Appendix 1

General Methodological Principles of Study Design (Section VI of the Decision Memorandum)

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the

primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it

may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess net health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

An intervention is not reasonable and necessary if its risks outweigh its benefits. Among other things, CMS evaluates whether reported benefits translate into improved net health outcomes. The direction, magnitude and consistency of the risks and benefits across studies are important considerations. Based on the analysis of the strength of the evidence, CMS assesses whether an intervention or technology's benefits to Medicare beneficiaries outweigh its harms.

Appendix 2
CMS Review Table for Bariatric Surgery

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results	Control Group
				Intervention Group	
Buchwald H 2004. Bariatric surgery: A systematic review and meta-analysis	review and meta-analysis N = 22,094	bariatric surgery patients; mean age = 39 female = 72.6%	I = bariatric surgery, O =weight loss, operative mortality	Excess weight loss averaged 61.2% overall, 47.5% for gastric banding, 61.2% for gastric bypass, 68.2% gastroplasty, and 70.1% for BPD or DS. Rates of operative mortality were 0.1% for purely restrictive procedures, 0.5 % for gastric bypass, and 1.1% for BPD ± DS. Diabetes completely resolved in 78.6%, & improved or resolved in 86%; hypertension completely resolved in 61.7% and improved or resolved in 78%; hyperlipidemia was improved in 70%; and OSA was resolved in 86%.	NA
Chau et al.2005. Pt characteristics impacting EWL after LAGB	Retrospective cohort	200 consec. LAGB. Median age = 44, BMI=45, 20%:80% M:F	I=LAGB O=Factors affecting %EWL	Logistic Regression –(α=0.05) that having DM (1.87), COPD (4.50) and age (1.02) were significantly assoc with >50% EWL& increasing BMI (0.92), HTN (0.64), Asthma (0.60) and being female (0.29) assoc with <50% EWL	NA
Dindo D 2003. Obesity in General Elective Surgery	Retrospective cohort N = 239	Zurich Switzerland mean age = 49 female = 72%	O = many surgical procedures, I= rate of complications	Obesity not a risk factor for complications with the exception of wound infection in open surgery (non-obese = 3%, obese = 4%)	NA
Dolan K 2004. A comparison of laparoscopic adjustable gastric banding and biliopancreatic diversion in super obesity	prospective case-control; matched to 23 BPD patients to 1319 LAGB patients	mean age = 39, female = 69.6%; all super obese patients matched on sex, BMI and age	I = open and lap BPD vs. LAGB O= EWL, complication rate, re-operation rate, LOS, resolution of OSA, DM, HTN	BPD EWL at 24 months = 64.4%; complications = 56.6%; re-operations = 30.4%; OSA = 75%; HTN = 66%; diabetes = 100%	lap: EWL at 24 months = 48.4%; complications = 8.7%; OSA = 66%; HTN = 66%; DM =75%

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results	Control Group
				Intervention Group	
Felix E 2003. Conversion of laparoscopic Roux-en-Y gastric bypass	retrospective cohort N = 1236	non-converted group: mean age = 40; female = 87% converted group: mean age = 48; female = 63%	I= LRYGB O = conversion rate	conversion rate: 3 reasons for conversion: 25% technical difficulty, 10% bleeding, 10% massive liver, males and older age increase chance for conversion	NA
Fernandez AZ 2003. Experience with over 3,000 open and Laparoscopic Bariatric procedures: multivariate analysis of factors related to leak and resultant mortality	Retrospective cohort N= 3073	Patients at VA Commonwealth University mean age=40.4 female= 81%	I=RYGB O=short-term mortality	Mortality = 1.5% Leak = 3.2%	NA
Fernandez AZ 2004. Multivariate risk factors for death following gastric bypass for treatment of morbid obesity	retrospective cohort N = 2011	open group: mean age = 40.7, female = 7% lap group: mean age = 41.8, female = 86.4%	I = open or lap bypass O = death rate, SBO, leak, pulmonary embolism	lap: mortality = .7% ; leak = 4.1%; SBO = 3.3%; pulmonary embolism = 1% open: mortality = 1.9%; leak = 2.5%; SBO = 3.3%; pulmonary embolism = 1.2% leak, pulmonary embolism and pre-operative weight are risk factors for death	NA
Flum D 2004. Impact of gastric bypass on operation survival: A population based analysis	retrospective cohort N = 3328	Washington state patients unoperated: mean age = 47, female = 63% operated: mean age = 43, female = 80%	I = bariatric surgery O = short term mortality, long-term survival	overall short-term mortality = 1.9%; surgeon inexperience leads to 4.7 times higher short-term mortality. mortality at 15 years: non-operated = 16.3% operated = 11.8%	NA
Fontaine K 2003. Years of life lost due to obesity	retrospective cohort	U.S. population 18-85 years old NHANES	I = none O = years of life lost (YLL)	obese males have more YLL than obese females, especially at younger ages	NA
Gonzalez R 2003. Gastric bypass for morbid obesity patients 50 years or older: Is laparoscopic technique safer?	retrospective cohort N = 52	mean age = 55 female = 87%	I = LRYGB vs. ORYGB O = EWL, co-morbidities: HTN, hyperglycemia, LOS, mortality, morbidity	overall: decrease in HTN, hyperglycemia, EWL at 3 months = 68% lap: LOS = 3.4; morbidity = 18%; mortality = 2.6%; ICU stay = 5% open: LOS = 5.9; morbidity = 26%; mortality = 0%; ICU stay = 36%	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results	Control Group
				Intervention Group	
Herron D 2004. The surgical management of severe obesity	review	U.S. population	I = bariatric surgery, medication O = weight loss	long-term weight loss less than 10% with diet and medication	NA
Lee WJ 2003. Clinical significance of central obesity in laparoscopic bariatric surgery	retrospective cohort	national Taiwan hospital catchment area mean age = 30.9 female=74.8%	I = laparoscopic bariatric surgery O = co-morbidities: hyperglycemia, triglyceride levels, EWL, major complications, hospital stay	central group: hospital stay = 4.3 (male), 4 (female); EWL at 3 years = 55% (male), 57.5% (female) peripheral group: hospital stay = 4.1 (male), 3.8 (female); major complications =3.06% (male), 0.44% (female); EWL at 3 years = 59% (male), 56% (female)	NA

Livingston EH 2002. Male gender is a predictor of morbidity and age a predictor of mortality for patients undergoing gastric bypass surgery	retrospective cohort
	N = 1067
		female = 78%
		mean age = 42.3
			I = gastric bypass
			O = mortality
				renal failure = 2.2% (male), 0.5% (female);
				mortality = 3% (male), 0.8% (female);
				leak = 3.5% (male), 0.8% (female)
					NA

Livingston EH 2004. Socioeconomic characteristics of the population eligible for obesity surgery	retrospective cohort	U.S. population National Health Information Survey (NHIS) 84% < 60 years old female = 64%	I = bariatric surgery, O= eligibles for surgery	2.8% of U.S. population eligible for bariatric surgery eligibles more likely to be impoverished, less-educated and African-American	NA
Livingston EH2004. Procedure incidence and in-hospital complication rates of bariatric surgery	retrospective cohort	U.S. population National Hospital Discharge Survey (NHDS)	I = none O = national incidence and complication rates; LOS; intestinal complications; cardiac and respiratory failure	in-hospital complication rate = 9.6%; procedure incidence = 125.2 per 100,000 discharges; LOS = 4.6; intestinal complications = 2.3%; cardiac and respiratory failure = .9%	NA
Pope GD 2002. National trends in utilization and in-hospital outcomes of bariatric surgery	National Inpatient Survey(NIS) N= 12203	US population having had bariatric surgery mean age = 40.2 female = 83.6%	I = none O= rates of bariatric surgery, co-morbidities, mortality, re-operation rate, LOS, pulmonary embolism	rate of bariatric surgery increased from 2.7 to 6.3/100,000 , co-morbidities ranged from 20.9% in 1990 to 31.6% in 1997; bypass comprised 86.1% of bariatric surgeries in 1997; In-hospital mortality = 0.37%; LOS = 4; pulmonary embolism = .07%; re-operations = 1.4%	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results Intervention Group	Control Group
Residori L 2003. Prevalence of co-morbidities in obese patients before bariatric surgery: Effect of race	retrospective cohort N = 300	mean age = 37.5 female = 86.8 40% Hispanic; 34% Caucasian; 25% African American ; 1% Asian	I = none O = pre-operative co-morbidity prevalence rates	57% of patients had at least one metabolic complication; diabetes prevalence = 30%; hyperlipidemia = 71.4%; hypertension = 68.8%	NA
Shen R. 2004. Impact of patient follow-up on weight loss after	retrospective cohort N = 355	mean age = 40.4	I = LAGB, RYGB, patient follow-up O = EWL	LAGB patients had increased EWL on average if they had 7 or more post-op visits; no difference in RYGB group; > 7 visits = 50.4% EWL, < 6 visits = 41.9% EWL	NA
Sjostrom C 2000. Differentiated long-term effects of intentional weight loss on diabetes and hypertension	Case-control N = 692	Swedish morbid obese patients mean age = 47 (control), 46 (surgery) female = 65.9%	I= bypass and restrictive surgery (VBG) O = long-term weight loss, co-morbidities	surgical group lost an average of 20.1kg at 8 years; OR for diabetes, for cases compared to controls = 0.16; OR for HTN, for cases compared to controls = 1.01	control group lost no weight over 8 years; diabetes 7.8 -24.9 at 8 years
Steinbrook R 2004. Surgery for severe obesity	Expert Opinion	U.S. Population	I = none O = projected bariatric procedure rates	100,000 expected from 2003	NA
Sugerman H 2004. Effects of bariatric surgery in older patients	retrospective cohort N = 80	age ≥ 60 at time of bariatric surgery. mean age = 63 female = 78%	I = banding, RYGB O = EWL, weight loss, mortality, complications, co-morbidity	EWL 49% after surgery; long-term mortality unclear, diabetes decreased 30% at 5 years; HTN decreased 30%, GERD decreased 51% wound infection in 4/88; leak in 2/88; pulmonary embolus in 1/88	NA
Shikora SA, et al. Laparoscopic roux-en-y gastric bypass results and learning curve of a high-volume academic program.	Retrospective cohort	750 morbidly obese pts. 85%:15% F:M. BMI 47	I= LRYGB – O= Complications/Mortality by experience	**1st hundred cases** **next 650** Complication rate 26% 13% Mortality rate 1% 0% Operating time 212 min. 132 min	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results	Control Group
				Intervention Group	
Suter et al. Laparascopic Gastric Banding: A prospective randomized study comparing the Lapband and the SAGB: early results	RCT	180 Morbidly obese pts	I= LAGB vs SAGB O= EWL, Co-morbidity Rx, QOL, Complications,	50% of the patients lost 50%of EWL in both groups. There was no difference between the groups for co-morbidity Rx, complication rates or QOL measure.	NA
Szold A 2001. Laparoscopic adjustable silicone gastric banding for morbid obesity: results and complications in 715 patients	retrospective cohort N=715	mean age=34.6 female= 76%	I= LAGB O= Complications	complications= 1.7% re-operation rate= 7.9%	NA
Zizza C 2003. Bariatric surgeries in North Carolina, 1990-2001: A gender comparison	retrospective cohort	North Carolina Hospital Discharge Data Base ≥18 years of age, 78-79% were state residents of NC female = 86%	I= bariatric procedures O =odds ratio of women to men having surgery	OR female: male of having bariatric surgery was 4.96 (4.39, 5.59), controlling for age and year of procedure, and residence in NC; mortality = 1.1% (female), 1.95% (male)	NA

Appendix 3

1. How well does the evidence address the effectiveness of Bariatric Surgery in the treatment of obesity in patients with one or more co-morbidities compared to non-surgical medical management?

** 1 – Poorly * 2 * 3 – Reasonably Well * 4 * 5 – Very Well*

1 2 3 4 5

	2. How confident are you in the validity of the scientific data on the following outcomes? *1 - No confidence* *2* *3 - Moderate Confidence* *4* *5 - High Confidence*	**3. How likely is it that the bariatric surgery, including RYGBP, banding and BPD will positively affect the following outcomes in obese patients with one or more co-morbidities compared to non-surgical medical management?** *1 – Not Likely* *2* *3 – Reasonable Likely* *4* *5 – Very likely*
Wt Loss (sustained)	1 2 3 4 5	1 2 3 4 5
Long-term Survival	1 2 3 4 5	1 2 3 4 5
Short-Term Mortality	1 2 3 4 5	1 2 3 4 5
Co-morbidities	1 2 3 4 5	1 2 3 4 5

4. How confident are you that the following bariatric surgeries will produce a clinically important net health benefit in the treatment of obese patients with one or more co-morbidities?

** 1 – No Confidence * 2 * 3 – Moderate Confidence * 4 * 5 – High Confidence*

RYGBP – open	1 2 3 4 5	**RYGBP – lap**	1 2 3 4 5
BPD - open	1 2 3 4 5	**BPD - lap**	1 2 3 4 5
Banding - open	1 2 3 4 5	**Banding - lap**	1 2 3 4 5

5. Based on the scientific evidence presented, how likely is it that the results of Bariatric Surgery in obese patients with one or more co-morbidities can be generalized to:

** 1 – Not Likely * 2 * 3 – Reasonably Likely * 4 * 5 – Very Likely*

a. The Medicare population (aged 65+): 1 2 3 4 5
b. Providers (facilities/ physicians) in community practice: 1 2 3 4 5

1. How well does the evidence address the effectiveness of Bariatric Surgery in the treatment of obesity in patients without co-morbidities compared to non-surgical medical management?

** 1 – Poorly * 2 * 3 – Reasonably Well * 4 * 5 – Very Well*

1 2 3 4 5

	2. How confident are you in the validity of the scientific data on the following outcomes? *1 - No confidence* *2* *3 - Moderate Confidence* *4* *5 - High Confidence*	**3. How likely is it that the bariatric surgery, including RYGBP, banding and BPD will positively affect the following outcomes in obese patients without co-morbidities compared to non-surgical medical management?** *1 – Not Likely* *2* *3 – Reasonable Likely* *4* *5 – Very likely*
Wt Loss (sustained)	1 2 3 4 5	1 2 3 4 5
Long-term Survival	1 2 3 4 5	1 2 3 4 5
Short-Term Mortality	1 2 3 4 5	1 2 3 4 5
Co-morbidities	1 2 3 4 5	1 2 3 4 5

4. How confident are you that the following bariatric surgeries will produce a clinically important net health benefit in the treatment of obese patients without co-morbidities?

** 1 – No Confidence * 2 * 3 – Moderate Confidence * 4 * 5 – High Confidence*

RYGBP – open	1 2 3 4 5	**RYGBP – lap**	1 2 3 4 5
BPD - open	1 2 3 4 5	**BPD - lap**	1 2 3 4 5
Banding - open	1 2 3 4 5	**Banding - lap**	1 2 3 4 5

5. Based on the scientific evidence presented, how likely is it that the results of Bariatric Surgery in obese patients without co-morbidities can be generalized to:

** 1 – Not Likely * 2 * 3 – Reasonably Likely * 4 * 5 – Very Likely*

c. The Medicare population (aged 65+): 1 2 3 4 5
d. Providers (facilities/ physicians) in community practice: 1 2 3 4 5