phone, internet, individual and/or group); location for intervention and infrastructure required; when and how much was delivered (e.g. number of sessions, duration and intensity); tailoring of the intervention; modifications made to the intervention during the trial; assessment of intervention fidelity on actual exposure).

We will undertake detailed coding of the active content of interventions, using the consensus-based behaviour change technique taxonomy v1 (48). In addition, since previous studies have also revealed substantial variability in the content, context and intensity of support provided to comparator groups (e.g., receiving treatment-as-usual or an augmented versions thereof) between trials of behavioural interventions, which is associated with trial effect sizes, we will also collect these data for the comparator group interventions (53-57), contacting authors for full details of interventions in all study arms. For example, in a limited selection of weight loss trials, Waters and colleagues (57) found a substantial range of weight loss for different control groups: -5.8 kg to + 4kg and a high level of associated heterogeneity. Clearly, this variability needs to be understood and taken into account when synthesising the evidence and comparing the effectiveness of interventions across trials (53-55).

Data collected during these analyses will be carried forward and used to help develop micro-costing of interventions for inclusion within the economic model.

Statistical analysis

We will report means or changes in means or proportions between groups. For continuous outcomes we will report mean difference or standardised mean difference (different scales for the same outcome), and risk ratio for dichotomous data, with 95% confidence intervals.

For each study, we will extract weight change as complete case data and baseline observation carried forward (BOCF) data reporting the mean, standard deviations (SD), and number of participants contributing. Where SDs are not presented we will calculate them from 95% confidence intervals or standard errors (SEs). If BOCF is not presented we will calculate it from completer data as described recently (58). We will classify multiple imputed data as similar to completer data because it is primarily based on the weight of people that were followed up. In a few cases, some useful data will be missing that would allow us to calculate the mean weight change, SD, or know the number followed up. Where possible, we will make reasonable assumptions to calculate these data and note these assumptions in the evidence tables. We will contact authors for missing data.

We will use Review Manager software (Version 5.3.5 or later as appropriate) for data synthesis for RCTs. Previous experience of reviewing trials of obesity interventions has revealed considerable heterogeneity in

the studies assessed. We will therefore use random effects meta-analyses in **SRs1-2, 5**. In studies with data at multiple follow-up times we will report data in meta-analyses with time periods aggregated to the nearest six months.

Where we are unable to combine data in meta-analysis, particularly for **SR2** where most studies will not be randomised, we will provide a narrative synthesis of data, as we undertook for UK-based studies in our previous health technology assessment report (46).

Subgroup analyses will explore whether the effectiveness of interventions differs according to whether all participants are selected on the basis of newly diagnosed or pre-existing obesity related co-morbidities (e.g. diabetes, hypertension) or not. If sufficient data are available, we will also explore the effect of BMI category, (e.g. <40kg/m^2 versus ≥40kg/m^2), sex, deprivation, age, and ethnicity on effectiveness. In sensitivity analyses we will explore the effect of assumed values for weight outcomes on meta-analyses.

We will use visual inspection and the I^2 statistic to assess heterogeneity in forest plots (51). We will undertake funnel plots to analyse reporting biases for forest plots with 10 or more studies which report mean differences.

If sufficient data allow, we will use (bivariate) mixed-effects meta-regression to examine which intervention (e.g. clusters of behaviour change techniques), comparison group, study and sample characteristics explain variation in intervention effect size. We will explore the impact of the following moderator variables, including those extracted for the TIDieR checklist, taking into account the active content given to the comparison group, e.g., (a) intensity (number and duration of sessions), (b) sample characteristics (including particular inclusion/exclusion criteria), (c) mode of delivery (face to face, group, web, apps, etc), (d) adherence to the treatment and fidelity of intervention delivery.

4.35 Qualitative review methodology – Systematic review 3

Qualitative studies have an important role to play in understanding how factors facilitate or hinder the effectiveness of health interventions, and how the process of interventions are perceived and implemented by users. The focus of this review will be on understanding the feasibility and acceptability of weight loss interventions for adults with BMI ≥35kg/m^2 and intervention providers, but in order to understand this, we will also examine wider themes relating to adults' experience of being obese.

Approach

Synthesis of qualitative studies is an emerging methodology and there are many approaches that can be used (59,60). Whilst being aware of the differing philosophical stances underlying various approaches to qualitative synthesis, we have chosen to adopt a pragmatic approach to our work in this area, which specifically aims to synthesise data that are relevant to informing policy and practice as in our previous review (46).

Our pragmatic approach corresponds most closely to a 'realist' perspective (60,61), as we are concerned with trying to find out not only 'what works' in terms of weight management for this group of adults and intervention providers, but also 'for whom, and under what circumstances'. At the same time, our approach is informed by and uses aspects of review methods such as critical interpretative synthesis (62); thematic synthesis (63,64); and analytical approaches developed from methods of inquiry such as grounded theory (65). We intend to employ deductive and inductive analytical approaches throughout the review process.

Initial research questions

Our broad initial research questions for the review of qualitative evidence will include "What is it like to engage with (or be a provider for) weight loss interventions for adults with BMI ≥35kg/m^2?" and "What is it about interventions for adults with BMI ≥35kg/m^2 that make them helpful or unhelpful". As the analysis is conducted iteratively, these questions may be refined and supplementary questions may be added.

Search strategy
See section 4.33

Study design
We will include:
A. Qualitative and mixed-methods studies linked to eligible RCTs, including any qualitative data reported as part of papers reporting quantitative outcomes;
B. Qualitative and mixed-methods studies linked to ineligible RCTs and identified non-randomised intervention studies including any reported qualitative data reported;
C. UK-based qualitative studies not linked to any specific interventions that draw on the experiences and perceptions of adults with BMI ≥35kg/m^2 (and/or providers involved in their care). We know from our previously funded NIHR HTA evidence synthesis (46) that a large body of published literature exists that has explored adults' experiences and perceptions of being obese. Within Category C, in order to obtain the most relevant data for this review (whilst also ensuring we generate a manageable amount of qualitative data for analysis within the timescale of the project), we will initially focus on only those studies that explicitly state that they have included the views of participants with BMI ≥35kg/m^2. However, if we find that very few studies in this category have been specific about included participants' BMI, we will include studies from the broader literature that have explored adults' experiences and perceptions of being obese, providing they report data specifically relating to views/experiences of strategies for weight loss.

Data extraction and management
All studies must include adults with BMI ≥35kg/m^2 (and/or the views of providers involved in their care) and must consider issues relating to weight management. We will include studies that were undertaken in developed countries only, and which are relevant to the UK. Two researchers will independently screen identified abstracts and where there is disagreement regarding eligibility, the full paper will be retrieved. Where consensus cannot be reached, it will be discussed at a research team meeting.

Adopting a similar approach to our previously funded NIHR HTA evidence synthesis (46), two reviewers will independently group the identified studies into the categories A, B and C described above. Separating intervention studies from non-intervention studies is a feature of the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre) mixed synthesis process (66). As the focus of our broader evidence synthesis is to assess the evidence for weight management interventions for adults with BMI ≥35kg/m^2, we believe that grouping the studies in this way will facilitate the integration of the quantitative and qualitative review processes.

A cyclical, sequential analysis will then be undertaken, as previously used (46). During Qualitative Cycle A, qualitative data from Category A studies (RCTs) will be analysed using the constant comparative method to identify and understand the aspects of the intervention processes and context that relate to our research questions. Then, during Qualitative Cycle B, using theoretical sampling, Category B studies will be identified and analysed in the same way and will confirm or refute the emerging themes and concepts identified during Qualitative Cycle A. During Qualitative Cycle C, Category C (non-intervention studies) will be theoretically sampled and analysed to further refine and validate our emerging analysis and theory.

For each study included in our sample we will extract information on its aims and methods, populations involved, etc., into the standardised data extraction form and we also conduct a thematic analysis of the content of the included publications. This analysis will start with a close reading of the publications to identify main recurring themes, followed by the generation of higher level themes capturing the phenomena described in the literature and mapping the relationships between them. This process will involve constant comparison of the emerging theoretical structures with the data from the analysed publications. The analysis will be undertaken by two members of the team, with the initial reading and coding conducted independently and any disagreements discussed until consensus is reached.

Quality assessment
The retrieved publications will be appraised for methodological rigour and theoretical relevance by two reviewers using Toye's (67) recently proposed criteria for quality in relation to meta-ethnography. They suggest two core facets of quality for inclusion in syntheses of qualitative evidence, namely (1) Conceptual clarity: how clearly has the author articulated a concept that facilitates theoretical insight; (2) Interpretive rigour: what is the context of the interpretation; how inductive are the findings; has the interpretation been challenged? Grading for quality will be conducted by two reviewers and results compared. Disagreements will be resolved by discussion and, if necessary, arbitration by a third reviewer.

4.36 Systematic review of economic evaluations – Systematic review 4
It is important to assess the efficiency as well as the effectiveness of newly adopted interventions on the NHS. An assessment of cost-effectiveness of weight management interventions is required to ensure healthcare payers get value for money. The health economics component will follow a two-step approach. First, we will summarise the current evidence base by systematically reviewing current economic evaluations (both within trial analyses and decision modelling studies) undertaken for weight loss and weight maintenance programmes (after weight loss) for people with BMI ≥35kg/m^2. Data extracted from cost-effectiveness studies will be presented as tabulated results, with narrative summaries of the cost-effectiveness of broad intervention groups (e.g. pharmacotherapy, behavioural interventions, and bariatric surgery). The narrative summary will help to provide an overall summary of the literature on broad types of interventions for weight management and will identify gaps in the current evidence base.

Retrieved studies are likely to be of limited methodological quality (e.g. short time horizons, not addressing co-morbidities, issues of assumptions surrounding weight maintenance in models), and may also have limited generalisability to UK decision making, particularly for the most severely obese patients. It is unlikely that any study will have simultaneously estimated cost-effectiveness for all of the interventions of interest in one single model. The second approach will therefore use a decision analysis model to synthesise all the evidence on treatment effectiveness and costs gleaned from **SR 1-5** in a single analysis. We have chosen to use a micro-simulation decision analysis model, developed by the UK Health Forum (68), which has previously been used to inform a number of leading guidelines and publications on cost-effectiveness of obesity interventions (2).

The model will be tailored to estimate the life-time costs, outcomes (BMI related disease development and QALYs) and cost-effectiveness from an NHS perspective, of the specific weight management interventions identified as most promising from the clinical-effectiveness review. This will include an analysis of bariatric surgery. The model will be used to determine if the most effective weight management interventions represent a cost-effective use of scarce NHS resources.

Data from the review of clinical effectiveness and the statistical analysis of treatment effect will be used to populate the economic model. Micro-costing approaches will be used alongside data sourced from the review of economic evaluations to determine the most appropriate intervention cost to use within the model. Data from both the clinical effectiveness and cost-effectiveness reviews will be used to identify useful sources of evidence, such as utilities, costs and epidemiological data to populate the economic model with the most up to date, UK relevant parameters. Results of included studies from the review of economic evaluations will be used for comparison with and validation of the economic model outputs.

Search Strategy
See section 4.33

Eligibility and inclusion criteria for studies
Studies that compare both costs and outcomes for interventions for the management of obesity in adults with BMI ≥35kg/m^2 will be included. Studies will be excluded if they do not attempt to relate cost to outcome data (for example with a cost-effectiveness or cost-utility analysis framework). Methodological

papers, papers that review economic evaluations (although their reference lists will be checked for additional papers to include), discursive analysis of costs/benefits, partial evaluation studies such as cost analysis, efficacy or effectiveness evaluations and cost of treatment/burden of illness papers will be excluded from formal review.

Interventions suitable for review will be as for **systematic reviews 1,2 and 5**. Weight loss or weight gain prevention after weight loss will need to be explicitly stated as the main goal of the intervention undergoing economic evaluation. Studies examining a combination of interventions, for example smoking cessation and weight loss, at the same time will not be included in the review. We will however include combinations of interventions for weight loss (such as pharmacotherapy and behavioural interventions, or behavioural interventions alongside bariatric surgery).

Selection of studies
One health economics' reviewer will assess all retrieved abstracts for inclusion and full texts will be retrieved and assessed for those appearing to match the inclusion criteria. All full text articles will be assessed against the NHS-EED guidelines for reviewers, which address and outline the key components for conducting economic evaluations. A second member of the review team with knowledge of health economics will cross check inclusion of studies at each stage. Decisions on inclusion of studies will be reached by consensus between the reviewers. Any disagreements will be discussed at regular meetings of the review team.

Data extraction strategy
Data extraction will be undertaken by one health economist. Data extraction forms will be checked by a second member of the review team with an understanding of health economics for consistency and accuracy. The data extraction process will focus on two key areas: (1) the results of the economic evaluations in terms of estimates of costs and effects and (2) the methods used to derive the results.

Reporting of results/Data synthesis
Because of the likely heterogeneity of the studies retrieved, we are unlikely to attempt any quantitative synthesis of the included studies. Instead, data from included studies will be summarised narratively. Key outcome data from the review of economic evaluations will include detailed information on intervention resource use and costs, costs to the NHS, costs to patients, their carers and to society, outcomes in terms of weight loss, mortality, Quality Adjusted Life Years (QALYs), incremental outcomes and incremental cost per treatment effect /QALY gained. Data on results of sensitivity analyses carried out, including deterministic and probabilistic sensitivity analyses as well as any sub-group analyses will be recorded and reported narratively.

Where incremental costs, incremental effects or incremental cost-effectiveness ratios have not been reported, when possible, we will undertake these calculations, based on data included in the studies. The aim of the narrative is to identify common results across broad intervention groups (such as bariatric surgery, behaviour change interventions or pharmacotherapy). Costs from older studies and those conducted outside the UK will be converted to UK 2016 values to aid comparison of studies within the narrative summary.

Quality Assessment
Common strengths and weaknesses will be identified through a quality assessment of included studies. This will follow the BMJ guidelines (69) for reviewers of economic evaluations for studies conducted alongside RCTs and using the Phillip's criteria for appraisal of decision analysis models (70). The results will be used to assess the quality of the current evidence base, but also to develop recommendations for future economic evaluation studies of weight-loss interventions more generally.

4.37 Economic evaluation and modelling

We will use the well-known UK Health Forum (UKHF, formerly National Heart Forum) “Obesity Micro-simulation Model”, which was developed for the Foresight Report (68). Since then it has provided annual obesity-growth forecasts for the Department of Health (England) and has supported similar work in over eighty countries. It has also been applied to test the cost-effectiveness of obesity interventions in a number of local settings. Recently the model was adapted to be used for NICE Managing overweight and obesity in adults—lifestyle weight management services (2).

The model is currently configured to examine obesity and other health related outcomes and will be used to estimate the future burden of diseases by making evidence based extrapolations of selected risk factors specific to the following BMI related diseases; hypertension and stroke, type 2 diabetes, cardiovascular diseases, musculoskeletal disorders including osteoarthritis, and obesity associated cancers including colorectal and breast cancer. Using Markov-type simulation of long-term health benefits, health care costs and cost-effectiveness of specified interventions, the model will be used to project the differences in QALYs, lifetime health-care costs and other outcomes as a consequence of selected interventions. Estimates of life-time healthcare costs and QALYs will be combined to present results as incremental cost-effectiveness ratios, using cost per kg lost and cost per QALY gained as key outcomes. Other analyses will be presented such as cost per case of type 2 diabetes avoided to generate results which are clinically meaningful.

We anticipate undertaking economic evaluations of several interventions depending on the effectiveness data from our reviews, e.g. more intensive behaviour change support for diet and physical activity change over a longer duration, including a specific weight maintenance programme; use of an initial intensive residential training programmes in addition to more intensive behaviour change support. The final selection of interventions to undergo economic evaluation within the micro-simulation modelling will depend on the results from the reviews of clinical effectiveness and statistical analyses of treatment effects. In addition to the most promising strategies from the clinical effectiveness review, we will explicitly evaluate a strategy of bariatric surgery along or in combination with other interventions in the model. The purpose of this analysis is to provide essential information to NHS decision makers of cost-effectiveness of bariatric surgery in this patient group.

Data used to populate the model will be sourced from the systematic reviews of clinical effectiveness and cost-effectiveness. A micro-costing process will be undertaken for each intervention included within the economic model. Resource use required to deliver interventions will be based on descriptions provided from retrieved studies. This will include, but is not limited to equipment; materials and staff time required to deliver the intervention; hospital and theatre staff and equipment costs for bariatric surgery; active ingredients of therapy; frequency, intensity and duration of delivery; whether therapy is group or individual based; property rental and other overheads; as well as any costs required to deliver a maintenance phase of the interventions. Where data are not available in published sources, authors will be contacted for further information regarding resource use required to deliver interventions. In the event of any remaining missing data, clinical expert opinion of the advisory group will be sought to bridge any gaps from a UK perspective. Where there are differences in resource use requirements to deliver similar interventions across studies, we will estimate average resource use and cost and include this within the economic model. Where possible, distributions will be fitted around reported resource use and costs for a description of uncertainty surrounding intervention cost within the economic model. Sensitivity analysis will be used to explore the impact of plausible alternative estimates of intervention cost on cost-effectiveness outcomes.

The model will be updated with appropriate cost data in 2016 values. The primary perspective of the analysis will be that of the UK NHS. The model base case will be life-time duration with sensitivity analyses exploring alternative time horizons. Costs and outcomes will be discounted at a rate of 3.5 % per annum in line with NICE guidance. Sensitivity analyses will test the impact of varying key model assumptions and inputs (such as uncertainty surrounding intervention cost and assumptions regarding weight maintenance over the longer time period). Probabilistic sensitivity analysis will show what impact varying key parameters in the analysis has on baseline cost-effectiveness results. Results will be expressed in terms of a cost-

effectiveness acceptability curves to summarise any uncertainty in our estimates of cost-effectiveness. A wider patient and societal perspective will be considered as a supplementary analysis if sufficient data are available from the systematic reviews.

4.38 Integration of findings SRs1-5 and economic model

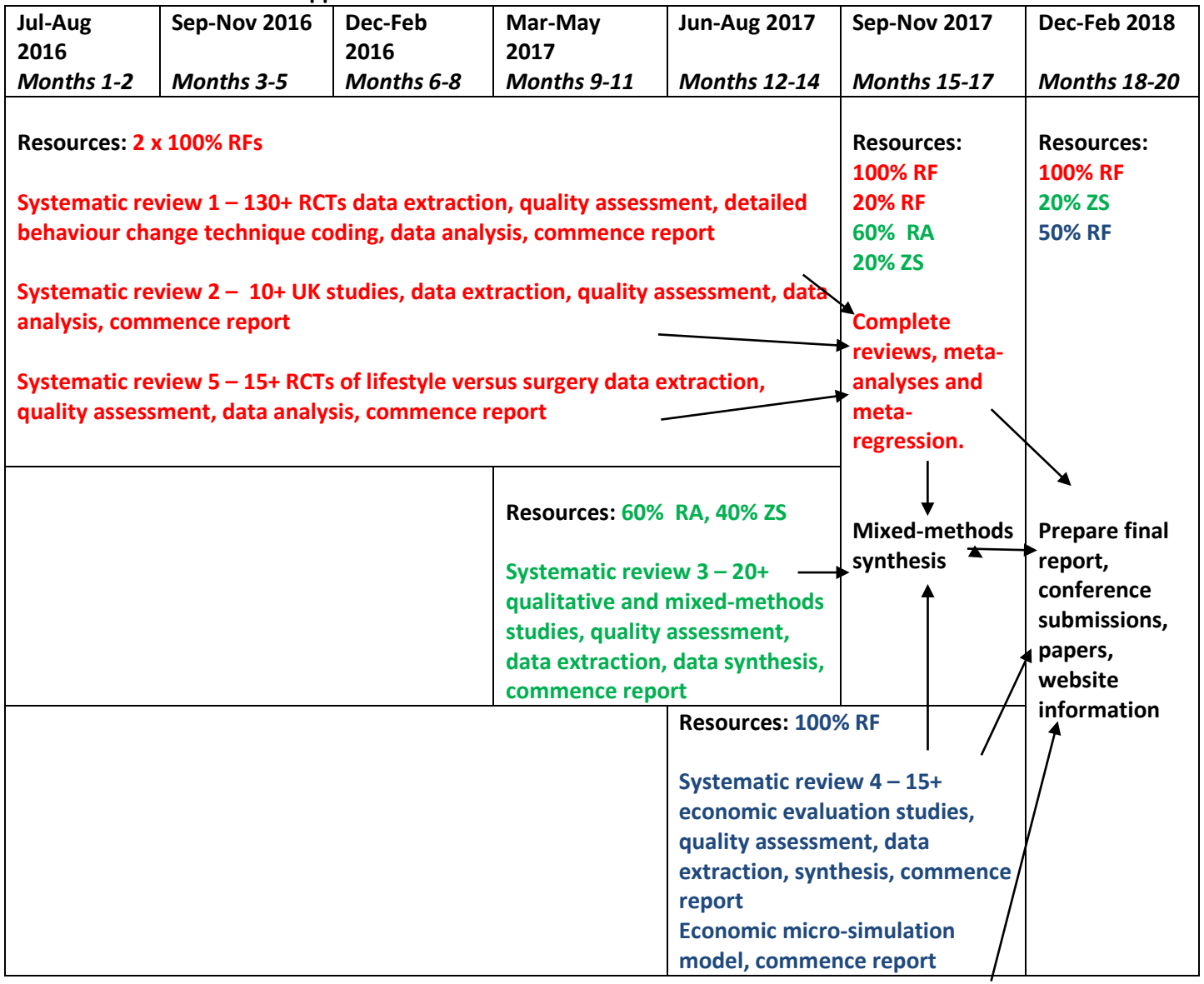
There is no single agreed method for synthesising and integrating quantitative (including health economics) and qualitative research evidence in a systematic review and this is a rapidly developing field (71). Drawing on a realist approach, we will integrate (by combining and juxtaposing) the qualitative and quantitative evidence to produce a detailed narrative summary of what weight management interventions work, with which adults, under what circumstances and which effective interventions offer value for money for the NHS.

From a realist perspective, it is important to conceptualise any intervention intended to improve health by considering the:
(1) Context that an intervention/programme will be situated within so that factors that might inhibit or enhance its effectiveness can be identified;
(2) Mechanisms of the intervention/programme and how the intended programme beneficiaries will interact and react to the intervention processes and mechanisms; and
(3) Outcomes, both positive and negative, that may arise from an individual's engagement with the proposed intervention.

A body of literature has emerged over recent years that has stressed the importance of considering health problems (such as obesity) from a so-called socio-ecological perspective (72-78). Hence, our methodological approach will investigate issues relating to the ***macro***, ***meso*** and ***micro*** level influences that shape and influence adults' (with BMI ≥35kg/m^2) perspectives and experiences related to engaging and participation with weight management programmes. By ***macro level*** influences we mean the wider social, cultural, economic and political factors that overarch and influence the ***meso level*** of workplace, community, family, friends, peers; whilst ***micro level*** refers to individuals' decisions about changing their weight.

Figure 2 illustrates how **systematic reviews 1-5** and the **economic model** will be brought together. Thus **systematic reviews 1, 2 and 5**, with coding of intervention content and meta-regression analyses will provide evidence on features of effective interventions and their limitations for transfer into practice (e.g. what works, for whom, how can this be delivered). These reviews will also allow comparison between existing UK programmes with evidence on outcomes from research studies. **Systematic review 3** will provide evidence on the feasibility, acceptability and appropriateness of interventions. **Systematic review 4** will identify the most rigorous and relevant evidence on cost-effectiveness, identifying key gaps in the literature. Data from **SRs 1, 2, 4 and 5** will be used to populate the high quality micro-simulation decision analysis **economic model** tailored to assess the cost-effectiveness of the interventions identified as most promising.

Figure 2 - Details of main staff employed on project, timelines and integration of project
RF = Research Fellow ZS = Applicant Zoë Skea RA = Research Assistant



5. DISSEMINATION AND PROJECTED OUTPUTS

For people to benefit from this project immediately and in the long term, it is essential that they are involved in the research and that there is a solid dissemination strategy. This involves disseminating the results to researchers (through sharing data and results, with evidence for improving research), to policy makers (evidence that may help improve guidelines for supporting people with obesity and for improving research), providers (evidence that may improve patient support), and patients, carers and members of the public (evidence on what patients, carers and providers can do to optimize self-management).

We will develop a study website, which will be used for disseminating the results, with access to all publications. Our advisory group will provide recommendations and feedback regarding website design and content. Proposed website sections will include:

- Policy makers:
  - Summary of main outcomes
  - Implications for policy and practice
- Researchers:
  - Full review protocols will be available and also registered on www.crd.york.ac.uk/NIHR_PROSPERO
  - Developed instruments
- Providers:
  - Evidence regarding effective interventions, including (clusters of) behaviour change techniques (BCTs) which can be added, or which ineffective (clusters of) BCTs can be removed, to improve patient self-management.
- Patients, carers and members of the public:
  - Summary of the project outcomes
  - Effective self-help strategies

We plan at least five primary open access publications from the project. Researchers from the project will present results of the project at the annual NICE conference, the annual NHS Scotland conference, UK Association for the Study of Obesity, and UK Society for Behavioural Medicine conferences. We plan to host workshops at the above conferences, allowing all the results to be presented together.

Alison Avenell and Paul Aveyard have established contacts in NICE, NHS England, Public Health England, SIGN and NHS Scotland. As was the case with the ROMEO project (46), we will liaise with these bodies to rapidly inform those working on guidelines. Working with the advisory group, we will also establish other methods for rapid dissemination of the results of research. For example, in our previous project the advisory group advised on the production of a user guide that was freely available as a pdf to download from the web (79). We will also work with lay members of the advisory group to disseminate our results by other means, e.g. videos, podcasts, on the study website.

6. PLAN OF INVESTIGATION AND TIMETABLE

For the timetable and milestones please see **Figure 2**.

7. PROJECT MANAGEMENT

The Chief Investigator (AA) and three co-applicants (ZS, DB, GM) are based at the Health Services Research Unit (HSRU), University of Aberdeen, which is where staff employed on the grant will be based. MdB leads the Aberdeen Health Psychology Group, University of Aberdeen. DB is also attached to the Health Economics Research Unit, University of Aberdeen. AA, ZS, DB, MdB and GM have extensive experience undertaking systematic reviews, including qualitative data synthesis, assessing and handling control group variability in bivariate mixed-effects meta-regression models, and economic evaluations for NICE and the NIHR HTA programme. Additional support is available as required from HSRU, e.g. literature searching, preparation of NIHR final reports.

PA from the University of Oxford will advise on all stages of the project, based on his experience working for NICE on PH53, including providing advice on inputs for the economic model. Laura Webber of the UK Health Forum will responsible for running the micro-simulation model used in the economic evaluation.

The management of the project will be coordinated by the University of Aberdeen team, led by AA. AA led two previous obesity systematic reviews for NIHR HTA, and has experience leading teams of multidisciplinary teams. Frequent, regular communication, including at least monthly teleconferences will be held for all applicants and researchers on the project.

The University of Aberdeen staff will adhere to standard University procedures, e.g. registration of the systematic review on Prospero database, confidentiality of final report required by NIHR.

7.1 Contributions of research team

Alison Avenell, Clinical Chair in Health Services Research, HSRU, University of Aberdeen: led the 2004 NIHR funded systematic review and economic evaluation of adult weight management (20), and 2014 NIHR funded systematic review of weight management for men (46). She runs diabetic clinics for type 2 diabetics with BMIs ≥35kg/m^2, has previously worked in a specialist weight management service in the NHS, and has provided input into the setting up of Tier 3 services in NHS Grampian. She will coordinate all parts of the project and co-supervise the two Research Fellows undertaking quantitative data extraction.

Paul Aveyard, GP, Professor of Behavioural Medicine, University of Oxford: leads weight management trials. Led evidence synthesis for Managing overweight and obesity in adults—lifestyle weight management services (NICE Guideline PH53) (2), worked with UKHF on economic modelling and cost consequence analysis. He has recently been involved in a systematic review of RCTs of VLCDs (85). He will provide the perspective of GP providers and commissioners (particularly for the NHS in England), advise on methodology adopted for recent NICE review PH 53 (2).

Dwayne Boyers, Health Economist, University of Aberdeen: undertakes Health Technology Assessments for NICE, economic evaluations alongside RCTs. Lead economist 2014 NIHR funded systematic review of weight management for men (46). Dwayne will supervise the Health Economic Research Fellow on the SR of economic evaluations and the economic modelling.

Marijn de Bruin, Personal Chair in Health Psychology, University of Aberdeen: research focuses on designing, evaluating and synthesizing interventions to support healthy lifestyles, particularly evaluating behaviour change techniques used in intervention and comparator groups to elicit more reliable estimates of effectiveness of interventions, using bivariate mixed-effects meta-regression. He will lead on behaviour change coding, quantitative and process outcome data extraction and meta-regression, co-supervising the Research Fellows undertaking quantitative data extraction and systematic reviews, and contribute to evidence integration.

Graeme MacLennan, Senior Statistician, HSRU: wide experience in statistical and design techniques related to RCTs, cluster RCTs, implementation research and meta-analysis. Provides statistical support for Health Technology Assessments commissioned by NICE. He will lead and supervise statistical analyses.

Zoë Skea is an experienced researcher with particular expertise in qualitative methodology and issues relating to patients' health care experiences. She has extensive experience of the design and conduct of health services research and has worked in complex multidisciplinary research projects including leading qualitative studies; mixed-methods studies and evidence syntheses. Zoë has considerable experience working with multidisciplinary research teams and managing research staff. Zoë will lead the qualitative review and mixed-methods synthesis and supervise the Research Fellow for this review.

Laura Webber, Director of Public Health Modelling, UKHF: builds models to assess health impact of changing rates of risk factors on chronic disease. Project manager of European Commission funded project

on Economics of Chronic Diseases. Co-authored guidelines on childhood weight management interventions for NICE. She will be responsible for running the health economic model, with inputs provided by Dwayne Boyers and the Health Economics Research Fellow.

8. PROJECT ADVISORY GROUP

We have already worked with three lay members of the Project Advisory Group, who advised on the project and helped draft the plain English summary. They have agreed to participate in the Project Advisory Group also. We have five additional advisors who have agreed to participate in the Project Advisory Group:

1.Dr Laura Stewart, Tayside Weight Management Service Lead and Dietitian.

2.Dr Jennifer Logue, Senior Lecturer, University of Glasgow: Chief Scientist Office/ NHS Education Scotland Clinician Scientist Intermediate Fellow. Clinical and research interests are the effects of obesity and weight management on co-morbidity, the most cost-effective means of achieving weight loss within the health service, design and provision of Tier 2 and 3 services. Chief Investigator of the Surgical Obesity Treatment Study, a NIHR HTA funded 10 year longitudinal cohort study of patients undergoing bariatric surgery in Scotland. Member of SIGN obesity guideline group.

3.Dr Su Sethi, NHS England, advisor on commissioning weight loss services, including Tiers 3 and 4.

4.Mr Richard Welbourn, Consultant Bariatric Surgeon, member of the bariatric specialist commissioning group, who led the Royal College of Surgeon's guidance on Tier 3 services (4).

5.Dr Jamie Blackshaw, Team leader for Obesity and Healthy Weight at Public Health England.

We plan a face to face meeting for the grant applicants, research team and Project Advisory Group at the beginning of the project, where we will describe the project and seek input into the protocol. During the project there will be 4 teleconferences to discuss the research evidence as it emerges, to discuss further research that should be undertaken by us for the project, and the interpretation of the results. At the end of the project there will be on further face to face meeting, where a draft of the final report will be discussed. All members of the Project Advisory Group will be invited to have authorship on the report. In particular, the Project Advisory Group will help ensure that the review is conducted in a systematic and transparent manner; check for over-interpretation of data; provide opinion on the credibility and plausibility of the thematic index and other emergent issues; and have the opportunity to provide sources of disconfirming data.

9. ETHICAL ARRANGEMENTS

Ethical approval is not required for this project.

AMENDMENT HISTORY

Amendment number	Protocol version number	Date issued	Author(s) of changes	Section(s) amended	Details of change(s)

15/09/04

REFERENCES

(1)National Institute for Health and Care Excellence. Obesity: identification, assessment and management of overweight and obesity in children, young people and adults. (Partial update of CG43). 2014. http://www.nice.org.uk/guidance/cg189

(2)National Institute for Health and Care Excellence. Managing overweight and obesity in adults—lifestyle weight management services. (Public Health Guideline PH53). 2014. http://www.nice.org.uk/guidance/PH53.

(3)Scottish Intercollegiate Guidelines Network. Management of obesity. Edinburgh; SIGN: 2010. http://www.sign.ac.uk/guidelines/fulltext/115/index.html

(4)Royal College of Surgeons. Commissioning guide: weight assessment and management clinics (tier 3), 2014. https://www.rcseng.ac.uk/healthcare-bodies/docs/weight-assessment-and-management-tier-3-services.

(5)Health and Social Care Information Centre. Health Survey for England – 2013, Health, social care and lifestyles. Leeds: Health and Social Care Information Centre; 2012. http://www.hscic.gov.uk/catalogue/PUB16076/HSE2013-Ch10-Adult-anth-meas.pdf

(6)Department of Health, Social Services and Public Safety. Health Survey Northern Ireland 2012-2013. The Northern Ireland Statistics and Research Agency, 2014.

(7)Scottish Health Survey 2013. http://www.gov.scot/Resource/0046/00464858.pdf http://www.gov.scot/Topics/Statistics/Browse/Health/scottish-health-survey/Publications/Supplementary2013

(8)Welsh Health Survey 2013. http://gov.wales/docs/statistics/2014/140930-welsh-health-survey-2013-en.pdf

(9)National Obesity Observatory. Obesity and ethnicity. Oxford: National Obesity Observatory; 2011. http://www.noo.org.uk/uploads/doc/vid_9444_Obesity_and_ethnicity_270111.pdf

(10)Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900,000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;373:1083-96.

(11)Grover SA, Kaouache M, Rempel P, Joseph L, Lau DC, Lowensteyn I. Years of life lost from diabetes and cardiovascular disease in overweight and obese people: a modelling study. Lancet Diabetes Endocrinol 2015;3:114–122

(12)Public Health England. Adult obesity and type 2 diabetes. Public Health England, 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/338934/Adult_obesity_and_type_2_diabetes_.pdf

(13)Reeves GK, Balkwill A, Cairns BJ, Green J, Beral V, for the Million Women Study Collaborators. Hospital admissions in relation to body mass index in UK women: a prospective cohort study. BMC Medicine 2014;12:45

(14)Korda RJ, Clements MS, Bauman AE, Jorm LR, Bambrick HJ, Banks E. Prospective cohort study of body mass index and the risk of hospitalisation: findings from 246,361 participants in the 445 and Up Study. Int J Obes 2013;37:790-9.

(15)Jia H, Lubetkin EI. The impact of obesity on health-related quality-of life in the general adult US population. J Public Health 2005;27:156-64.

(16)Scott KM, Bruffaerts R, Simon GE, Alonson J, Angermeyer M, de Girolamo G. Obesity and mental disorders in the general population: results from the world mental health surveys. Int J Obes 2008;32:192-200.

(17)Department of Health. Healthy lives, healthy people: a call to action on obesity in England. Department of Health, 2011.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213720/dh_130487.pdf

(18)Grieve E, Fenwick E, Yang HC, Lean M. The disproportionate economic burden associated with severe and complicated obesity: a systematic review. Obes Rev 2013;14:883-94.

(19)Dobbs R, Sawers C, Thompson F, Manyika J, Woetzel J, Child P, et al. Overcoming obesity: an initial economic analysis. McKinsey Global Institute, 2014.

(20)Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. Health Technol Assess 2004;8:21.

(21)Jensen MD, Ryan DH, Donato KA, Apovian CM, Ard JD, Comuzzie AG,et al. Guidelines (2013) for managing overweight and obesity in adults. Obesity 2014;22(S2):S1-S410.

(22)The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013. doi: 10.1056/NEJMoa1212914.

(23)The Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: The Look AHEAD Study. Obesity 2014;22:5-13.

(24)Unick JL, Beavers D, Bond DS, Clark JM, Jakicic JM, Kitabchi AE, et al. The long-term effectiveness of a lifestyle intervention in severely obese individuals. Am J Med 2013;126:236-42.

(25)The Look AHEAD Research Group. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol 2014;2:801-9.

(26)Lazo M, Solga SF, Horska A, Bonekamp S, Diehl AM, Brancati FL, et al. Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes. Diabetes Care 2010;33:2156-63.

(27)White DK, Neogi T, Rejeski WJ, Walkup MP, Lewis CE, Nevitt MC, et al. Can an intensive diet and exercise program prevent knee pain among overweight adults at high risk? Arthritis Care Res 2014. doi: 10.1002/acr.22544

(28)Rejeski WJ, Ip EH, Bertoni AG, Bray GA, Evans G, Gregg EW, et al. Lifestyle change and mobility in obese adults with type 2 diabetes. N Engl J Med 2012;366:1209-17.

(29)The Look AHEAD Research Group. Impact of intensive lifestyle intervention on depression and health-related quality of life in type 2 diabetes: the Look AHEAD Trial. Diabetes Care 2014;37:1544-53.

(30)Phelan S, Kanaya AM, Subak LL, Hogan PE, Espeland MA, Wing RR, et al. Weight loss prevents urinary incontinence in women with type 2 diabetes: results from the Look AHEAD Trial. J Urol 2012;187:939-44.

(31)Breyer BN, Phelan S, Hogan PE, Rosen RC, Kitabachi AE, Wing RR, et al. Intensive lifestyle intervention reduces urinary incontinence in overweight/obese men with type 2 diabetes: results from the Look AHEAD Trial. J Urol 2014;192:144-9.

(32)Wing RR, Rosen RC, Fava JL, Bahnson J, Brancati F, Gendrano IN, et al. Effects of weight loss intervention on erectile function in older men with type 2 diabetes in the Look AHEAD Trial. J Sex Med 2010;7:156-65.

(33)Kuna ST, Reboussin DM, Borradaile KE, Sanders MH, Millman RP, Zammit G, et al. long-term effect of weight loss on obstructive sleep apnea severity in obese patients with type 2 diabetes. Sleep 2013;36:641-9.

(34)Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012;308:2489-96.

(35)Espeland MA, Glick HA, Bertoni A, Brancati FL, Bray GA, Clark JM. Impact of an intensive lifestyle intervention on use and cost of medical services among overweight and obese adults with type 2 diabetes: the Action for Health in Diabetes. Diabetes Care 2014;37:2548-56.

(36)National Institute for Health and Clinical Excellence. Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. (Clinical Guideline CG43). 2006. http://www.nice.org.uk/guidance/cg43.

(37)Jagielski A, Leong WB, Thomas GN. Medical and behavioural weight management interventions for extreme obesity: a systematic review of systematic reviews. http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014012988#.VQlyY4lFCM8

(38)Azar K, Lv N. Lifestyle interventions for moderate and extreme obesity: a systematic review and meta-analysis. http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014012988#.VQl06YlFCM8B

(39)Tsai TG, Wadden TA. The evolution of very-low calorie diets: an update and meta-analysis. Obesity 2006;14:1283-93.

(40)Dietz WH, Baur LA, Hall K, Puhl RM, Taveras EM, Uauy R, et al. Obesity 5. Management of obesity: improvement of health-care training and systems for prevention and care. Lancet 2015 http://dx.doi.org/10.1016/S0140-6736(14)61748-7

(41)Department of Health, Obesity and Food Policy Branch. Developing a specification for lifestyle weight management services. Best practice guidance for tier 2 services. Department of Health, 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/142723/Weight_Management_Service_Spec_FINAL_with_IRB.pdf

(42)Royal College of Physicians. Action on obesity: comprehensive care for all. Royal College of Physicians, London: 2013.

(43)Stewart F, Avenell A. Lifestyle management interventions for severe obesity before and/or after bariatric surgery: a systematic review and meta-analysis. Obesity Surgery in press

(44)Blackshaw J, Montel S, King S, Jarvis A, Valabhji J. Report of the working group into: joined up clinical pathways for obesity. NHS England, 2014. http://www.england.nhs.uk/wp-content/uploads/2014/03/owg-join-clinc-path.pdf

(45)House of Commons Health Committee. Impact of physical activity and diet on health. London; The Stationery Office: 2015.
http://www.publications.parliament.uk/pa/cm201415/cmselect/cmhealth/845/845.pdf

(46)Robertson C, Archibald D, Avenell A, Douglas F, Hoddinott P, van Teijlingen E, et al. Systematic reviews of and integrated report on the quantitative, qualitative and economic evidence base for the management of obesity in men. Health Technol Assess 2014;13:35

(47)Hoffman TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ; 348:g1687.

(48)Michie S, Richardson M, Johnston M, Abraham, Francis J, Hardeman W, et al. The behavior change techniques taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behaviour change interventions. Ann Behav Med 2013;46:81-95.

(49)Cooke A, Smith D, Booth A. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. Qual Health Res 2012:22;1435-43.

(50)Booth, A. Searching where there is light? – in defence of 'supplementary' search methods. NICE Joint Information Day, London 13 February 2013.

(51)Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

(52)Ueffing E, Tugwell P, Welch V, Petticrew M, Kristjansson E, Campbell Equity Methods Group. Equity checklist for systematic review authors. Version 2011–11–08.
The Cochrane Collaboration: Cochrane and Campbell Equity Methods Group; 2011.
http://equity.cochrane.org/sites/equity.cochrane.org/files/uploads/Equity%20Checklist%20for%20Systematic%20Review%20Authors%20-%202011–11–08.doc

(53)Wagner GJ, Kanouse DE. Assessing usual care in clinical trials of adherence interventions for highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2003;33:276-7.

(54)de Bruin M, Viechtbauer W, Schaalma HP, Kok G, Abraham C, Hospers HJ. Standard care impact on effects of highly active antiretroviral therapy adherence interventions. A meta-analysis of randomized controlled trials. Arch Intern Med 2010;170:240-50.

(55)de Bruin M, Viechtbauer W, Hospers HJ, Schaalma HP, Kok G. Standard care quality determines treatment outcomes in control groups of HAART-adherence intervention studies: implications for the interpretation and comparison of intervention effects. Health Psychol 2009;28:668-74.

(56)Bishop FL, Fenge-Davies AL, Kirby S, Geraghty AW. Context effects and behaviour change techniques in randomised trials: a systematic review using the example of trials to increase adherence to physical activity in musculoskeletal pain. Psychol Health 2015;30:104-21.

(57)Waters L, St George A, Chey T, Baurman A. Weight change in control group participants in behavioural weight loss interventions: a systematic review and meta-regression study. BMC Med Res Methodol 2012;12:120.

(58)Kaiser KA, Affuso O, Beasley TM, Allison DB. Getting carried away: a note showing baseline observation carried forward (BOCF) results can be calculated from published complete-cases results. Int J Obes 2012;36:886-9.

(59)Barnett-Page E, Thomas J. Methods for the synthesis of qualitative research: A critical review. BMC Med Res Methodol 2009;9:59.

(60)Spencer L, Ritchie J, Lewis J, Dillon L. Quality in qualitative evaluation: a framework for assessing research evidence. London, Cabinet Office: 2003.

(61)Pawson R. Evidence-based policy: a realist perspective. London; Sage: 2006.

(62)Dixon-Woods M, Sutton A, Shaw R, Miller T, Smith J, Young B, et al. Appraising qualitative research for inclusion in systematic reviews: a quantitative and qualitative comparison of three methods. J Health Serv Res Policy 2007;12:42–7.

(63)Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Meth 2008;8:45.

(64)Harden A, Brunton G, Fletcher A, Oakley A. Teenage pregnancy and social disadvantage: systematic review integrating controlled trials and qualitative studies. BMJ 2009;339:b4254

(65)Strauss A, Corbin J. Grounded theory methodology: an overview. In: Denzin NK, Lincoln YS, eds. Handbook of qualitative research. 3rd ed. Sage, California; Thousand Oaks: 1994.

(66)EPPI-Centre. EPPI-Centre methods for conducting systematic reviews. London; EPPI-Centre, Social Science Research Unit, Institute of Education University of London: 2007.

(67)Toye F, Seers K, Allcock N, Briggs M, Carr E, Andrews JA, Barker K. 'Trying to pin down jelly' - exploring intuitive processes in quality assessment for meta-ethnography. BMC Medical Research Methodology 2013;13:4

(68)McPherson K, March T, Brown M. Foresight, tackling obesities, future choices – modelling future trends in obesity and the impact on health. Government Office for Science, 2007. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/295149/07-1662-obesity-modelling-trends.pdf

(69)Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ 2013;346:f1049 doi: 10.1136/bmj.f1049

(70)Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2004;8:36.

(71)Pope K, Mays N, Popay J. Synthesising qualitative and quantitative health evidence. Berkshire, England; Open University Press: 2007.

(72)Butland B, Jebb S, Kopelman P, McPherson K, Thomas S, Mardell J, et al. Foresight. Tackling Obesities: Future Choices - Project Report 2nd edition [document on the Internet]. London: Government Office for Science; 2007. http://www.bis.gov.uk/assets/foresight/docs/obesity/17.pdf.

(73)Hanlon P, Carlisle S, Hannah M, Lyon A, Reilly D. A perspective on the future public health: an integrative and ecological framework. Perspect Public Health 2012;132:313-9.

(74)Swinburn B, Egger G, Raza F. Dissecting obesogenic environments: the development and application of a framework for identifying and prioritizing environmental interventions for obesity. Prev Med 1999;29:563-70.

(75)Whitehead M, Dahlgren G. What can be done about inequalities in health? Lancet 1991;338:1059-63.

(76)Rayner G, Lang T. Ecological public health: Reshaping the conditions of good health. London: Routledge; 2012.

(77)McLeroy KR, Bibeau D, Steckler A, Glanz K. An ecological perspective on health promotion programs. Health Educ Q 1988;15:351-77.

(78)Stokols D. Translating social ecological theory into guidelines for community health promotion. Am J Health Promot 1996;10:282-98.

(79)Men's Health Forum and Public Health England. How to make weight loss services work for men. https://www.menshealthforum.org.uk/sites/default/files/pdf/how_to_weight_final_lr_1.pdf

(80)Public Health England. Making the case for tackling obesity – why invest? Public Health England publications, 2015. https://www.noo.org.uk/securefiles/150414_1230//Making_the_case_for_tackling_obesity_reference_sheet_factsheet.pdf

(81)Scarborough P, Bhatnagar P, Wickramasinghe KK, Allender S, Foster C, Rayner M. The economic burden of ill health due to diet, physical activity, smoking, alcohol and obesity in the UK: an update to 2006-07 NHS costs. J Public Health (Oxf) 2011;33:527-35.

(82)Jagielski A, Leong W, Thomas GN. Medical and behavioural weight management interventions for extreme obesity. http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014010473

(83)Welbourn R, Dixon J, Barth JH, Finer N, Hughes CA, le Roux C, Wass J, on behalf of the Guidance Development Group. NICE-accredited commissioning guidance for weight assessment and management clinics: a model for a specialist multidisciplinary team approach for people with severe obesity. Obes Surg 2016 DOI 10.1007/s11695-015-2041-8.

(84)Public Health England. National mapping of weight management services. Public Health England, 2015.https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/484115/Final_Weight_Management_Mapping_Report.pdf

(85)Parretti HM, Jebb SA, Johns DJ, Lewis AL, Christian-Brown AM, Aveyard P. Clinical effectiveness of very-low energy diets in the management of weight loss: a systematic review and meta-analysis of randomized controlled trials. Obes Rev 2016 doi: 10.1111/obr.12366