Cost-effectiveness of different levels of uptake of bariatric surgery in a large population: Cohort Study and Markov Model

Summary of Research

There has been a rapid increase in severe and morbid obesity in England. The use of surgical procedures to promote weight loss, referred to as bariatric surgery (BS), has emerged as a remarkably effective intervention for severe and morbid obesity. Surgery may result in substantial weight loss, maintained over 10 years, as well as lower incidence of comorbidity and reduced mortality. NICE has recommended that BS may be considered for individuals with body mass index (BMI) ≥40 Kg/m^2 or with BMI 35-39 Kg/m^2 and comorbidities that have not responded to medical care. Recently the International Diabetes Federation (IDF) has recommended that BS should be considered standard treatment for individuals with diabetes and BMI 35-39 Kg/m^2, or when BMI is 30-34 Kg/m^2 and diabetes is unresponsive to medical therapy. In England about 8,000 bariatric surgical procedures are performed each year, but many more are potentially eligible. The research asks to what extent a publicly-funded health care system, such as the NHS, should facilitate access to bariatric surgery? The research aims to estimate the comparative cost-effectiveness of different levels of uptake of bariatric surgery in a large population of obese individuals.

The incremental costs and health benefits of different intervention strategies will be estimated by means of a probabilistic Markov model. Simulation using the model offers a technique that will facilitate estimation of the potential long-term outcomes of different levels of uptake of bariatric surgery within a time-scale that is relevant for commissioners, service providers and users. The Model will include states for diabetes, heart disease, stroke, obesity-related cancer, depression, asthma, and back and joint pain. Empirical data inputs to the model will be provided through analysis of data for a large obese population registered in primary care, derived from the CPRD (Clinical Practice Research Datalink). Estimates for the clinical effectiveness of bariatric surgery will be derived from updated systematic reviews.

The research will specifically evaluate three intervention strategies: i) expanding access within existing recognised indications for bariatric surgery as defined by NICE; ii) expanding access by extending the range of indications for bariatric surgery as proposed by the IDF; iii) expanding access with a focus on the distributional consequences of different intervention strategies. This may include facilitating access for specific age-groups, deprivation categories or giving priority on the basis of gender. The primary outcome will be incremental Quality Adjusted Life Years, after taking into account the incremental costs of intervention, as Net Health Benefit. Secondary outcomes will be life years with long-term conditions and symptomatic states. Input from patients and the public will be obtained to compare the model outputs against people's actual experiences of accessing care. Outputs from the project will inform decision-makers and stakeholders of the anticipated costs and health outcomes of different strategies for facilitating access to BS. Main findings will be disseminated through workshops, seminars and conferences as well as through project reports and peer-review publications. The research will produce a methodological approach that can be used to evaluate other clinical and public health interventions for obesity.

Background and Rationale

Overweight and obesity are increasing rapidly in many high- and middle-income countries and obesity is second to smoking as a leading cause of preventable death globally. In England, the proportion of adults that are overweight or obese has increased from 52.9% in 1993 to 62.8% in 2010, while obesity has increased from 14.9% to 26.1% of adults over the same period.[1] Cardiovascular mortality is declining, and life expectancy is increasing, but these favourable trends are threatened by the increase in obesity and diabetes.

Individuals with obesity are classified as having severe obesity when the body mass index (BMI) is 35-39 Kg/m^2 and morbid obesity when the BMI is ≥40 Kg/m^2. The increase in severe and morbid obesity in England has been extremely rapid. From 1993 to 2010, morbid obesity increased eightfold from 0.2% to 1.6% of all men, and nearly tripled from 1.4% to 3.8% of all women.[1]

Obesity is associated with a wide range of negative health consequences and these risks increase with increasing BMI. Severe and morbid obesity are independently associated with increased incidence of long-term conditions including type 2 diabetes mellitus, cardiovascular diseases, and several types of cancer.[2] In the UK, obesity may account for 4% of all cancers in men (including 27% of oesophageal cancer and 25% of kidney cancer) and 7% of cancers in women including (9% of breast cancers and 34% of endometrial cancers).[3] Symptomatic conditions associated with obesity include asthma, joint problems, back pain and depressive symptoms.[2] Obesity is associated with states of elevated risk and pre-disease including hypertension and hyperlipidaemia.[2] Morbidity generally begins at younger ages in obese people and multiple morbidity becomes frequent as the condition progresses.

Severe and morbid obesity are associated with substantial increases in health care utilisation and costs related to the management of obesity and associated comorbidities. For example, type 2 diabetes is strongly associated with obesity; the health care costs of diabetes alone are estimated to be about £14 billion per year in the UK. Obesity is associated with more sickness absence from work contributing to substantial indirect costs through productivity losses.[4] The Office for Health Economics estimated that wider use of obesity surgery may give economic benefits through reduced welfare payments and additional paid work.[5]

The impacts of obesity are unequally distributed being more frequent in women and lower socioeconomic groups, contributing to inequalities in health.[6]

Given the negative impact of severe and morbid obesity on health and health care costs, weight loss has been proposed to lead to important health and economic benefits. The use of surgical procedures to promote weight loss is referred to as 'bariatric surgery' (BS). Bariatric surgery (BS) has emerged as a remarkably effective intervention for severe and morbid obesity. Surgery may result in loss of 20% of body weight by two years,[7,8] with substantial weight loss maintained over 10 years.[9] Surgery is associated with lower incidence of comorbidity compared with non-surgical management,[10] and mortality is reduced.[9] Overall, the benefits of BS are judged to outweigh the risk of immediate and longer-term complications associated with the procedure, and BS is judged to have acceptable cost-effectiveness. Interventions that do not include surgery generally have very limited impact on the body weight of people with severe or morbid obesity.[11]

In spite of the considerable evidence of clinical effectiveness, only about 8,000 bariatric surgery procedures were implemented in the National Health Service (NHS) in England in 2010/11, with 75% of these in women. [12-14] These may account for about 0.5% of persons with morbid obesity. Operation rates vary widely among English regions and there is also significant uptake of surgery in the private sector.[13]

The prevention and control of obesity is a complex problem that requires population-wide intervention across multiple sectors of the economy and society. This proposal acknowledges that the social, economic and individual lifestyle determinants of obesity require addressing through wider public health strategies. Nevertheless, people with severe and morbid obesity share the right of all individuals to the highest attainable standard of health.[15] The burden of long-term conditions resulting from severe and morbid obesity has great importance for health services, and consequently for all members of society.

This proposal concerns the appropriate use of bariatric surgery in the management of individuals with severe and morbid obesity. The research asks to what extent a publicly-funded health care system, such as the NHS, should facilitate access to bariatric surgery? Given the substantial immediate and short-term costs of BS, what are the impacts of different levels of BS activity on health care costs and health outcomes across the population at risk, and how are costs and benefits distributed over time? Answering these questions requires consideration of the effects of different levels of access or uptake of bariatric surgery in the population at risk. This research will provide policy-makers and commissioners of services with evidence on the potential cost-effectiveness of different levels of uptake of bariatric surgery in the population at risk.

Evidence explaining why this research is needed now

The term bariatric surgery (BS) refers to surgical procedures that are designed to promote weight loss in obese individuals. A number of different BS procedures are in current use, these have traditionally been classified as 'restrictive', 'malabsorptive' or 'mixed' procedures. Restrictive procedures reduce gastric volume, leading to reduced dietary intakes. The most frequently performed procedure is laparoscopic adjustable gastric banding (LAGB). This is associated with fewer complications than more invasive procedures, but also has a smaller effect on body weight. The Roux-en-Y gastric bypass operation employs a mixed approach, with the creation of a reduced stomach pouch connected to the distal small intestine. The gastric bypass procedure generally has a greater effect on body weight, but carries a greater risk of short- and long-term complications than a restrictive procedure. In the US, gastric by-pass accounts for half to two thirds of procedures, while in Europe LABG generally accounts for a half to two thirds of procedures.[16] However, the use of sleeve gastrectomy has been increasing and now makes up 40% of operations at some UK centres (M Reddy, personal communication). In common, with previous reports[14,12] this research will initially treat BS as a single group of procedures. However, in later analyses differences in the effectiveness, adverse effects and costs of different procedures will be incorporated into the model. BS is associated with significant operative mortality and long term morbidity (for example, internal hernia following gastric bypass or gastric band slippage) and these will be factored into the cost-effectiveness model (Table 1).

Several systematic reviews have already reported on the effectiveness of weight-management interventions from the perspective of the individual obese patient. The effectiveness of non-surgical weight management programmes was reviewed by Loveman et al.[11] who concluded that weight loss was generally very limited, and weight regain usual. This review will be important for this research in providing a comparator for surgical intervention. The clinical and cost-effectiveness of bariatric surgery were systematically reviewed for the NIHR HTA Programme by Picot et al.[17]. An earlier review was completed for the National Institute for Health and Clinical Excellence (NICE) for the 2006 guideline on obesity management.[18] Other reviews have evaluated the effects of bariatric surgery on specific clinical end-points, including diabetes[16] and cardiovascular risk[19], with several narrative reviews being reported.[20-22] Together these reviews are important in providing estimates of the clinical effectiveness of bariatric surgery for this research. A selective summary of the major findings is given in Table 1.

Picot et al. found that bariatric surgery was effective at reducing body weight in morbid obesity.[17] The review included two randomised controlled trials[7,8], which demonstrated loss of body weight of 20% or greater at two years following surgery, compared with 1.4% to 5.5% in non-surgical obesity treatment. The Swedish Obese Subjects cohort study, with matched controls, showed that weight loss may be maintained for at least 10 years following bariatric surgery, while weight gain is generally observed following non-surgical

management.[9] However, the benefits of bariatric surgery are not restricted to weight loss. After BS, there is a lower incidence of diabetes, cardiovascular disease and cancer, mortality is reduced, as are symptoms of depression, asthma and joint problems, with quality of life being improved (please see table 1 for more information). Resolution of comorbidity may be more relevant to health care costs than weight loss, and is not always directly associated with weight loss. After gastric bypass surgery there is a high rate of early resolution of diabetes which may precede maximal weight loss.

Table 1: Selected examples of the evidence of clinical and cost-effectiveness of bariatric surgery (BS).

Measure	Effect of bariatric surgery (BS)
Weight change	Compared with non-surgical treatment, BS gave weight loss of 20Kg at 2 years[17,7] and a BMI reduction of 6.7 Kg/m^2 at 10 years.[9]
Clinical diabetes mellitus	The incidence of diabetes is lower for up to 15 years after BS (HR=0.17)[23]. In diabetes, the proportion achieving good blood glucose control is 30% higher at 12 months after BS, compared with intensive medical therapy[24,16]; 60% more patients achieve remission of diabetes at 2 years (RR=5.5)[7,16]
Cardiovascular (CVD) risk	BS associated with reduced systolic and diastolic blood pressure, lower LDL-cholesterol and higher HDL cholesterol at 6[25] or 10 years with sustained weight loss.[26]
Cardiovascular (CVD) events	BS associated with fewer fatal or non-fatal first CVD events (myocardial infarctions and strokes) (HR=0.67) and fewer CVD deaths over 14.7 years (HR=0.47) [27]
Cancer incidence	Up to 18 years following BS, there are fewer first cancer diagnoses (HR=0.67), but the reduction may only be in women and not men[28]
Mortality	All-cause mortality reduced up to 15 years after BS (adjusted HR=0.71). Deaths from CVD and cancer were lower after BS, there was a small increase in mortality within 90 days of BS (see below).[9]
Other comorbidity	Includes relative reductions in symptoms from depression (55%), degenerative joint disease (41% to 76%) and asthma (82%).[22]
Quality of Life (QoL)	BS associated with higher SF-36 scores at six years[29] and better scores on a battery of QoL measures over 10 years.[30]
Adverse effects of surgery	Peri-operative mortality of BS may be approximately 0.04 to 0.5%.[31,16] Major complications within 30 days may occur in about 1% of LAGB procedures but up to 8% of gastric bypass procedures[31,16] depending on quality of care.[32] Between 5 and 15% may experience significant morbidity at one year.[16]
Health care utilization	Hospital inpatient stays and outpatient visits are higher for the first 6 years after BS but are then similar to controls. Drug prescription costs were lower from six years after BS.[33]

HR, hazard ratio; RR, relative risk.

Bariatric surgery is more costly than non-surgical management of obesity.[17] Ackroyd[34] reported incremental costs of +£2000 per participant over the first five years. This highlights a concern for policy-makers, that the health care costs of surgical intervention are generally immediate or short-term while gains, in terms of health benefits and costs, are delayed. There

is only low to moderate probability that surgery is cost-effective within two years, but over a 20-year time horizon, there is a very high probability that bariatric surgery will prove cost-effective at thresholds of £20,000 or £30,000 per Quality Adjusted Life Year (QALY).[17,34] The value of estimates varies in different health care systems and according to the type of surgical procedure and duration of follow-up. However, while a range of estimates have been produced by different studies,[4] there is a consensus that BS will generally by cost-effective in the treatment of individuals with severe or morbid obesity. An Office for Health Economics [5] model reported that economic impacts were appreciable when indirect costs including estimated hours worked and welfare benefits were considered.

Adverse effects of bariatric surgery

The mortality rate associated with gastric bypass surgery is approximately 0.5%. In addition, there are longer-term morbidity concerns associated with bariatric operations. Gastric banding is associated with a significant risk of erosion and band slippage rate; gastric bypass patients can represent with internal hernias. Patients who have received bariatric surgery require long-term monitoring and this has significant cost implications.

Criteria for selection for Bariatric Surgery

The increasing evidence for the clinical and cost-effectiveness of BS raises questions concerning the selection of patients for surgery.

The UK National Institute for Health and Clinical Excellence,[18] in its guidelines on obesity, recommended that bariatric surgery should be considered for individuals who have: i) a BMI ≥40 Kg/m2, or ii) for individuals with BMI 35-40 Kg/m if comorbidities that could be improved through weight loss were present, and iii) if non-surgical management has not achieved sufficient weight loss over 6 months, the individual is committed to long-term follow-up, is fit for surgery and can be treated in a specialist surgical service.

Presently, access to BS in the United Kingdom is quite restricted, although use of BS procedures is increasing. Based on the age-specific prevalence for morbid obesity reported in the Health Survey for England[1], there were approximately 336,000 men and 806,000 women with morbid obesity alone in England in 2010, of whom 303,000 men and 676,000 women were aged 25 to 74 years. Approximately, 8,000 procedures for obesity are implemented annually in England,[13] accounting for about 0.5% of morbidly obese individuals. This contrasts with about 28,000 coronary artery by-pass grafts performed annually. Based on a combination of epidemiological data, current clinical practice, and expert opinion, 2007 NICE guidance suggested a population benchmark rate for bariatric surgical procedures, to be achieved in five years' time, of 0.01% of the general population per year.[35] This implies that only a small minority of people with severe or morbid obesity would receive BS. However, the long-term costs and outcomes of deploying bariatric surgery across the population at the rate suggested by NICE, or other rates, are not known.

The International Diabetes Federation (IDF) has recently challenged prevailing thinking by advancing a more liberal approach to the use of BS in relation to diabetes. A recent IDF position statement[36] recommends that: i) ' Surgery should be an accepted option in people who have type 2 diabetes and a BMI of 35 or more'; ii) 'Surgery should be considered as an alternative treatment option in patients with a BMI between 30 and 35 when diabetes cannot be adequately controlled by optimal medical regimen, especially in the presence of other major cardiovascular disease risk factors'. [36] This position statement proposes a significant expansion in the criteria for utilization of BS, specifically for people who have both diabetes and obesity.

At the population level, the role of surgery in the treatment of obesity will depend on the costs and health benefits achieved at different levels of uptake of bariatric surgery in the population at risk. Thus a population strategy for bariatric surgery should consider the benefits, harms and costs that accrue both to those that do not receive surgery, as well as those that do. This requires consideration of the impact of intervention on the prevalence of different categories of obesity, the occurrence of morbidity and mortality and the impact on the quality and duration of life in relation to the expenditure of health care resources. The societal distribution of outcomes and costs in terms of inequalities in health must also be considered. Groups that live in conditions of social and material deprivation have a higher prevalence of morbid obesity, especially in women, as well as higher mortality and shorter healthy life-expectancy. This suggests that obesity surgery is likely to be more cost-effective in lower socioeconomic groups or in areas of greater deprivation.

We acknowledge that the private sector plays a significant role in the delivery of bariatric surgery. According to the National Bariatric Surgical Registry, approximately a third of the operations registered were done in the private sector. However, clinical experience suggests that many of the bariatric operations performed in the private sector are for patients who do not meet present NICE criteria. These procedures may be performed for cosmetic and functional reasons, rather than to reduce morbidity or increase lifespan. We plan to include only those private sector operations which fulfil the selection criteria discussed above.

This proposed research will estimate the potential population health outcomes and cost-effectiveness of different levels of uptake of bariatric surgery. The research will contribute to an evidence informed policy on utilisation of bariatric surgery in a population, such as England, that has a high prevalence of severe and morbid obesity.

Aims and Objectives

Bariatric surgery is a very effective treatment for severe and morbid obesity but is not widely utilised in the population at risk although, for the individual obese patient, intervention with BS is cost-effective. There is considerable unmet need with more than one million individuals potentially eligible in England but only about 8,000 bariatric surgery procedures per year. Research to date has not yet addressed the question of what level of bariatric surgery intervention should be delivered to the population at risk. In other words, to what extent should the NHS facilitate access to bariatric surgery, and for whom?

The aim of this proposed research is to answer the service delivery question: What is the comparative cost-effectiveness of different levels of uptake of bariatric surgery in a population with a high prevalence of severe and morbid obesity?

Specific objectives

The research will specifically evaluate the cost-effectiveness of three intervention strategies: i) expanding access within existing recognised indications for bariatric surgery as defined by NICE; ii) expanding access by extending the range of recognised indications for bariatric surgery as proposed by the IDF; iii) expanding access with a focus on the distributional consequences of different intervention strategies. The research will also evaluate how health outcomes and costs are distributed by gender, age group and among socioeconomic groups, thus evaluating the potential impacts on inequalities in health related to obesity. While we acknowledge that there are ethnic differences in obesity and risk of diabetes, these are not considered in this research because use of ethnicity as a criterion for selection poses ethical issues (as well as practical concerns of data availability and quality) that are beyond the scope of this project.

Interventions

For the purpose of this research, bariatric surgery will be defined as the use of surgical procedures, in obese individuals, for the purpose of achieving weight loss. Three main groups of bariatric surgical procedures will be considered:

i) Gastric Banding;
ii) Gastric bypass;
iii) Sleeve gastrectomy.

Although there are more recently developed bariatric procedures, such as endoscopic plication and endosleeve, these should be regarded as experimental and unproven techniques at present. These are not funded in the National Health Service at present and in the absence of any long term effectiveness data on these techniques, we will focus on the three operations outlined above as representing a 'gold standard'.

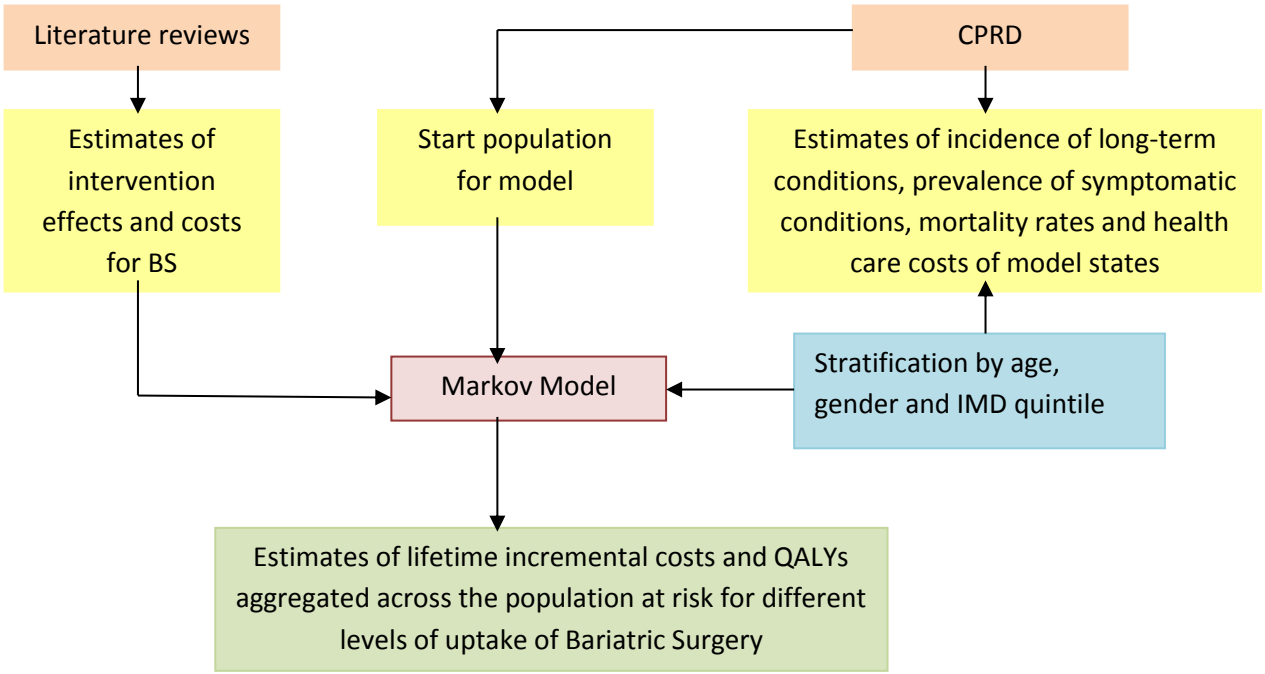
Initially, bariatric surgical procedures will be considered as a single group. Subsequently, we will model patterns of utilisation of the three main bariatric surgical procedures taking into account their different outcomes, costs and immediate and long-term complications.

Main measures and anticipated outputs

The primary health outcome of interest will be Quality Adjusted Life Years (QALYs). Secondary health outcomes will be the prevalence of severe or morbid obesity; number of person years lived with long term conditions (including diabetes mellitus, heart disease, stroke and obesity-related cancers); and the number of life years lived with symptomatic conditions (including depression, asthma and joint and back pain). Health care utilization and health care costs will also be estimated. The Net Health Benefit (in QALYs) will be estimated as the primary measure of interest for each intervention strategy. Results will be reported as rates per 1,000 obese persons entering the model.

The outputs from the research will provide those responsible for commissioning and organising surgical services, as well as patients and the public, with evidence to inform policies on the utilisation of bariatric surgery for populations in which severe and morbid obesity are frequent.

Figure 1: Schematic diagram outlining research. BS, bariatric surgery; CPRD, Clinical Practice Research Datalink; IMD, indices of multiple deprivation.



Research Plans / Methods

Design and conceptual framework
The overall design of the research is outlined in Figure 1. A Markov Model will be constructed and populated with empirical data drawn from a primary care database. Estimates of intervention effectiveness will be drawn from up-to-date systematic literature reviews. Simulations run using the Model will provide estimates of lifetime incremental costs and QALYs aggregated across the population at risk for different levels of uptake of bariatric surgery.

This research recognises that rigorous evidence concerning the outcomes of bariatric surgery will ideally be obtained from systematic reviews of randomised controlled trials. Evidence concerning the clinical and cost-effectiveness of bariatric surgery, as a treatment for individuals with morbid obesity, has been reviewed for NICE, as well as the NIHR HTA Programme. This evidence will inform the present research.

This project aims to evaluate the extent to which the NHS, as a publicly funded health care system, would be justified in facilitating increased access to bariatric surgery. There are several potential options for increasing access but three approaches will be distinguished for this research as outlined above: i) expanding access within existing recognised indications for bariatric surgery; ii) expanding access by extending the range of recognised indications for bariatric surgery; iii) expanding access with a focus on distributional considerations, as well as on aggregate benefits across the whole population. This approach will focus on the potential of bariatric surgery to reduce inequalities in health. This may include facilitating access for specific population groups, who meet existing recognised indications for bariatric surgery, but in whom greater health benefits may be expected. This may include facilitating access for specific age-groups, socioeconomic groups or giving priority on the basis of gender.

It might be argued that research has shown that BS has acceptable cost-effectiveness for the management of obese individuals and should therefore be made readily available. However, the impact of BS on the population with obesity needs to be more clearly understood. What will be implications of different implementation strategies on BS activity (number of procedures), on the prevalence of severe and morbid obesity and associated comorbidities, and on overall health status, mortality and health care costs? This research will provide an in-depth analysis of these questions.

The research will take the perspective of the National Health Service. Health service costs will be included. Wider societal costs, including changes in productivity, which are hard to estimate precisely, will not be included. The research will adopt a lifetime time horizon. However, the distribution of discounted incremental costs and benefits over time will be specifically evaluated.

The primary outcome will be Quality Adjusted Life Years, after taking into account the incremental costs of intervention. Some simulations may be associated with negative incremental costs (where the intervention is cost-saving) or negative incremental QALYs (as when standard care dominates), Net Health Benefits[37] will therefore be estimated as:

$$\text{Net Health Benefit} = \text{Incremental QALYs} - (\text{Incremental Costs}/\text{Threshold})$$

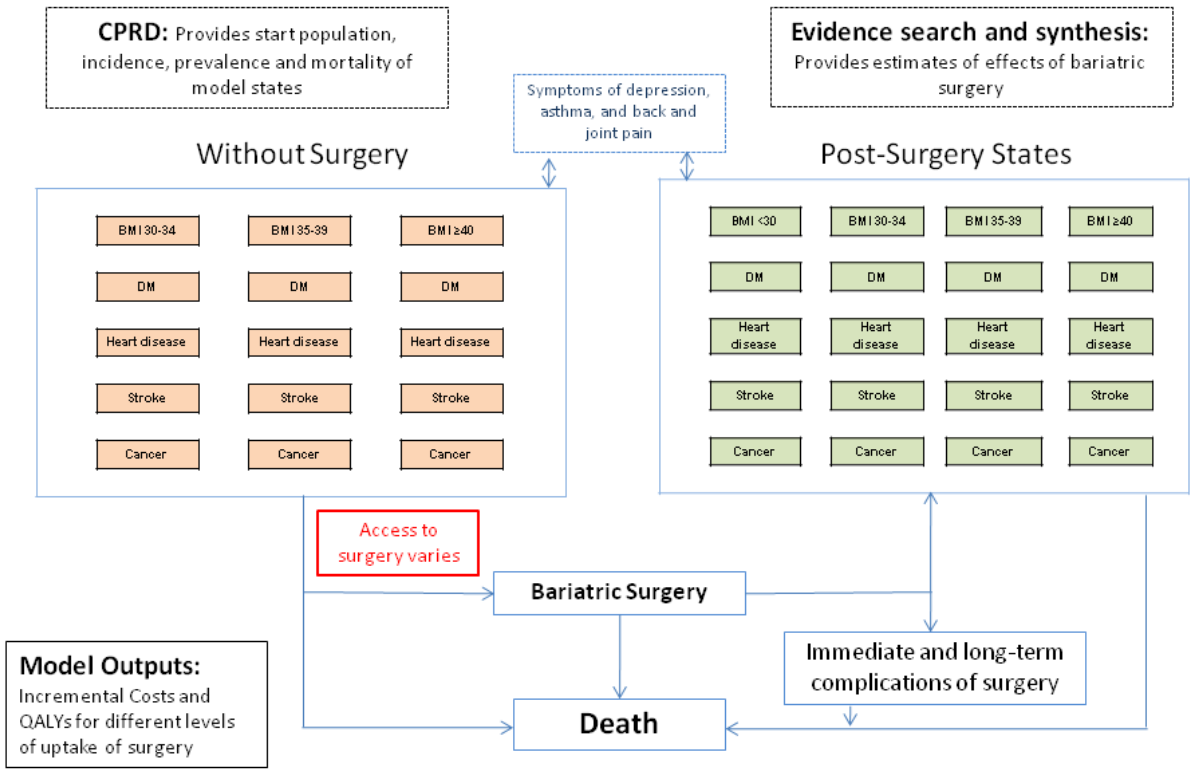
where the Threshold is the maximal acceptable value of cost per QALY, in the UK this is often taken as £30,000 per QALY. Cost-effectiveness acceptability curves will also be constructed using a range of values for the Threshold.

The incremental costs and health benefits of different intervention strategies will be estimated by means of a probabilistic Markov simulation model. Simulation offers a technique that will facilitate estimation of the potential long-term outcomes of different levels of uptake of bariatric surgery within a time-scale that is relevant for commissioners, service providers and users. Extensive sensitivity analyses will be implemented so that users of the research can be provided with a clear understanding of the potential consequences of varying key assumptions.

Empirical data inputs to the model will be provided through analysis of data for a large population registered in primary care, derived from the CPRD (Clinical Practice Research Datalink, formerly known as General Practice Research Database (GPRD)). Estimates for the clinical effectiveness of bariatric surgery will be derived from updated systematic reviews.

Work leading up to this proposal
The research will benefit from the methods developed for a research project implemented for the National Prevention Research Initiative (NPRI, phase 3) that has already developed a Markov model that can be adapted for this research (manuscript submitted for publication). The research will be informed by knowledge derived from the PhD project of Helen Booth who is studying the evolution of obesity and comorbidity in CPRD.[38] The research will also benefit from synergies with the NIHR Biomedical Research Centre (BRC) at Guy's and St Thomas' Hospital. The Principal Investigator is a member of the BRC Population Cluster board and the BRC's Faculty of Translational Medicine, he leads the epidemiology and evaluation theme for the Population Cluster. The BRC will facilitate patient and public involvement in the project. The BRC is also facilitating online access to CPRD at King's College London.

Figure 2: Simplified schematic diagram of Markov Model.



BMI, body mass index; CPRD, Clinical Practice Research Datalink; DM, diabetes mellitus; QALY, quality adjusted life year.

Outline of Markov Model

Figure 2 provides an outline of the Markov Model. In order to simplify the diagram not all states, or transitions between states, are represented. The model structure is informed by previously reported research,[39] it will be developed from a Model already programmed for NPRI. The Model will be run separately for men and women and, in analyses for the third objective, by IMD deprivation quintile.

BMI categories
The model will include states for obese participants, divided into BMI categories. Initially, categories will include 'obese' (BMI 30-34 Kg/m^2), 'severe obesity' (BMI 35-39) and 'morbid obesity' (BMI ≥40). Transitions between obesity categories over time will be estimated from data for the CPRD cohort. However, the application of published equations relating BMI to age, derived from epidemiological studies, will also be explored.[40] Stratification by BMI category will be extended throughout the model.

Long-term conditions
Long-term conditions associated with obesity will include, as a minimum, 'diabetes', 'non-valvular heart disease', 'stroke' and 'obesity associated cancer' (defined separately for men and women). States that include two, three or four of these long-term conditions will be included in the model, consistent with the frequent occurrence of multiple morbidity in obese people, and the known progression of diabetes to cardiovascular endpoints. We have noted that health care costs are strongly associated with the number of long-term conditions in CPRD, therefore this aspect of the patient pathway is important for its cost-effectiveness implications.[41] However, at each level of morbidity, the different long term conditions will remain as separate identifiable states. This is important because the IDF strategy specifically focuses on clinical diabetes as a selection criterion for bariatric surgery. Transition probabilities associated with long-term conditions will be estimated from CPRD data by 10 year age group and sex.

Symptomatic states
'Depression', 'asthma' and 'back and joint pain' will be included as symptomatic states. The rationale for treating these states differently from the long-term conditions is that these may relapse and remit over time, with varying impact on well-being and health care costs. We have already included 'depression' in our NPRI model.[41] For this research, 'asthma' and 'back and joint pain' will be included in the design of the model because of their strong association with BMI. The proportion with one, two or three symptomatic states will be recalculated in each annual cycle, based on transition probabilities drawn from empirical estimates from CPRD. Each symptomatic state will be associated with its own decrement in utility and increment in health care costs.

Bariatric surgery and introduction of intervention effects
The model will be used to simulate the long-term outcomes of different levels of uptake of bariatric surgery when deployed into the base population sampled from CPRD. In order to achieve this, there will be a varying probability that eligible participants will transition into a bariatric surgery state lasting one year and subsequently into post-bariatric surgery states. Post-bariatric surgery states will be counterparts of the states occupied by participants who did not receive surgery. However, post-surgery states will be associated with excess costs of health care utilization associated with surgery. Transitions between BMI categories will also be modified following surgery in order to reflect the reduction in BMI observed following surgery. Transitions into long-term conditions and symptomatic states will also be modified following surgery, consistent with the benefits of surgery on these health measures. Intervention effects will be introduced into the model as (log) relative risks, which will be derived from systematic reviews. Post-operative mortality and morbidity will be included in the Model.

Adverse effects of surgery
The adverse effects of surgery will also be introduced into the Model using several different techniques. The excess mortality associated with surgery will be modelled through transitions into the 'dead' state. Transition probabilities will be modelled based on reported estimates for mortality following bariatric surgery. There will be finite increases in mortality transitions both in the year of operation, reflecting operative mortality, as well as in subsequent post-operative years, representing long term hazards of surgery. Costs of health care utilisation will be increased following bariatric surgery representing in part the additional costs of treating immediate and long-term complications of bariatric surgery. There will also be defined states in the model that represent long-term complications following surgery, with transitions into these states defined from reports of complications following bariatric surgery.

Role of the private sector
The role of the private sector will be included in the model. Use of the private sector, enables patients to gain access to the benefits and harms of bariatric surgery, but the immediate costs of surgery are borne by individuals, families and insurers. There may be benefits to the NHS in terms of reduced costs of surgery, but the longer term costs incurred by BS patients may be undiminished. The Model will allow a variable proportion of patients to transition into surgery via private providers. The Bariatric Surgery Register will provide information that will allow us to model private sector activity.

Model progression
As the cohort progresses through the model, participants may progress to another BMI category and may develop one or more long-term conditions. In any state, there will be variable proportion that transition to a symptomatic state. Participants will age one year per cycle, and the model will continue until all participants have either died or reached age 100. The model will be fully probabilistic and programmed in R software. The final design of the model must balance both computational simplicity and the complexity of processes of disease progression. We recognise that the proposed form of the model is moderately complex but we have experience of programming a similar model through our research for NPRI. We acknowledge that some modest further simplification may be required for implementation.

Setting and Data Source
The setting for the study will be the general population with obesity, aged 20 years and over, in the United Kingdom. The registered population of the CPRD will be used to represent the target population for the study. Since only CPRD practices in England provide linked IMD 2010 deprivation scores at individual participant postcode level, data analyses will be based on patients registered with CPRD practices in England that participate in this data linkage. The research will further focus on population sub-groups defined by BMI category, gender, age-group and deprivation quintile in England. CPRD data have been shown to be representative of the UK population in terms of age and sex distribution and deprivation category. Clinical diagnoses recorded into CPRD have high validity.[42] We have recently reported on clinical BMI recording in CPRD.[38] These analyses showed that there is under-recording of BMI in primary care, but individuals without BMI records have a low incidence of morbidity [Helen Booth, personal communication 1st November 2012] which suggests that under-recording may be more frequent in healthy individuals with normal body weight. The present analyses will be restricted to individuals in CPRD with BMI records ≥30 Kg/m^2. We will make comparisons between GPRD data and Health Survey for England estimates, where the two sources include comparable information, in order to evaluate possible bias from misclassification of BMI category in CPRD.

Data specification

A cohort will be sampled from CPRD practices that participate in the data linkage scheme in England and contribute research quality data to CPRD during the period 2007 to 2012. A total sample of 300,000 will be drawn by drawing a random sample of 50,000 individual participants, without replacement, from the population of registered participants at eligible CPRD practices in each year. Eligible participants will be aged 20 years and older, since bariatric surgery is less likely to be used at younger ages and then requires special consideration. Eligible participants will have most recent BMI record before the index date of ≥30Kg/m^2. For data analyses to provide incidence, prevalence and mortality estimates, sampling will be stratified by BMI category (including 30-34, 35-39 and ≥40 Kg/m^2) in order to obtain similar size samples in each BMI category. However, an unstratified random sample of 300,000 obese participants will provide the start population for the Model. This starting sample may be viewed as representing the obese population of a commissioning organisation or local government area. An additional sample that only includes individuals who have received bariatric surgery procedures will also be sampled to provide empirical data inputs to the model. The data sources for the model are summarised in Table 2.

Table 2: Summary of data sources for Markov model.

Input	Source	Notes
Base Population	CPRD	Data for approximately 300,000 obese adults aged 20 years and older, stratified by age, sex, IMD quintile and BMI category
Incidence of long-term conditions	CPRD	Diabetes, heart disease, stroke, obesity-related cancer.
Prevalence of symptomatic conditions	CPRD	Depression, asthma, back and joint pain
Mortality	CPRD	Mortality for each state estimated from CPRD
Health care utilization	CPRD	Estimated from CPRD records for each state
Unit costs of health care utilization	PSSRU[43]	Reference source. Additional costs of surgery will also be estimated from NHS sources.
Unit prescription costs for medicines	FDBE[44]	First DataBank Europe (FDBE) Multilex Drug Data File Database
Utility values	Sullivan[45]	Compendium of values provides utility of each state
Intervention effects	e.g. Picot et al.[17]	Literature reviews

Data analysis

The purpose of data analyses will be to provide empirical estimates to populate the Markov Model. For each state in the Model we require to estimate incidence rates that govern transitions into the state, incidence rates that govern transitions out of the state, as well as mortality rates that govern transitions to death. We will also estimate the prevalence of depression, asthma, and back and joint pain for each state in the Model.

Case definitions will be based on sets of Read codes and, where appropriate, medical product codes for drug prescriptions. We have already reported appropriate definitions for several Model states. [46,47,41] 'Diabetes' will include type 2 diabetes only. 'Non-valvular heart disease' will include ischaemic heart disease, hypertensive heart disease, congestive cardiac failure and cor pulmonale. 'Stroke' will include all strokes as reviewed elsewhere.[46] 'Obesity-related cancer' will be defined separately for men and women and will include cancers shown to be associated with obesity.[3] The 12 month period at the start of each participant's record will be omitted to avoid including diagnoses of prevalent cases. Incidence and mortality rates

will be estimated in a time-to-event framework which will provide estimates from which probabilities can be estimated for the model.[37] Robust standard errors will be used to allow for clustering by general practice, although experience shows that this adjustment generally has negligible effect in CPRD analyses.

We will estimate rates of health care utilization from CPRD records. These will include utilisation of primary care, including family practice consultations, telephone consultations, home visits and emergency and out-of-hours consultations; secondary care, including hospital admissions, outpatient visits, day case visits and emergency visits; and all drug prescriptions issued. Utilisation rates will be based on person-time at risk. Estimates for the unit cost of health service use will be obtained from reference sources [43]. Unit costs will be applied to each category of health care utilisation in order to estimate health care costs. Prescription costs will be obtained by linking each Multilex drug code record in GPRD with the prescription cost obtained from the First DataBank Europe (FDBE) Multilex Drug Data File Database.[44] Further details have been reported elsewhere.[41]

Table 3: Sample size considerations.

		Precision (2 x standard error)	
	Assumptions	**Sample in obesity category**	**Stratified by age group and gender**
Number		80,000	6,667
Prevalence	50%	+/-0.35%	+/- 1.2%
Prevalence	2%	+/-0.1%	+/- 0.34%
Incidence, stroke	1 per 1,000[48]		
Person years analysis over 5 years' data		Upper Limit: 1.10 Lower Limit: 0.91	Upper limit: 1.4 Lower Limit: 0.7

Sample size considerations

The large sample size will be sufficient to provide precise estimates of the parameters required for the Markov model. The total sample will be about 300,000. Based on the prevalence of obesity categories in CPRD [H Booth, personal communication, 27th November 2012], stratified sampling will yield at least 100,000 with each of obesity and severe obesity but there may be about 80,000 sampled with morbid obesity. Estimates will have acceptable precision, even after stratification by gender and six age groups (see Table 3). Deprivation effects will be addressed through regression modelling.[37] As we currently hold a CPRD licence, we have flexibility to increase the efficiency of the study by sampling by model state if required.

Evidence search and synthesis

The research will draw on previous systematic reviews and primary research publications to provide evidence of the health outcomes and costs of BS. The evidence search and synthesis will therefore include identifying, and updating where necessary, relevant systematic reviews.

Purpose

The purpose of the review is to systematically retrieve, appraise and synthesise available research evidence. We aim to provide information for the model by answering the following questions: i) What are the projected short- and long-term effects of bariatric surgical procedures on health states included in the Model (Figure 2)? The review will include as outcomes, operative mortality and adverse effects following surgery, as well as long-term conditions and symptomatic states; ii) What are the projected long-term changes in health care utilisation after bariatric surgical procedures?

Search strategy

In implementing and reporting the review, we will closely follow the recommendations for good practice.[49] A protocol will be drawn up that will define the focus for the review by listing the outcome measures to be evaluated and the types of study designs to be included. Initially, we prefer to include randomised studies. However, as studies with long follow-up are mainly cohort studies, these will also be included when there is an well selected comparison group. Wide ranging searches will be implemented for each of the review questions using personal reference collections; electronic databases (including PubMed/Medline; Web of Knowledge; Embase; Cochrane Database of Systematic Reviews); screening citations of retrieved papers; advice from authors and other experts; conference proceedings; and hand-searching journals for the preceding 24 months. We will primarily search for recent systematic reviews of randomised controlled trials with relevance to the focus, we will also include reports of randomised controlled trials and cohort studies where appropriate. Retrieved abstracts will be screened and selected papers will be retrieved and examined for relevance to the focus of the review. Only English language publications will be included. Papers published since 1980 will be included. Details of searches and the numbers of papers selected at each stage will be recorded.

Review strategy
Studies will be appraised to evaluate methodological quality and potential for error and bias, including both internal and external validity. A structured checklist will be used for appraisal. Since systematic reviews, randomised trials and cohort studies may be included we initially plan to assess quality and risk of bias using established tools.[50,51] Assessment will be made by two reviewers using a standard form and discrepancies resolved through discussion. Data extraction will cover inclusion and exclusion criteria, numbers recruited, numbers lost to follow-up, subject characteristics, key outcome measures and their variability. Data extraction will be performed independently by two reviewers using a standard proforma and any discrepancies will be reviewed and agreed.

Methods for synthesis
Initially, descriptive data for each study will be presented in the form of tables, together with summary data for each outcome measure. A narrative summary of the results will be compiled. Quantitative data for the same outcomes will be synthesised using meta-analytic methods. These will be implemented using the meta-analysis commands in Stata version 12. We will evaluate heterogeneity and explore this using meta-regression where appropriate. Funnel plots and associated tests will be implemented to evaluate publication bias.

Outputs from the review: These will include quantitative estimates of i) the projected short- and long-term effects of bariatric surgical procedures on health states included in the Model; and ii) the projected long-term changes in health care utilisation after bariatric surgical procedures.

Markov Model Implementation
The Markov model will be constructed, building on our NPRI model. The Markov model will be employed to estimate the long-term outcomes and costs of strategies to expand access to bariatric surgery.

Model estimation

The probabilistic Markov model will be estimated by cohort simulation, implemented through a program written in R software.[52] The start population entering the model will have the same distribution by age, gender, BMI and deprivation as in the CPRD sample. All simulations will be stratified by single year of age with the initial population aging by one year per cycle. Participants will exit from the model when they die or reach 100 years of age. The model will be run for each sex, and subsequently each deprivation quintile, separately. Outcomes and costs will be compared for Intervention and Standard Care over 80 annual cycles. This number of cycles will allow the entire cohort that enters the Model to progress either to death or to reach age 100 and exit the model.

Annual transition probabilities for the Model will obtained by sampling from the beta-binomial distribution, using CPRD data as inputs. Where the data are sparse, as when stratification by deprivation quintile is required, then a time-to-event regression modelling framework will be used, with transition probabilities being estimated with the use of Cholesky decomposition, as outlined by Briggs et al.[37] (p102).

Utilities for each state will be obtained from data published in a compendium of values.[45] Utility values for each state will stratified by single year of age but will be the same for men and women. Utility values will be sampled from the beta distribution. QALYs will then be obtained as the product of the participant years in a given state and the utility value associated with the state. The costs of each state will be sampled from the gamma distribution with the mean value from CPRD, by ten year age group, sex, condition and symptomatic status, as the empirical input.

The effectiveness of the intervention will be modelled using estimates drawn from the systematic literature search. We expect to include in the model, effects of BS on: transitions between BMI categories; incidence of disease states including diabetes, heart disease, stroke and obesity-related cancers; prevalence of symptomatic states including asthma, back and joint pain, and depression; and mortality in model states. We anticipate that intervention effects will be included as (log) relative risks and their standard errors, with values being sampled from a (log) normal distribution.[37] We will specifically explore whether there is evidence that intervention effects vary by age group and sex, body mass index category, and duration of time since surgery. Where appropriate this effect modification will be incorporated into the model.

Additional costs of BS surgery will also be included in the model. Successful BS, requires a substantial clinical team including surgeons, anaesthetists, operating theatres with special equipment, special beds, special outpatient services including psychiatric support and dietitians among others. The organisation of surgical services, and the selection of particular surgical procedures, are not the main focus of the research. However, as the project develops it may be necessary to consider the extent to which costs of BS, and risks of adverse events, are related to different clinical and organisational models of care. We intend to include the costs of complications of bariatric surgery in our estimation models. Evidence on the costs of BS will be informed by evidence from the literature review. In addition, we will analyse data for cases in CPRD that have received BS procedures to evaluate health care costs. We will also obtain empirical data from reference sources[43] and from NHS organisations. Professor Sebastian Lucas, a colleague, who contributed to the NCEPOD report *'Too Lean a Service'* has also agreed to contribute advice.[32] The form in which these additional costs of BS are incorporated into the model will be determined through the course of this research. One approach will be to include a tariff by year since BS, based on empirical data for the NHS costs incurred following BS. Another approach may be to utilise relative risk estimates for specific forms of health care

utilisation, as reported by Neovius et al.[33]. Cost estimates will be stratified by age group, sex, BMI category and time since BS procedure.

Total costs and QALYs will be obtained by summing across the 80 cycles of the model included in each simulation. There will be 2,000 simulations run for each of intervention or standard care scenarios. Results will be expressed as rates per 1,000 participants entering the model. Mean costs, and the 95% range, will obtained from the data for 2,000 simulations. Incremental costs and QALYs will be obtained as the difference between intervention and standard care scenarios. Costs and QALYs will be discounted using a rate of 3.5%, but QALYs will also be discounted at a rate of 1.5% as a sensitivity analysis. Incremental costs will be plotted against incremental QALYs to present a cost-effectiveness ellipse.[53] Net health benefits (NHB), at a threshold value of £30,000 per QALY, will be calculated as the difference between the increment in QALYs and the increment in costs divided by the threshold value of cost per QALY.[54] Cost-effectiveness acceptability curves will be plotted using a range of threshold values. The model will be implemented with a half cycle correction for the estimation of QALYs and costs.

The model will be fully probabilistic and uncertainty in the inputs to the model will be carried through into the outputs of the model by sampling from appropriate probability distributions. In addition, sensitivity analyses will be implemented. These will vary key assumptions concerning the effects and costs of the intervention strategies. For example, the effectiveness of BS may be lower in routine practice than in research studies. The rate of discounting of health outcomes will be varied as outlined above.

Table 4: Design of experiments.

Objective	Comparison	Intervention
1. Expanding access within present indications (NICE strategy)	Present rates of BS from HES / National Bariatric Surgery Register	NICE recommendation: 0.01% of general population receive surgery per year; NICE recommendationx1, x2, x5 and x10
2. Expanding indications for accessing BS (IDF strategy)	Present rates of BS as above	IDF recommendation to expand access to patients with BMI 35-39 with diabetes and BMI 30-34 and poorly controlled diabetes
3. Focusing on inequalities	Present rates of BS as above	NICE and IDF recommendations with Net Health Benefits compared for each IMD quintile, and by gender and age group

Design of Experiments

The initial phases of the research will design and program the Model and then populate this with estimated values derived from CPRD and literature reviews. Once this is accomplished we will be in a position to conduct experiments to estimate the cost-effectiveness of different levels of uptake of bariatric surgery. Three main analyses will be undertaken:

1) Cost-effectiveness of expanding access within existing recognised indications for bariatric surgery (NICE Model).
In its bench-marking exercise, NICE[35] assumed that 60% of people meeting existing criteria for surgery would be judged eligible, 40% of these would accept surgery if offered and 1.6% of the 'eligible and willing' population could be treated each year. This benchmark rate of 0.01% of the general population was to be achieved by 2012. Current rates for surgery, which vary across the country, can be estimated from initially from Hospital Episode Statistics (HES) using secondary sources. We recognise limitations of HES. Limitations of coding mean that BS procedures cannot always be recognised as such. Procedures performed for the NHS in private hospitals are also not recorded. Private sector operations that are privately funded are not a focus of this research but we recognise that these contribute significantly to overall activity. In order to address some of these limitations we will aim to utilise data from the National Bariatric Surgical Register (NBSR). (see http://demo.e-dendrite.com/csp/bariatric/FrontPages/nbsrfront.csp). Marcus Reddy (a co-applicant) is a member of the NBSR Data Committee. The simulations will estimate incremental costs and QALYs based on a comparison of present rates of BS with the NICE recommendation and 2, 5 and 10 times the NICE recommendation (Table 4). We will also explore whether there is a threshold above which it is no longer cost-effective to increase access to surgery.

2) Cost-effectiveness of expanding access by extending the range of recognised indications for bariatric surgery (IDF Model).
The simulations will compare present rates of BS with IDF recommendations in which BS is a standard treatment for people with diabetes and BMI ≥35 Kg/m^2 or when BMI is 30-35 Kg/m^2 and 'control' is poor despite maximal therapy. Similar assumptions concerning 'eligibility' and 'willingness' will be used as in the NICE model.

3) Expanding access with a focus on distributional considerations, as well as on aggregate benefits.
This approach will focus on the potential of bariatric surgery to reduce inequalities in health. Initially, the model will be run for each IMD deprivation quintile, using quintile specific estimates for disease incidence, prevalence and mortality derived from CPRD. The cost effectiveness of the different intervention strategies will be compared for each IMD quintile. In addition, the cost-effectiveness of intervention in men or women, or in defined age categories will be evaluated.

Clinical engagement
We recognise that a wider group of clinicians than the study team should be engaged in the research. We therefore plan to hold seminars under the auspices of the NIHR Biomedical Research Centre (BRC) at Guy's and St Thomas' Hospital. The seminars will be held at the design stage of the project and at the end of the project. We will invite interested clinicians from the Academic Health Sciences Centre, King's Health Partners, as well as its partners in South London, including St George's University of London and from primary care in South London. King's Health Partners has active programmes of bariatric surgery both at Guy's and St Thomas' and King's College Hospitals. The purpose of the seminars will be to provide an opportunity for a wider clinical audience to inform the design, conduct and reporting of the project.

Patient and Public Involvement
We are aware that the topic of this research is of considerable importance to patients who may be eligible for obesity surgery. We therefore aim to produce and disseminate results that are relevant a wide range of groups, including members of the public and people who may be obese. We will gain access to public and patient involvement (PPI) advice through the NIHR

Biomedical Research Centre at Guy's and St Thomas' Hospital. Sophie Newbound, who manages the BRCs PPI programme, will engage in the project in order to facilitate public and patient input. There is a regular post-operative patient Group Forum held at St George's Hospital and we will approach participants with a view to involving them in the study. We have also been in communication with the Obesity Weight Loss Surgery Support charity (http://www.owlss.org.uk/), who have offered to facilitate introductions to interested members of the public. The design of the model will be discussed with patients and service users who will be identified as outlined above. We plan to hold workshops at which the interim and final results of the research can be discussed with a public audience to gain their interpretation of the data, advice on how the model and the outputs can be refined, and to discuss ways to disseminate the findings to relevant groups and networks. Peter Littlejohns, a co-applicant, has significant experience of communicating research results to public audiences through his previous role with NICE. This process will facilitate the 'calibration' of research outputs against people's own experiences of accessing care. These experiences of patients and members of the public will enable us to set the research results in a wider context, and test the outputs of the research model against the reality of accessing care.

Projected outputs

The main outputs from this research will be estimates of the rates of gain, or loss, in QALYs and costs per 1,000 obese participants entering the model. Rates for person years lived with long-term conditions, or symptomatic states, per 1,000 obese subjects entering the model will also be reported. 95% intervals for these measures will be estimated from the distribution for 2,000 simulations. As well as reporting results that are aggregated across the lifetime horizon of the model, results will be reported by year from the start of intervention because the time profile of costs and benefits are likely to differ. Each of these measures will be compared for the three strategies for intervention including the 'NICE strategy', the 'IDF strategy' and the targeted strategy for BS intervention. Sensitivity analyses will be reported that identify the consequences of varying key assumptions.

The research will also produce a methodological tool that can be used to evaluate other clinical and public health interventions for obesity.

Dissemination

The project outputs will provide policy-makers, commissioners of services, clinicians and patients with a detailed understanding of the implications of expanding access to BS for health care costs and health outcomes. This will contribute to informing future strategies for commissioning, organising and delivering services for BS.

We will write a report and papers for peer-review publication. Dissemination of these findings to wider audiences will be facilitated through the KCL press office. In the final three months of the project, we plan to hold a workshop at which key study findings will be presented. We will invite a wide range of stakeholders to the workshop including national and local level decision-makers, clinicians in primary and secondary care, public health specialists and patients and members of the public. A summary of the workshop presentations will be posted on our Divisional web-site. Concise summaries of the research results will be disseminated to key stakeholders.

Through Peter Littlejohn's links with NICE, we will be able to use the evidence from this project to inform guidance issued by NICE concerning the use of BS in the wider context of the management of obesity.

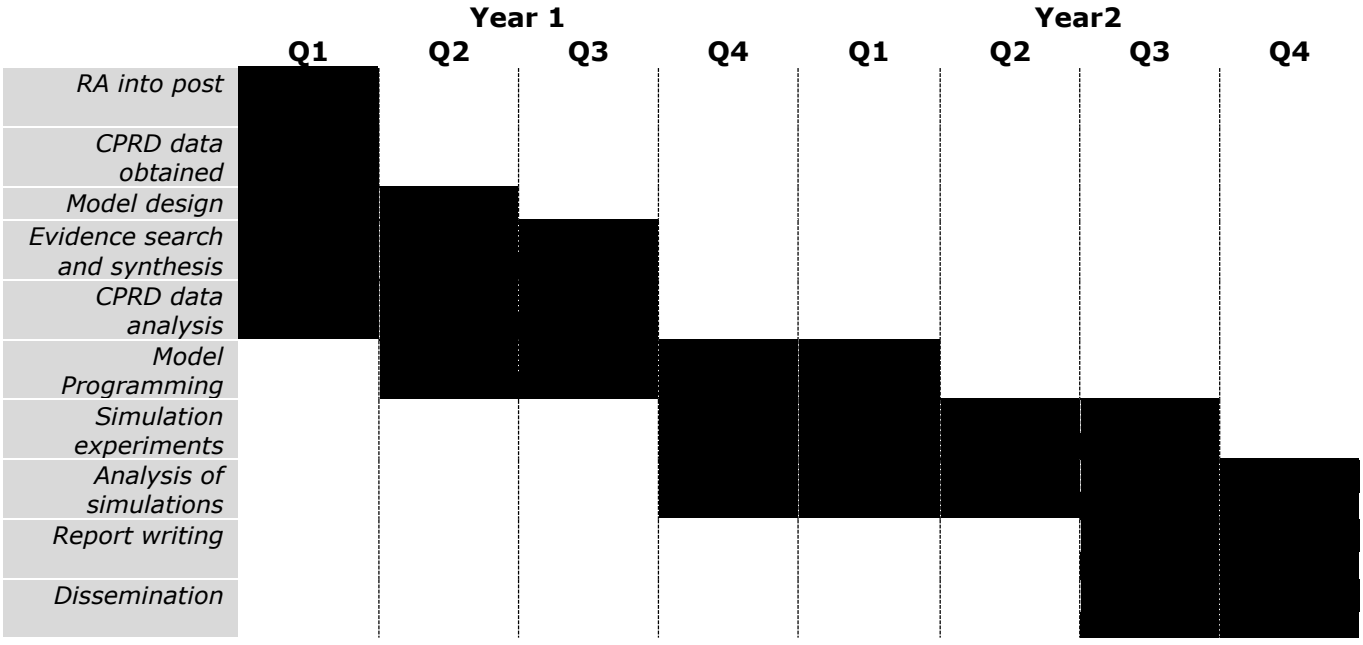
Through Marcus Reddy's links with the National Bariatric Surgical Register, and its associated professional organisations, we will make presentations at national and international conferences and other meetings in order to inform clinicians of the findings of our research.

Through our links with patient organisations, we will be able to disseminate the findings to patients and the public. For example, through short news items to be posted on the web-site of collaborating organisations.

Plan of investigation and timetable

This will be a two year project. The plan of investigation and timetable are outlined in the chart. The project will begin when the research assistant comes into post. S/he will commence on evidence search and synthesis to obtain updated estimates of the intervention effects and costs of Bariatric Surgery. In the first quarter, we will access CPRD datasets for individuals within CPRD who are obese or who are obese and have received BS interventions. CPRD analyses will be commenced and will continue for approximately 9 to 12 months. In the first two Quarters, we will work on refining the design of the Model based on the outline given in the proposal. In the second quarter, we will begin the work of programming the Model into a program to be run in R. Initial simulation experiments will be started in the fourth quarter of year 1. These will be analysed and the results will inform refinement of the model. More definitive simulations will be implemented and analysed in the first three quarters of year 2. Report writing and dissemination activities will be commenced in the last two quarters of the project.

Figure 3: Plan of investigation.



Approval by ethics committees

CPRD data are fully anonymised. Approval for use of CPRD, and linked data, will be obtained from MHRAs Independent Scientific Advisory Committee (ISAC). Neither Research Ethics Committee nor NHS Research and Development (R&D) review will be required

Project Management

Martin Gulliford will provide overall leadership and supervision. He will work closely with the immediate team, including the Research Assistant, Alex Dregan, Judith Charlton, Helen Booth and Caroline Rudisill to deliver all data inputs to the model, ensure model programming and

completion of simulations. The wider team including Mark Ashworth, Toby Prevost, Marcus Reddy and Peter Littlejohns will communicate regularly. Meetings of the research team will be held at regular intervals as required.

Expertise and justification of support required

The project will be implemented by multi-disciplinary team with skills in clinical medicine, surgery and primary care; epidemiology and public health; statistics; model programming; health economics; and public engagement. *Martin Gulliford* will provide overall leadership and supervision. Expertise in public health, clinical medicine, clinical surgery and primary care and general practice will be provided by Martin Gulliford, Peter Littlejohns, Marcus Reddy and Mark Ashworth. *Marcus Reddy* specialises in bariatric surgery and is a member of the data committee of the National Bariatric Surgical Register. *Omar Khan* will provide additional advice and expertise in bariatric surgical issues. *Mark Ashworth* has wide experience of primary care and primary care research. He and Martin Gulliford have collaborated on a number of CPRD research studies. *Judith Charlton* has wide experience of CPRD research. She has published more than 25 papers using CPRD data. She has extensive knowledge of CPRD datasets and wide experience of Stata programming for CPRD analysis. Judith has a background in computer programming and has skills in R programming for Markov modelling. *Helen Booth* is a PhD student at King's College London. Her research is investigating obesity and comorbidity in a primary care population and this will provide knowledge that will inform the development of this project. *Alex Dregan* is Lecturer in Epidemiology at King's College London. Alex has significant experience of longitudinal data analysis and CPRD research. He will contribute to design and analysis of CPRD analyses required for this project. *Caroline Rudisill* is Lecturer in Health Economics in the Department of Social Policy at the London School of Economics and Political Science (LSE). She will provide all health economic advice to the project, drawing on the wider resources of LSE Health as required. Caroline leads teaching on resource allocation and cost-effectiveness analysis at LSE Health. Caroline's research interests are in using economic evaluation to make coverage decisions and examining how risk perceptions impact on health and health care-related behaviours. She has a particular interest in the use of economic incentives for preventive behaviours. She is a team member of the Wellcome Trust-funded Centre for Incentives and Health. *Toby Prevost* is Professor of Medical Statistics at King's College London. He has wide experience of medical statistics and clinical trials. He will provide all statistical advice to the project. *Peter Littlejohns* is Professor of Public Health at King's College London and was previously Medical Director for NICE. In this capacity, Peter oversaw the development of guidelines on obesity management including recommendations for bariatric surgery. He has wide experience of the application of evidence synthesis, health technology assessment and economic evaluation to policy development. Peter also has significant experience of engaging with the public in the application of research knowledge to service development.

References

[1] NHS Information Centre. *Health Survey for England 2010 Trend Tables.* Leeds: NHS Information Centre (2009) Source: http://www.ic.nhs.uk/pubs/hse10trends **[2]** James WPT: *Obesity. In: Oxford Textbook of Public Health, 5th Edition.* Oxford: OUP (2009). **[3]** Parkin DM, Boyd L: Cancers attributable to overweight and obesity in the UK in 2010. *Br J Cancer* **105**, S34-S37 (2011). **[4]** Terranova et al: Bariatric Surgery: Cost-Effectiveness and Budget Impact. *Obesity Surgery* **22**, 646-653 (2012). **[5]** O'Neil P: *Shedding the Pounds: Obesity Management and Bariatric Surgery in England.* London: Office for Health Economics (2010). **[6]** McLaren L: Socioeconomic Status and Obesity. *Epidemiol Rev* **29**, 29-48. (2007). **[7]** Dixon JB et al: Adjustable gastric banding and conventional therapy for type 2 diabetes. *JAMA* **299,** 316-323 (2008). **[8]** O'Brien PE: Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program. *Ann Intern Med* **144**, 625-633 (2006). **[9]** Sjostrom L et al: Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* **357**, 741-752 (2007). **[10]** Kaul A, Sharma J: Impact of

bariatric surgery on comorbidities. *Surg Clin North Am* **91,** 1295-1312 (2011). **[11]** Loveman E et al: The clinical effectiveness and cost-effectiveness of long-term weight management schemes for adults: a systematic review. *Health Technol Assess* **15**(2), 1-182 (2011). **[12]** Burns EM et al: Introduction of laparoscopic bariatric surgery in England. *BMJ* **341,** c4296 (2010). **[13]** National Obesity Observatory: *Bariatric Surgery for Obesity* (2010)Source: http://www.noo.org.uk/uploads/doc/vid_8774_NOO%20Bariatric%20Surgery%20for%20Obesity%20FINAL%20MG%20011210.pdf **[14]** NHS Information Centre: *Statistics on Obesity, physical activity and diet.* Leeds, (2012) **[15]** Hunt P: Right to the highest attainable standard of health. *Lancet.* **370**, 369-371 (2007). **[16]** Dixon JB et al: Bariatric surgery for type 2 diabetes. *Lancet* **379**, 2300-2311 (2012). **[17]** Picot J, et al: The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity. *Health Technol Assess* **13(**41), 1-190, 215-357 (2009). **[18]** NICE: *CG43 Obesity: Full guideline, section 5b - management of obesity in clinical settings (adults): evidence statements and reviews.* London: NICE, (2006) **[19]** Poirier P et al: Bariatric surgery and cardiovascular risk factors. *Circulation* **123**, 1683-1701 (2011). **[20]** Adams TD: Gastrointestinal surgery: cardiovascular risk reduction and improved long-term survival in patients with obesity and diabetes. *Curr Atheroscler Rep* **14**, 606-615 (2012). **[21]** Clifton PM: Bariatric surgery: effects on the metabolic complications of obesity. *Curr Atheroscler Rep* 14(2), 95-100 (2012) **[22]** Heneghan HM: Gastrointestinal surgery for obesity and diabetes: weight loss and control of hyperglycemia. *Curr Atheroscler Rep* **14**, 579-587 (2012) **[23]** Carlsson LMS et al: Bariatric Surgery and Prevention of Type 2 Diabetes in Swedish Obese Subjects. *N Eng J Med* **367**, 695-704 (2012). **[24]** Schauer PR et al: Bariatric surgery versus intensive medical therapy in obese patients with diabetes*. N Engl J Med* **366**, 1567-1576 (2012). **[25]** Adams TD et al: Health benefits of gastric bypass surgery after 6 years. *JAMA* **308**, 1122-1131 (2012). **[26]** Sjostrom CD: Impact of weight change, secular trends and ageing on cardiovascular risk factors: 10-year experiences from the SOS study. *Int J Obes* **35,** 1413-1420 (2011). **[27]** Sjostrom L et al: Bariatric surgery and long-term cardiovascular events. *JAMA* 307, 56-65 (2012). **[28]** Sjöström L et al: Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncology* **10**, 653-662 (2009). **[29]** Kolotkin RL, Davidson LE, Crosby RD et al: Six-year changes in health-related quality of life in gastric bypass patients versus obese comparison groups. *Surg Obes Relat Dis* 8, 625-633 (2012). **[30]** Karlsson J et al: Ten-year trends in health-related quality of life after surgical and conventional treatment for severe obesity: the SOS intervention study. *Int J Obes* **31**, 1248-1261 (2007). **[31]** Kim J-H, Wolfe B: Bariatric/Metabolic Surgery: Short- and Long-Term Safety. *Current Atherosclerosis Reports,* 1-9. **[32]** Martin IC et al: *Too Lean a Service*. In. NCEPOD. London, (2012) **[33]** Neovius M et al: Health care use during 20 years following bariatric surgery. *JAMA* **308**, 1132-1141 (2012). **[34]** Ackroyd R: Cost-effectiveness and budget impact of obesity surgery in patients with type-2 diabetes in three European countries. *Obes Surg* **16**, 1488-1503 (2006). **[35]** NICE: Bariatric surgical service for the treatment of people with severe obesity. Commissioning guide (2012) http://www.nice.org.uk/media/87F/65/BariatricSurgeryFINALPlusNewToolUpdates.pdf **[36]** International Diabetes Federation *Bariatric Surgical and Procedural Intervention in the Treatment of Obese Patients with type 2 diabetes*. Brussels, Belgium, (2012) Source: https://www.idf.org/webdata/docs/IDF-Position-Statement-Bariatric-Surgery.pdf **[37]** Briggs A et al: *Decision Modelling for Health Economic Evaluation.* Oxford University Press, Oxford (2006). **[38]** Booth HP: Epidemiology of clinical body mass index recording in an obese population in primary care: a cohort study. *J Public Health* [online pub] (2012). **[39]** Herman WH et al: The Cost-Effectiveness of Lifestyle Modification or Metformin in Preventing Type 2 Diabetes in Adults with Impaired Glucose Tolerance. *Ann Int Med* **142**, 323-332 (2005). **[40]** Heo M et al: Hierarchical linear models for the development of growth curves: an example with body mass index in overweight/obese adults. *Stat Med* **22**, 1911-1942 (2003). **[41]** Bhattarai N, Charlton JC Rudisill AC and Gulliford MC: Prevalence of depression and utilization of health care in single and multiple morbidity: a population-based cohort study. *Psychol Med* [online pub](2012). **[42]** Herrett E et al: Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol.* **69,** 4-14 (2010). **[43]** Personal Social Service Research Unit (PSSRU): Unit costs of health and social care. Curtis L. (ed.). University of Kent, (2010) **[44]** First DataBank Europe: FDBE Multilex Drug Data File. (2011) **[45]** Sullivan PW et al. Catalogue of EQ-5D Scores for the United Kingdom. *Med Decis Making* **31**:800-4. (2011). **[46]** Gulliford MC et al: Selection of medical diagnostic codes for analysis

of electronic patient records. application to stroke in a primary care database. *PLoSONE* **4***:e7168.* (2009). **[47]** Bhattarai N, Charlton J, Rudisill C, Gulliford MC: Coding, recording and incidence of different forms of coronary heart disease in primary care. *PLoS One* **7**, e29776 (2012). **[48]** Stewart JA et al: Ethnic differences in incidence of stroke: prospective study with stroke register. *BMJ* **318**, 967-971 (1999). **[49]** CRD: Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews vol. second edition. Centre for Reviews and Dissemination, York (2004) **[50]** Downs SH, Black N: The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions*. J.Epidemiol.Community Health* **52**, 377-384 (1998). **[51]** Higgins JPT: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343** (2011). doi:10.1136/bmj.d5928. **[52]** *R: A language and environment for statistical computing.* R Foundation for statistical computing., Vienna, Austria, (2010) **[53]** Nixon RM et al: How to estimate cost-effectiveness acceptability curves, confidence ellipses and incremental net benefits alongside randomised controlled trials. Cambridge MRC BSU (2011). Source: http://www.mrcbsu.cam.ac.uk/Publications/Preprints/nixon-wonderling-grieve-05.pdf **[54]** Gray AM et al: *Applied Methods of Cost-effectiveness Analysis in Health Care*. Oxford University Press, Oxford (2011).