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WEIGHT LOSS AND TYPE 2 DIABETES:

A PROSPECTIVE RANDOMISED CONTROLLED INTERVENTION STUDY OF BEST PRACTICE MEDICAL MANAGEMENT VERSUS THE ADDITIONAL PLACEMENT OF THE LAP-BAND SYSTEM IN OVERWEIGHT PATIENTS

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BACKGROUND

The increasing problem of type 2 diabetes.

We are in the midst of two epidemics – diabetes and obesity. Obesity and diabetes are likely to be the two greatest public health problems this century. In collaboration with the World Health Organization, the International Diabetes Institute recently estimated that there were 160 million diabetics in the world in the year 2000 and that this will increase to 280 million by the year 2025. The majority of these will have Type 2 diabetes.

In Australia, the AusDiab studies have defined the extent and rate of growth of the problem[1, 2]. During 1999 and 2000, 11,247 Australians aged 25 or over and residing in 42 randomly selected regions, both urban and rural, across Australia were surveyed. The AusDiab report of 2000 indicated the prevalence of type 2 diabetes in these people was 7.5%. This is twice the prevalence that was estimated by the Busselton study[3] to be present in Australia in 1981. A 5 year follow up study of the initial participants was performed in 2004 and 2005 and measured the rising incidence of diabetes. It reported that, for each year of the follow up period, another 0.8% of the adult population developed diabetes, representing approximately 275 new cases each day. There are now more than 1 million Australians with diabetes.

Diabetes leads to major morbidity, reduces length of life and places a high burden on the healthcare system. It is a major risk factor for heart disease, kidney disease, blindness, amputations and birth defects. It shortens life expectancy by 15 years and is a major cost to the national health budget.

The increasing problem of overweight and obesity

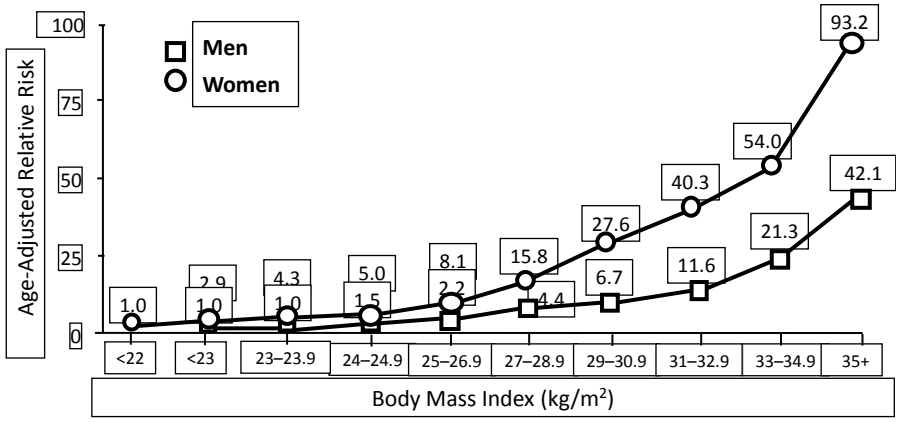
The AusDiab studies also showed the common and increasing adiposity with Australian

adults. In AusDiab 2000, 39.1% of those surveyed were overweight and a further 20.5% were obese (BMI > 30kg/m^2), a total of approximately 60% with excess weight. For the majority, it was central adiposity with abnormal waist circumference in 56% of the total sample. Comparison with earlier data from various national surveys shows an increasing problem. In prevalence of overweight has increased from 37% in 1980, 43% in 1989, 53% in 1995 and then 60% in 2000.

Relationship between type 2 diabetes and excess body weight

Nearly 90% of people with type 2 diabetes are overweight or obese. A curvilinear relationship between excess body weight and the risk of developing type 2 diabetes has been demonstrated in two large epidemiological studies. In the Nurses' Health Study[4], 112,000 nurses were followed for 16 years. The single most important predictor of type 2 diabetes was excess weight. With the risk of type 2 diabetes set at 1 when the BMI was 21 kg/m^2, the risk at BMI 25 was 5 times higher, at BMI 30 was 27 times higher and at BMI 35 was 93 times higher. Similar findings have been reported in a study of 51,000 male health professionals[5] surveyed between 1986 and 1992. With a risk set at 1.0 for BMI of 23 or less, the relative risk of diabetes was found to be 42 times greater at BMI of 35 or more. Figure 1 shows these relationships.

Figure 1. Relationship Between BMI and Risk of Type 2 Diabetes



Even in the presence of known high genetic risk this association with obesity remains strong. In Pima Indians with one or both parents having diabetes, the age-adjusted relative risk was 90 times greater for BMI >40 compared with BMI < 20[6].

Why does weight loss matter in type 2 diabetes?

The mechanism for the link between obesity and diabetes is becoming clearer. Genetically and metabolically we are designed to hunt and to gather. We have now created a society in which we sit and we eat. It is estimated that the average American consumes 8.5% more calories and is about half as active as they were 20 years ago. We would expect similar data for Australia. With intake exceeding output, fat accumulates. There are two fundamental requirements for the development of type 2 diabetes - insulin resistance and an inadequate pancreatic beta cell response to high insulin requirements. The most prevalent associate to insulin resistance is excess adipose tissue, especially when localized to central regions[7]. Visceral fat deposits are very sensitive to stimuli that mobilize free fatty acids. Free fatty acids are, in turn, powerful inducers of both hepatic and muscular insulin resistance[7]. In addition, an increased flux of free fatty acids from visceral fat deposits leads to increased hepatic glucose output producing hyperglycemia and reactive hyperinsulinaemia. Abnormal beta cell function often has a genetic basis[8]

and precedes the development of diabetes [9]. Beta cell function deteriorates with age[10], but more rapidly in those with impaired glucose tolerance [11] and diabetes, especially if poorly controlled. In addition, insulin resistance and increasing obesity increase the rate of beta cell deterioration in those with type 2 diabetes[12]. Thus, deterioration of beta cell function is integrally involved in a positive feedback loop with obesity, insulin resistance and hyperglycemia[12]. Type 2 diabetes is an inexorably progressive disease due to this progressive loss of beta cell function [13].

Effects of weight loss on type 2 diabetes

Weight loss is known to be a highly effective therapy for type 2 diabetes. Numerous observational studies have shown a direct link between the amount of weight loss and likelihood of remission of diabetes. Anderson et al[14] have summarized the findings of studies using low energy diets. Typically, with a low energy diet of 1000 – 1200 kcal/day, short term weight loss of 10% of total body weight can achieve significant reduction of fasting plasma glucose by 15 – 30 % from baseline. The challenge has been not so much the achieving of weight loss but sustaining the weight loss . Without substantial and durable weight loss the health benefits will not be seen

Weight loss through bariatric surgery provides a more substantial and durable weight loss than optimal medical therapy. We have recently compared the effectiveness of optimal medical weight loss program (diet and physical activity, very low energy diets, pharmacotherapy) with laparoscopic adjustable gastric banding in a randomised controlled trial conducted in people with mild obesity (BMI of 30-35)[24]. At two years after commencement, the LAGB group lost 21.6% of total body weight compared with 5.5% in the medical arm. They showed a major improvement in the prevalence of the metabolic syndrome which was present in 38% of both arms of the trial at commencement. At two years this was reduced to 3% in the LAGB group and there was no significant reduction in the medical group. The surgical group also showed a major and broad improvement in quality of life. There was no difference in the incidence of adverse events.

This powerful weight loss effect of bariatric surgery translates into improved outcomes for the patients with type 2 diabetes. Pories et al[15] was the first to seriously challenge conventional thinking with his provocative article in 1995 entitled *"Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes"*. He reported up to 14 year follow up on 608 patients after gastric bypass. Of 146 patients with type 2 diabetes, 83% had remission of the diabetes through the follow up period. Similar effects have since been reported for laparoscopic adjustable gastric banding[16], biliopancreatic diversion[17] and laparoscopic gastric bypass[18].

In a recent randomised controlled trial of the treatment of type 2 diabetes in obese subjects, we demonstrated that substantial weight loss was associated with remission of the disease in 76% of patients. Remission was defined as having a normal fasting blood glucose level and HBA1c of less than 6.2% while not taking oral hypoglycaemics or insulin. The patients who had remission had a mean loss of total body weight of 21%. In this study, a weight loss of greater than 10 - 14% of body weight appeared to be required to achieve remission as it provided the best combination of sensitivity (85%) and specificity (88%) for diabetes remission Of the 60 subjects in the trial, only 4 of 34 (12%) who lost less than 10% body weight obtained remission whereas 22 of 26 (85%) who lost more than 14% body weight obtained remission. There were none in the 10 – 14 % weight loss category.

In response to the accumulating clinical evidence, several European Diabetes Associations and the American Heart Association recommend patients with diabetes should seek to attain a BMI of less than 25 kg/m^2. Clearly weight loss makes a difference and should be aggressively sought. What level of BMI is optimal? The data from the Nurse's Health study among others indicate that the more weight loss achieve, the more likely remission of diabetes will be achieved and maintained. It could be argued from the Nurses' Health study and the male Health Professionals' study that an optimal weight target would be at the lower limit of normal weight, i.e. BMI of 18.5. In reality, a practical approach should be applied which balances the effectiveness with the risk, effort, complexity and cost.

How can significant and durable weight loss be achieved?

The options for achieving weight loss included lifestyle changes of eating less and exercising more, pharmacotherapy and bariatric surgery. The best option for each patient is the one that is least invasive method that works for them. If lifestyle change can lead to normal BMI then drug therapy or bariatric procedures are not needed. Current data however do not give support to a general effectiveness of this option. Norris et al[19] performed a meta-analysis of the long-term effectiveness of lifestyle and behavioural weight loss interventions. Their review did confirm that improvement in blood glucose control was intimately related to degree of weight loss[19]. However, from 22 studies with follow up of 1-5 years, they found that the pooled weight loss for any intervention compared to usual care of a low calorie diet was 1.7kg or 3.1% of baseline body weight. Furthermore it appears that not only do currently available lifestyle and pharmacological strategies only provide small to modest levels of weight loss, but that those with diabetes experience a greater difficulty in losing weight than non-diabetics[20-22]. Additionally, the costs associated with medical weight loss therapies for obese type-2 diabetics are high and ongoing[23] making the small benefit yield relatively expensive.

Our study of obese with type 2 diabetes has established a weight loss target of 10-14% total body weight loss for obese (BMI 30-40) to achieve remission of type 2 diabetes. If a similar target is applied to the overweight BMI 25-30, current data on non-surgical weight loss programs indicate that most would not be able to achieve this amount of weight loss and therefore remission of diabetes.

We hypothesize that it is likely that LAGB would achieve this weight loss target and a high level of remission of disease. The proposed study seeks to examine this hypothesis by using a randomised controlled format to compare the effects, side effects and costs of LAGB with usual medical therapy, including a weight loss program, in the overweight persons with type 2 diabetes.

The LAGB procedure has the potential for achieving acceptability as a central part of the treatment of the overweight patient with diabetes. It consists of a laparoscopically placed silicone ring with an inner balloon. It is placed at the cardia of the stomach. The tightness

of the band on the cardia is adjusted by injection of saline into a peripherally placed reservoir. It causes weight loss by reducing appetite, by providing a sense of satiety. Interest in food is reduced and when the person does eat, there is an early sense of fullness so that they can be satisfied with a small amount of food. The adjustability of the band is the key to achieving satiety. By adding fluid to the band via a simple injection of saline into a subcutaneous port, the feeling of satiety is increased. If we remove fluid, the sense of hunger returns.

The band is placed laparoscopically. It requires minimal dissection of tissues and so generates only mild discomfort, rapid recovery and a high level of safety. It is commonly performed as an outpatient procedure and, in the proposed study, the participants will be discharged home within two hours of completion of the procedure. The procedure is reversible, again as an outpatient procedure, and as no significant change has been made to the normal anatomy, complete reversal is expected.

Our surgical group have experience to date with more than 4,500 patients having this procedure and have shown it to be effective, associated with low morbidity and offering a much more gentle path to durable weight reduction than was achieved with gastric stapling. Multiple reports of our experience and outcome have been published. There have been no deaths, the perioperative complication rate is less than 1% and a mean weight loss achieved with a follow up from 3 to 14 years of greater than 50% of excess weight.

The Rationale for the Research Plan

The randomised controlled trial of patients with type 2 diabetes and a BMI between 30 and 40[25] showed that the obese diabetic patient achieves better outcome with LAGB than with continuation of their medical treatment. In association with a substantial reduction of their obesity, they have better control of their diabetes, reduction in the elements of the metabolic syndrome and improved quality of life.
We now wish to establish if similar benefits will accrue to those who are overweight but

not obese. Is weight loss as effective in the overweight as the obese in leading their diabetes into remission? Do they show a similar response to weight loss? Is their quality of life improved? Is this approach to the treatment of their diabetes a cost-effective use of healthcare resources? Can we learn more about how the remission of diabetes occurs?
In this study we will seek to answer these questions. Again using a randomised controlled trial format, we plan to compare the outcomes for a group of overweight (BMI 25-30) type 2 diabetics having LAGB placement with a similar group who are offered continuation of a program of optimal medical therapy. We will compare their outcomes initially at 12 months after commencement of the assigned therapy and again at 5 years after commencement. The principal outcomes monitored will be remission of diabetes, remission of the metabolic syndrome, improvement in other comorbidities of obesity, improvement in quality of life, adverse events and costs of therapy. Insulin resistance and beta cell function will be measured before commencement and at 12 months.

Hypotheses:

1. Substantial weight loss (> 10% body weight) in the overweight person with type 2 diabetes (T2D) will lead to remission of the disease.
2. There will be a correlation between the amount of weight loss and the likelihood of remission.
3. LAGB placement will be more cost- effective in achieving remission than a program of best medical care when modelled over the medium term..
4. The method for achieving weight loss does not determine the effectiveness.
5. There are increases of insulin sensitivity and beta cell function during weight loss.

Aims:

1. Compare, using a randomised controlled trial, the relative efficacy, durability, acceptability and costs of weight loss induced by LAGB, and a program of

optimal medical care

2. Observe the relationship between weight loss and remission of diabetes irrespective of the study arm
3. Measure changes in insulin resistance and beta cell function to identify the drivers of remission of T2D with weight loss.
4. Measure the direct healthcare costs during the trial (cost-efficacy study) and to derive a model of lifetime health and its costs from the remission data of the trial (cost-effectiveness study)

The principal measures of outcome will be:

1. Diabetes remission, defined as fasting and 2h glucose levels less than 7.0 and 11.1 mmol/L before and after a 75g oral glucose load (primary outcome)
2. Weight loss
3. The biochemical assessment of glycaemic control of type 2 diabetes using HbA1c.
4. Assessment of comorbidities including abnormalities of blood pressure, serum lipids and liver function.
5. Medication used to treat hyperglycaemia, hypertension and dyslipidaemia.
6. Morbidity and mortality associated with diabetes, obesity or treatment of these conditions.
7. The achievement and sustainability of weight loss.
8. The costs of all healthcare interventions during the trial

Potential Significance: A recent report by Access Economics, commissioned by Diabetes Australia, indicated that excess weight was the primary cause for approximately 240,000 people with T2D. Most of these people are overweight but not obese. We now know that for the obese LAGB is a more effective and cost–effective option compared to continuing medical management. We need to know if it also the best options for the overweight person with T2D. The proposed study will enable us to document carefully the efficacy of LAGB in comparison with standard medical care for T2D in a prospective, randomized, controlled fashion.

Entry into the study would require that the patient -:

1. Be between 18 and 65 years of age,
2. Have a body mass index greater than 25 and less than 30 kg/m^2.
3. Have been diagnosed with type 2 diabetes in the last 5 years.
4. Be able to understand the options and study requirements and to comply with the requirements of each program.
5. Willing to be randomized.

Patients would be excluded from entry -:

1. If there was lack of acceptance of the randomization process,
2. If there were a history of previous abdominal surgery which would potentially preclude laparoscopic placement of the band.
3. If there was a history of previous obesity surgery
4. If there were any contraindication to LAGB placement.
5. If there were medical issues which contra-indicated the application of either arm of the study. These would include; acute myocardial infarction within the past 6 months, dementia, active psychosis, concurrent experimental drug use, pregnancy or intending to conceive in the next two years, lactation, illicit drug use, excessive alcohol intake, use of drugs known to affect body composition, cytotoxic drugs, internal malignancy, or major organ failure.
6. Systemic lupus erythematosis or other auto-immune disease.
7. Direct hypothalamic damage as a cause of obesity.
8. If they were unable to understand the risks, realistic benefits and compliance requirements of the Lap-Band intervention and conventional management of diabetes.
9. The patient had type 1 diabetes, GAD antibodies, or diabetes was secondary to specific diseases such as haemachromatosis or chronic pancreatitis.

Recruitment:

Initial recruitment into the study would be achieved by a general awareness campaign, which emphasized a study of weight loss on type 2 diabetes in the overweight patient.

This would be particularly directed to the patients at the Baker IDI. Interested candidates would be provided with detailed information regarding the problems of diabetes and excess weight on at least two occasions along with detailed information of the two treatment arms of the study.

Initial assessment would include clinical and biochemical documentation of diabetes, the collection of various weight parameters and anthropometric measures and the identification of other co-morbidities. The assessment would include a review by a specialist physician for co-morbidities of diabetes and obesity. Initial investigations would include measurements of fasting glucose, c-peptide, haemoglobin A1c and serum insulin. Additional assessment include fasting lipids (total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol), iron studies, plasma homocysteine, RBC folate, vitamin B12, renal function, high-sensitivity C-Reactive protein as an inflammatory marker, urine for microalbuminuria and sex hormones including free androgen index.
In addition:

- an intravenous glucose tolerance test will be performed at entry and exit from the study to measure beta cell function. These measures will be done after cessation of insulin sensitizers such as metformin and without use of VLCDs such as optifast. Measure c-peptide on all samples.
- A fasting serum sample will be collected at entry and exit from measurement of adiponectin, resistin, leptin and other possible adipokines or gut hormones.
- Scoring cardiovascular risk using the ANZ Cardiovascular Risk Factor calculator – smoking, sex, age, lipids, glucose, blood pressure.

Initial Common Program before Randomization

After initial assessment, a period of one month would be used to obtain optimal glycaemic and blood pressure control. During this period a program of general advice and

education regarding type 2 diabetes appropriate **eating** patterns and appropriate **exercise** would be instituted. Patients would be prescribed any additional medication necessary to control blood glucose, hypertension or other comorbidity. The patient's weight, blood pressure, anthropometric measures and biochemical data would be assessed at the end of the one month and used as a baseline for the study.

The eligible patients will be randomly assigned by the co-coordinating centre to receive:
(1) a continuing program of medical treatment which will have a conventional program of advice and education regarding eating and exercise and include conventional medical therapy for diabetes and associated conditions (Program 1) or:
(2) the LAGB procedure as an additional intervention (Program 2).

Patients will be randomly assigned to one of the two groups and followed on an intention to treat basis. There may be more than 50 patients entering the program before 25 are randomized to each arm. The random assignment will be computer generated by a staff member of CORE not directly involved in the study and fifty opaque envelopes containing patient assignment will be prepared. Randomization will be clustered into groups of random size of between 8 and 12 to ensure even distribution without bias. Only when a subject has fulfilled all study criteria will allocation take place. The patient’s assignment will be performed by the data manager who will have no direct contact with the subject either before or after assignment. The clinicians involved in the assessment or treatment of patients will have no role in the assignment process.

Program 1 Patients randomized to the control arm of the study would continue to receive ongoing best available medical practice for the treatment, education, support and follow up, of type 2 diabetes and obesity. This will involve physician review every 3 months in the first year and 6-monthly thereafter, unless more frequent review is deemed necessary. Patients will consult a dietician and diabetes educator at least once, and up to 6 times a year. Very low calorie diets will be available for those wishing to use them. Medical therapies will be determined by a treating physician-specialist in diabetes management and adjusted on an individual basis. This individualized approach will reflect usual current best community based clinical practice. Participants will be advised to perform at least 150 minutes of moderate-intensity physical activity each week. Metformin will be recommended to all participants unless they have a normal oral glucose tolerance test during the trial. HbA1c will be targeted to less than 7.0%. Blood pressure will be targeted to <120/80mmHg to participants with albuminuria or a history of cardiovascular disease, and to <130/80mmHg for others. Antihypertensive drug therapy will be intensified if these targets are not achieved following a 3-month period of lifestyle change. Anti-platelet therapy and statins will be prescribed to all participants with a history of cardiovascular disease and to those over the age of 40 who had an additional cardiovascular risk factor. Medications will be weaned if the treating physician judges that the participant would continue to meet treatment targets, which will be reassessed within three months of such medication change.

Program 2 In addition to all aspects of program 1, patients randomized to Program 2 will have the LAGB procedure performed by standard technique within one month of randomization. The procedure would be expected to require between 25-30 minutes of operating time. Patients will be admitted to hospital on the morning of the procedure and would be discharged home within two hours of its completion. A barium meal will be performed before discharge to document appropriate band placement. There will be a transition from initial liquid food intake through to solid food intake over a four-week period. The program of LAGB adjustments and follow up will be performed at the Centre for Bariatric Surgery, The Avenue, Windsor, according to current usual practice. Patients will be first reviewed and initial adjustment of the LAGB made at four weeks after the

placement. They will then be reviewed every two weeks until the correct adjustment is achieved (typically three visits) and then reviewed every 4 - 6 weeks, according to clinical need.

Endpoints: *The principal end point will be clinical and biochemical remission of diabetes at two years. This is defined as having fasting and 2h plasma glucose levels of less than 7.0 and 11.1mmol/L after a 75g oral glucose load.*

Additional endpoints of the study relate to blood glucose control, diabetic comorbidity control, indirect measures of insulin resistance and beta cell function, weight and weight change, functional status, cost and side effects of treatment at two years after randomization.

1. Glycosylated Hb would be used as the outcome measure of glucose control. A difference in of 1.0% of HbA1c or greater would be considered clinically significant.
2. Insulin resistance and beta cell function would be estimated using the homeostatic model assessment model (HOMA) calculated in a standard way from fasting plasma glucose and C-peptide concentrations.
3. Beta cell function will also be calculated by intravenous glucose tolerance test with repeated measurements of serum insulin.
4. Fasting triglyceride, total cholesterol and HDL-cholesterol.
5. Blood pressure: mean systolic or diastolic blood pressure.
6. Change in medication required in managing diabetes, dyslipidaemia, hypertension and other comorbidity of diabetes or obesity.
7. Change in associated obesity comorbidities including: ovulatory dysfunction, sleep apnea, enzyme markers of liver function, asthma and gastroesophageal reflux.
8. Weight loss as measured by the percentage of excess weight loss, total weight loss, % excess BMI lost, Final BMI. Excess weight and BMI is defined as that weight above a BMI of 25.
9. Nutritional measures: hemoglobin, iron studies, vitamin B12, folate, fasting homocysteine, albumin, calcium and phosphate.
10. Functional Status will be measured using:
    - **A.** The Rand 36-Item Health Survey (SF-36) – a multi-purpose survey of general health and outcomes. It uses patient responses to measure each of eight health concepts, and can be scored as an 8-scale profile of summary physical and mental health outcomes. It also includes a self-evaluation of

outcomes which have been shown to capture changes in health during the past year.

B. Multi-dimensional Body-Self Relations Questionnaire - an 18 point standardised questionnaire of self-image.

C. Beck Depression Questionnaire – a 21 point measure of feelings of self-worth, competence and effectiveness

D. Employment Status of patients will be ascertained including the average number of hours worked each week and the amount of time lost through ill health or other reasons.

11. Complications and side effects: Any complications of the LAGB including peri-operative morbidity, early postoperative obstruction at the level of the band, deep venous thrombosis, infection etc. Later complications would include band obstruction, intolerance, gastric slippage or pouch development, erosion, access port leaks, infection and tubing problems. Any complication of medical therapy used in the treatment of diabetes, obesity or their related comorbidities.
12. Costs of therapy, including hospital, medical and allied professional costs and the costs of pharmaceuticals and prescribed nutrient supplements. A pharmaco-economic evaluation would be made.

Data Analysis

For the purpose of calculating numbers of patients in the trial, a principal end point of the study will be remission of diabetes at two years after entry into the study. On the basis of the RCT of obese diabetics, we expect remission approximately 15% of the non-surgical group based on the outcomes of the recent RCT. We regard a difference between groups of 45% would be clinically significant i.e. 60% remission in the LAGB group. On this basis 38 patients will need to be studied to provide over 95% confidence of detecting a difference with a power of 0.93, using a two-tailed test. On the basis of an expected 20% loss of candidates following randomization, a total initial recruitment of 50 patients is planned.

Data will be grouped according to the program to which the patients were randomly assigned (intention-to-treat analysis).

The baseline demographic data will be assessed with either Chi-squared test (Fisher's exact test) or unpaired Student-t test or Mann-Whitney test, as appropriate. In the study of efficacy, the groups will be compared using the Fisher's exact test for categorical data and by Student t-test or Mann-Whitney for continuous data. Data on costs will be totaled quarterly and the cumulative cost/patient will be compared.

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