Protocol: Version 5, August 31, 2016

1. Abstract

Both Sleeve Gastrectomy (SG) and Roux-en-Y Gastric Bypass (RYGB) increase GLP-1 concentrations, although this is of lesser magnitude in SG compared to RYGB. We have data to suggest that endogenous GLP-1 is at least partially responsible for reducing free-choice caloric intake after RYGB, providing a mechanism underlying differences between procedures. Inhibition of GLP-1 action with Exendin-9,39 after RYGB accelerates gastric emptying. These observations suggest that factors other than anatomy regulate the upper gastrointestinal response to food ingestion. It is therefore reasonable to consider that the postprandial rise in GLP-1 might affect feeding behavior after RYGB, and to a lesser extent SG, where the increase in GLP-1 is less marked.

Title:	Exendin (9,39) and Satiety After Bariatric Surgery
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Principal Investigator:	Adrian Vella MD
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I. Hypothesis and Specific Aims

The *overall aim* of this application is to determine the contribution of the elevated incretin hormone concentrations seen after certain types of bariatric surgery to the regulation of food intake and satiety. Roux-en-Y Gastric Bypass (RYGB) and sleeve gastrectomy (SG) are the commonest forms of bariatric surgery and raise Glucagon-like Peptide-1 (GLP-1) secretion although to markedly different degrees. Recently, we demonstrated that inhibition of GLP-1 actions by Exendin-9,39 accelerates gastrointestinal transit implying a role of GLP-1 in gastrointestinal function after gastric bypass (1). Given that GLP-1 affects upper gastrointestinal function, it seems reasonable to postulate that GLP-1 may play a role in food intake after gastric bypass (2; 3). In support of this we have generated preliminary data to show that Exendin-9,39 increases oral intake after bariatric surgery.

Specific Aim: Determine the effects of GLP-1 Receptor blockade on caloric intake and gastrointestinal transit in subjects after SG and after RYGB.

1° Hypothesis: *Blockade of the GLP-1 receptor in subjects after RYGB produces equivalent caloric intake to that observed after SG.*

2° Hypothesis: *Blockade of the GLP-1 receptor accelerates gastrointestinal transit in subjects after RYGB but not after SG.*

II. Background and Significance

1) Obesity is a public health problem. In the United States the prevalence of obesity is rapidly increasing with 65% of adults and 17% of adolescents and children classified as being overweight or obese(4). This represents a doubling of obesity prevalence in adults, and a tripling in adolescents over the previous 25 years. Obesity is associated with multiple diseases, such as type 2 diabetes, non-alcoholic steatohepatitis and osteoarthritis, as well as being associated with increased frequency of risk factors for cardiovascular disease(5). Approximately 9% of national healthcare costs have been attributed to excess weight(6). The US Preventive Services Task Force has recommended that body mass index (BMI) is routinely assessed and weight management recommended for obese patients(7).

Behavioral intervention with lifestyle and dietary modification usually achieves modest weight loss(7). While generally safe, most regain the weight lost within 5 years. Pharmacotherapy for obesity is considered for patients who have failed efforts at lifestyle modification and who have a BMI $\geq$ 30Kg/M^2 or a BMI $\geq$ 27Kg/M^2 in the presence of comorbidities such as diabetes(8). However, there have been significant concerns about the long-term safety of such medications and the currently available medications have relatively limited efficacy(9). Bariatric surgery is usually considered for patients who have a BMI $\geq$ 40Kg/M^2 or a BMI $\geq$ 35Kg/M^2 associated with comorbidities such as diabetes(8). Restrictive surgeries such as adjustable gastric banding (AGB) limit the capacitance of the stomach. Roux-en-Y gastric bypass (RYGB) is the most commonly performed bypass procedure and produces gastric restriction together with selective malabsorption. RYGB involves creation of a gastric pouch by separating the stomach across the fundus. Drainage of this 10-30ml pouch is achieved by a gastrojejunostomy. The distal end of the jejunum is then anastomosed ~ 150cm below the gastrojejunostomy effectively bypassing the distal stomach, duodenum and proximal jejunum. Duodenal switch (DS) is a variation of biliopancreatic diversion and involves a sleeve gastrectomy with division of the duodenum below the pylorus. The distal ileum is anastomosed to the short stump of the duodenum producing a ~ 100cm channel for nutrient absorption. The other end of the duodenum is closed and the remaining small bowel connected onto the enteral limb 75-100cm from the ileocecal valve. (See Ref (5) for illustrations & review). Observational studies suggest that bariatric surgery is the most effective intervention for weight loss producing an average weight loss of 30-35% that

is maintained in ~ 60% of patients at 5 years(10). This has led to a dramatic increase in the number of procedures performed annually from 13,365 in 1998 to an estimated 102,794 in 2003(11). A newer procedure, sleeve gastrectomy (SG) is a restrictive operation which has increased dramatically; comprising 34% of the ~ 110,000 bariatric surgeries performed in 2013 and may become the most frequent bariatric procedure in North America(12). SG may be cheaper than RYGB in terms of operative costs and because it is not a malabsorptive procedure, the costs of follow-up, and care of morbidities arising from malabsorption, should be lower(13). **Bariatric surgery effectively produces sustained weight loss in obesity and is widely performed in the United States**

2) Comparative effectiveness of RYGB and SG. It has been suggested that remission rate is associated with the length of bypass (~85% for standard RYGB, ~93% for long-limb RYGB and ~98% with duodenal switch(14; 15). Recent prospective, randomized controlled trials have however reported lower remission rates for diabetes with RYGB, although it remains superior to medical therapy(16-18). Kashyap et al. has suggested that differences in fat loss and β-cell function between RYGB and SG occur ≥ 1 year after surgery(19). Of the 2 studies with 3 year follow-up, one undertaken in nondiabetic subjects(20) did not demonstrate clear differences in weight loss while in the other (diabetic subjects) there were small, but significant, differences with RYGB superior to SG in terms of weight and glycemic control(21). However, there are obvious anatomic differences between procedures which result in differences in enteroendocrine secretion: postprandial GLP-1 concentrations are lower after SG compared to RYGB in the comparative studies undertaken in humans(19; 22-25). On the other hand, a liquid meal, especially after gastric restriction, may not recreate conditions present after a solid meal(26). Whether these differences can explain a divergence in metabolic outcomes remains unknown.

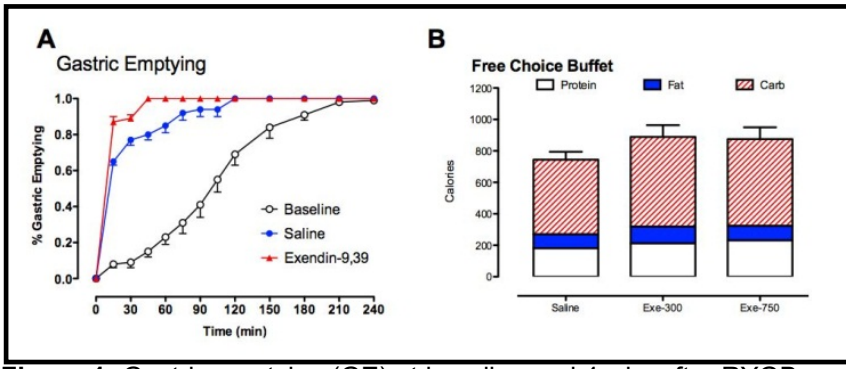

Figure 1: Gastric emptying (GE) at baseline and 4 wks after RYGB **(A)**. After surgery subjects were studied with (Exendin-9,39) or without (Saline). GLP-1R blockade accelerated GE. In a separate experiment, 240 minutes after a mixed meal, subjects ate from a free choice buffet. Calories consumed are recorded **(B)**. GLP-1R blockade increased food consumption.

3) GLP-1 and appetite. Both SG and RYGB increase GLP-1 concentrations, which directly affect β-cell function; however, this is of lesser magnitude in SG compared to RYGB(1; 27). We have data to suggest that endogenous GLP-1 is at least partially responsible for reducing free-choice caloric intake after RYGB, providing a mechanism underlying differences between procedures (Fig. 1). Neuronal GLP1R mediates the anorectic effects of GLP-1(28). Inhibition of GLP-1 action with Exendin-9,39 after RYGB (Fig. 1A) accelerates gastric emptying (1). This observation suggests that factors other than anatomy regulate the upper gastrointestinal response to food ingestion. The attraction of certain foods decreases after RYGB(29) and appetite may be altered by enteroendocrine secretion(30; 31). A potential mechanism is via GLP-1 which alters gastrointestinal transit, gastric accommodation(1; 3; 32) and has direct effects on hypothalamic nuclei outside of the blood-brain barrier(33). GLP-1 and GLP-1 receptor agonists decrease food intake and cause weight loss(34; 35). GLP-1 also modulates taste sensitivity in rodents(36-39). The peripheral concentrations of GLP-1 observed in the early postprandial period in subjects post-RYGB are similar to those observed after infusion at 1.5pmol/kg/min – an infusion rate that alters GI function(40). More recently, activation of the GLP-1 receptor decreased food intake and food-related brain responses in patients with type 2 diabetes and in obese subjects as measured by functional Magnetic Resonance Imaging (MRI). These actions were blocked by Exendin-9,39(41). It is therefore reasonable to consider that the postprandial rise in GLP-1 might affect feeding behavior after RYGB, and to a lesser extent SG, where the increase in GLP-1 is less marked (19; 22-25).

III. Progress Report and Preliminary Studies

A. Measurement of gastrointestinal symptoms, gastric accommodation and gastric emptying. High concentrations of GLP-1 after RYGB modulate gastric emptying but it is uncertain if these could alter satiety. We have experience in the measurement of gastric accommodation (2; 42-44) and gastric emptying (45-48) as well as gastrointestinal symptoms (44; 49-53).

B. Infusion of Exendin-9,39. We have prior experience using Exendin-9,39 infusion for GLP-1 receptor blockade (1; 54).

IV. Research Design and Methods

Study Subjects: A total of 50 subjects (25 post-RYGB and 25 post-SG) will be recruited. We will recruit otherwise healthy subjects who have undergone bariatric surgery within the past 10 years... We will exclude subjects with diabetes post-bariatric surgery. Healthy status will indicate that the participant has no known active systemic illness and no history of symptomatic microvascular or macrovascular disease. To be eligible subjects must be willing to participate in all the studies outlined. **Screening Visit:** Subjects will provide written informed consent. To ensure they are healthy, subjects will undergo a history and physical examination; blood collection for complete blood count and chemistry group; urine collection to exclude pregnancy, vital signs, blood pressure, pulse, height and weight.. Habitual activity levels (55), and bowel symptoms (56) will be assessed. **Body Composition:** % body fat will be measured using dual-energy X-ray absorptiometry (iDXA scanner; GE, Wauwatosa, WI).

Exclusion Criteria: Subjects <20 years of age will not be studied to minimize the possibility of type 1 diabetes. Subjects > 70 years of age will not be studied to minimize the potential confounding effects of age on glucose tolerance. Healthy status will indicate that the participant has no known active systemic illness.

1) Experimental Design: Subjects will be studied in random order (at least 2 weeks apart) during which they will be infused with either Exendin-9,39 or saline during the study. On each occasion, subjects will be admitted at approximately 0600, to the Mayo Clinic outpatient CRTU (Charlton Building) on the morning of study after an overnight fast of 8 hours. At approximately 0615 (-210 min), a cannula will be inserted retrogradely into a vein of the dorsum of the hand. This will be placed in a heated Plexiglas box maintained at 55^{o}C to allow sampling of arterialized venous blood. A cannula will also be placed in the vein of the contralateral hand to allow infusions (Fig.10). Prior to study start at approximately 0720 (-10 min) subjects will use a Visual Analog Scale (VAS) to measure appetite and hunger (57). At approximately 0730 (0 min) subjects will consume a mixed meal consisting of one scrambled egg, 15 g of ham, and Jell-O containing 35 g of glucose. The egg will be labeled with 0.5 mCi ^{99m}Tc-sulfur colloid to enable measurement of gastric emptying as before (58). At this time, (0 min) an infusion of saline with start and continue till the end of the study, The meal will occupy a volume that is tolerable to patients who have undergone restrictive upper gastrointestinal surgery. Blood will be collected to measure glucose and hormone concentrations. **Gastric Emptying:** Anterior and posterior gamma camera images will be obtained immediately after ingestion of the radiolabeled meal, every 15 min for the first 2 h, then every 30 min for the next 2 h (total 4 h after the radiolabeled meal), as before (50; 52; 53; 59). **VAS scores and free-choice caloric intake:** will be measured at 30 minute intervals for the remainder of the study (44). At approximately 1130 (240 min) a free-choice standard buffet (consisting of lasagna, pudding and milk) will be placed in the room. The amount of items eaten from the buffet (including partially consumed buffet items) will be recorded. The study will end at 1230 (300 min) when infusions will be stopped, cannulae removed and the subject can then leave the CRTU. On the **Exendin-9,39** study day, at 0 min (0730), Exendin-9,39 will be infused @ 750 pmol/kg/min (following a bolus of 2250 pmol/kg administered at time 0 – as before (54)), for 1 hour (0-60 min). The rate of Exendin-9,39 will be decreased to 300 pmol/kg/min for the next 3hours (61-240 min). At that time, the rate will be increased to 750 pmol/kg/min for the remainder of the study (241-300- min).

1) Power Calculation: In a prior experiment we observed an overall mean value ± (SD) of Gastric Emptying = 145±(27)min(60) and 745±(86)Cal(44). Assuming similar variation, 25 subjects per group would provide approximately 85% power (at a 2-sided 0.05 α level), to detect a 15% change in GE_{50} (time taken to empty 50% of gastric contents) and a 10% change in caloric intake in each group in response to Exendin-9,39.

1) Statistical Analysis: Data will be presented as (observed) mean ± SEM. The initial analyses will compare the within-group effect of treatment (Exendin-9,39) with the data observed in the study where saline is infused. This analysis will use a paired t-test, or signed-rank test, as warranted. An ANCOVA model incorporating the corresponding baseline study value as a covariate (e.g. GE_{50}) will be used to test differences in the response to Exendin-9,39 between groups (RYGB vs. SG). The ANCOVA model will also include age, gender and weight as covariates. A *p*-value < 0.05 will be considered to be statistically significant.

1) Interpretation: We will test the hypothesis that blockade of the GLP-1 receptor (GLP1R) in subjects after RYGB increases caloric intake to amounts that do not differ from those consumed after SG in the presence or absence of Exendin-9,39 infusion. We anticipate that after RYGB, subjects presented with a free choice buffet will eat less than subjects after SG during saline infusion. However, Exendin-9,39 increases caloric intake during a free choice buffet after RYGB. This supports the suggestion that the high concentrations of GLP-1 observed after RYGB alters feeding behavior, decreasing caloric intake. Given the lower concentrations of GLP-1 observed after eating in SG, we anticipate that Exendin-9,39 will have little effects, if any, on caloric intake in subjects post-SG.

To test our secondary hypothesis, we will measure gastrointestinal transit using a labelled meal as outlined above during the two studies. We anticipate that in subjects after RYGB, inhibition of endogenous GLP-1 by Exendin-9,39 will accelerate gastrointestinal implying that the high concentrations of GLP-1 observed after RYGB delay gastrointestinal transit. Conversely, in the absence of very significant elevations in endogenous GLP-1 after SG, we expect little effect of Exendin-9,39 on gastrointestinal transit – as observed previously in subjects with an intact upper gastrointestinal tract (1).

Summary / Future Directions: There is evidence to suggest that post-prandial GLP-1 concentrations after RYGB influence satiety and caloric intake. This might be a mechanism by which RYGB has superior long-term effects on weight compared to SG. If this is indeed the case, GLP-1-based therapy could be utilized to maximize the benefit of surgical intervention after SG in subjects who are failing to lose weight or have suboptimal response to surgery. The combination of GLP-1 receptor agonist therapy and SG may provide equivalent or superior benefit to RYGB with less post-operative morbidity and mortality in the future. This application is intended to provide mechanistic data to support this notion prior to testing in a prospective, randomized controlled trial.

Analytic Techniques: All analytic techniques described in this and subsequent protocols are either established in the applicant's laboratory or are routinely performed in the Mayo GCRC Mass Spectrometry, Immunochemical Core laboratories of the Mayo CTSA. All blood will be immediately placed on ice, centrifuged at 4°C, separated and stored at -80°C until assay.

Glucose concentrations will be measured using an Analox glucose analyzer. C-peptide and glucagon concentrations will be measured using reagents purchased from Linco Research Inc., St. Louis, MO. Insulin will be measured using a chemiluminescence assay with reagents obtained from Beckman (Access Assay, Beckman, Chaska, MN). *GLP-1 hormone concentrations* will be measured: blood will be collected in ice-cooled EDTA-plasma tubes. Immediately after collection 100 μM of a dipeptidyl peptidase-4 (DPP-4) inhibitor, Aprotinin (Linco Research, St. Charles, MO) will be added to the sample tube to prevent DPP-4 mediated degradation of intact GLP-1. All blood will be immediately placed on ice, centrifuged at 4°C, separated and stored at -80°C until assay. Hormone concentrations will be measured as previously described (61; 62). In addition, ghrelin, leptin and peptide YY (PYY) concentrations will also be measured by radio-immunoassay using reagents supplied by Linco Research (St. Louis, MO).

V. Human Subjects

Detailed Description: Suitable volunteers will be asked to visit the CRTU on a total of three occasions, including screening. During the first or screening visit they will meet with a member of the study team and

undergo a history and physical examination to ensure that they fulfill entry criteria. If eligible, they will be asked to undergo determination of body composition. Subjects will be admitted on the morning of the study day. The morning of the study, a cannula will be placed to allow IV infusion. Infusions will be started. In addition a retrograde hand vein for blood draws will be placed. This hand will be placed in a Perspex hot-box heated to 55 deg C. Blood will be sampled several times (via the retrograde hand vein) to obtain arterialized venous samples. Subjects will be studied in random order (at least 2 weeks apart).

Population: Subjects will be recruited from Mayo Clinic Nutrition Clinic, Olmsted County residents and surrounding counties, who have previously indicated a willingness to participate in research – and who meet entry criteria. The racial composition of the county is outlined in the table below (%) using data from the 2000 population census. No children or prisoners will be recruited.

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other	Total
Female	0.15	2.8	1.8	1.5	43.8	0	51.5
Male	0.15	2.8	1.8	1.5	43.7	0	48.5
Total	0.3	5.6	3.6	3.0	87.5	0	100.0

Research Materials: We will be obtaining blood samples to measure hormone and glucose concentrations.

Recruitment of Subjects: Subjects will be recruited by means of referral, advertisement, past study participants who have consented to be contacted for future research and from the Mayo Clinic Nutrition Clinic. Study participants that meet eligibility may be contacted by letter or phone call. Individuals expressing interest may be contacted by phone or e-mail, where a member of the study team will review inclusion/ exclusion criteria. Eligible subjects will be invited to participate in the study and to come to the CRTU for a screening visit.

The following are exclusion criteria;

(a) Age < 20 or >70
(b) For female subjects: positive pregnancy test
(c) Functional or organic bowel symptoms
(d) Any systemic illness, microvascular or macrovascular disease
(e) Subjects with diabetes post-bariatric surgery
(f) Bariatric surgery > 10 years ago

Potential Risks: Blood sampling. Blood samples are collected by venipuncture for this study. Bruising can occur with venipuncture, as can fainting, etc. Risk Monitoring / Risk Reduction: The samples are collected using aseptic technique in designated venipuncture areas of the Clinic where facilities are available should untoward reactions (fainting, etc.) occur. Given the aseptic nature of the sample collection and the small risk of bruising, the monitoring plan is focused on advising volunteers to call the investigators should they have unusual pain or discomfort from the venipuncture site. Blood drawn within a 12 week period will not exceed 550mL (one pint).

Vascular catheter placement. Catheter insertion, intravenous infusion and blood withdrawal are associated with a small risk of phlebitis. Risk Monitoring / Risk Reduction: This will be minimized by careful attention to sterile technique. If phlebitis occurs, it will be treated conservatively with heat and when appropriate, with antibiotics. The catheters will be cared for by experienced CRTU nurses in order to minimize the risk of these complications. In all protocols, “arterialized – venous” blood will be obtained by placing a hand in which a catheter has been inserted in a heated box during the study. The temperature inside the box is maintained at ~55°C. With prolonged exposure to continuous heat, there is a potential

risk of local skin irritation or a minor burn. If this occurs, it will be treated appropriately. Catheter risks will be discussed with the volunteers prior to obtaining consent for the study.
Hormone Infusion. Infusions carry a risk of allergic reactions, bruising, discomfort at the site of infusion, and infection. Risk Monitoring / Risk Reduction: All infusates are prepared by trained personnel in a laminar flow cabinet using aseptic technique. Infusions take place on the CRTU where facilities are available should untoward reactions occur. Exendin-(9,39)(CS Bio, Inc.) will be prepared in a similar manner after IND approval by the FDA and after protocol approval by the IRB. Prior experience with Exendin-9,39 use in humans do not suggest the presence of specific adverse events (e.g. nausea) attributable to these compounds.
Radiation. Subjects will be exposed to radiation in this study. Lean body mass will be measured at the time of screening using DEXA (dual energy X-ray absorptiometry). The egg meal will be labeled with 0.5 mCi ^{99m}Tc sulfur colloid to enable measurement of gastric emptying. Anterior and posterior gamma camera images will be obtained immediately after ingestion of the radiolabeled meal, every 15 min for the first 2 h, then every 30 min for the next 2 h (total 4 h after the radiolabeled meal), Risk Monitoring / Risk Reduction: In all instances, the amount of radiation that a volunteer will receive will be well below levels that result in significant risk of harmful effects. Proposed radiation exposure will be reviewed by the Mayo Clinic Radiation Safety Board prior to initiation of any study. Women who could become pregnant will be required to have a negative pregnancy test prior to participation in each study.

During their time in the CRTU, volunteers will be closely monitored by their assigned study nurses, who routinely measure and document vital signs and complete pain / discomfort questionnaire-based assessments on an hourly basis. These are recorded in the volunteer's medical record. The designated CRTU nurse will monitor the IV lines and infusion sites for patency / absence of pain and inflammation every 30 minutes.

Confidentiality. . All of the materials collected are for research purposes only, and data will be kept in strict confidence. Confidentiality is assured by use of identification codes. All data, whether generated in the laboratory or at the bedside, will be identified with a randomly generated identification code unique to the subject. Risk Monitoring/Risk Reduction: The nature of the information obtained will be explained in detail to each participant. Safety screening labs, vital signs and medications (IV infusions) will become part of the medical record. The following study data collected, ICL results, DEXA, Gamma Camera scans, and questionnaires will not become part of the medical record. All information will be stored anonymously in the database and only the PI or one of his designates will have access to the data. The database is secured with password protection. The informatics manager receives only coded information which is entered into the database under those identification numbers. Electronic communication with outside collaborators involves only unidentifiable information. Confidentiality of all medical records is strictly maintained by established procedures. The original study data are kept in the study facility and are entered into a computer under the direction of a biostatistician. Physical records are stored under lock and key. AE reports and annual summaries will not include subject-identifiable material. Each will include the identification code only.

Data Safety and Monitoring Plan. The ultimate goal of this application is to further our understanding the role of different therapies in the management of diabetes. The DSMP utilized will adhere to the protocol approved by the Mayo Clinic IRB. We propose the following plan: -
Data quality and management: The principal investigator will review all data collection forms on weekly basis for completeness and accuracy of the data as well as protocol compliance. An adverse event (AE) is any untoward medical occurrence in a subject temporally associated with participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.) or any combination of these.
Adverse events grading: The common grading scale listed below will be used to grade AEs:

0 No adverse event or within normal limits or not clinical significant

1 Mild AE, did not require treatment
2 Moderate AE, resolved with treatment
3 Severe AE, resulted in inability to carry on normal activities and required professional medical attention
4 Life threatening or disabling AE
5 Fatal AE

Frequency of Data Review for this Study –The frequency of data review for this study differs according to the type of data and can be summarized in the following table.

Data type	Frequency of review	Reviewer
Subject accrual (adherence to protocol regarding demographics, inclusion/exclusion)	Weekly	Principal Investigator
Adverse event rates (injuries)	Weekly	Principal Investigator,
Compliance to treatment	Monthly	Principal Investigator,
Out of range laboratory data	Weekly	Principal Investigator,
Stopping rules report regarding statistical power implications of drop outs and missing data	Quarterly	Principal Investigator,

VI. Gender/Minority Mix

The majority of residents in Rochester, Minnesota and surrounding counties are White; recent population estimates from over the past decade have indicated that minorities make up a significantly larger segment of our communities. According to census area data such cultural groups as the Somalis, Hispanic/ Latinos, and South East Asians have increased the percentage of minorities living in Rochester and the surrounding counties from 3% in 1990 to nearly 10% in 2000. Despite the increases in the number of minorities within rural Rochester, Minnesota, it is likely that recruitment will fall short in the area of minority participation. However, we are actively working with the minority outreach specialist in the Center for Patient Oriented Research and Tribal Elders from the local minority populations, to develop complementary community-based strategies for recruitment of minorities at Mayo Clinic Rochester.

VII. References:

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