Pilot Study of the Physiological Effects of an Integrative Medicine Approach in Irritable Bowel Syndrome

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1.0 INTRODUCTION

1.1 Introduction

Irritable bowel syndrome (IBS) is one of the most common disorders for which patients seek integrative medicine care. IBS is generally defined as having a constellation of symptoms that can include gas, bloating, nausea, abdominal pain, cramping, diarrhea, and constipation. Research suggests a number of potentially underlying causes including bacterial dysbiosis, abnormal electrical function/peristalsis, poor digestive function, and inflammation. In fact, inflammation is likely a common endpoint of the various causes. Chronic inflammation can result from and cause many of the underlying pathophysiological processes associated with IBS.

The typical goal of the integrative medicine approach is to develop an individualized plan to help restore homeostasis to the gastrointestinal system targeting a reduction in inflammation as an important element in helping to relieve symptoms. One of the most problematic issues though is to determine where in the GI tract the inflammation is occurring and then evaluating improvements in inflammation as any intervention proceeds. Although underutilized, what is emerging as one of the best ways of evaluating inflammation in the body, particularly in difficult to observe regions, is through the use of Fluorodeoxyglucose (FDG) positron emission tomography (PET). FDG is taken up in the body much like glucose and is particularly taken up in areas of inflammation where there is increased metabolism. Therefore, this technology can be used to assess inflammation, and measure the reduction in inflammation as the result of integrative interventions that target dietary modifications designed to reduce inflammation. With this proposed study, we plan to use FDG PET-MRI technology to develop a more specific and sensitive approach for evaluating areas of inflammation associated with IBS and measuring improvements in that inflammation in response to effective integrative interventions.

1.2 Integrative Medicine in IBS

Irritable bowel syndrome affects up to 20% of the population and is a functional gastrointestinal disorder primarily associated with symptoms such as gas, bloating, abdominal pain, diarrhea, and constipation. IBS is typically associated with inflammation in the gut related to a variety of factors including dysbiosis (abnormal bacterial flora), food related reactions, dysrhythmia of neuromuscular control of the gut, and psychological stress.[1,2,3] These factors, and a number of others, might occur individually or in conjunction with the other factors. Symptoms can severely limit a patient's activities due to abdominal discomfort and altered bowel habits. Studies of different interventions such as the low FODMAP or mind-body interventions[4] typically result in a symptomatic response in approximately 50% patients.[5,6] Thus, no single approach to treatment has been fully successful at this time. Integrative medicine approaches are frequently sought by patients due to the chronicity of the symptoms, the clinical impairment, and the lack of traditional medical treatments. The goal of the present study is to be the first to fully evaluate the various mechanisms associated with IBS and evaluate an integrative therapeutic approach focusing on diet and nutrition and individualized to the causes associated with the

patient's symptoms.

1.3 Utilizing PET-MRI Imaging in IBS Patients

This study will also make use of FDG PET-MRI which has the additional advantage of allowing imaging of the entire body, and particularly the GI tract, in order to detect areas of inflammation that might be associated with chronic pain conditions. FDG is a diagnostic tracer utilized to measure the metabolic rates of normal and abnormal tissues. This radiopharmaceutical is transported across the cell membrane by the same transporters that carry glucose. Deoxyglucose is phosphorylated by hexokinase to deoxyglucose-6-phosphate. However, in contrast to glucose-6-phosphate, which is eventually metabolized to carbon dioxide and water, deoxyglucose-6-phosphate is not a substrate for glucose-6-phosphate dehydrogenase. Therefore, deoxyglucose-6-phosphate and its derivatives are essentially trapped in most tissues long enough to allow imaging with modern PET instruments. Thus, FDG uptake reflects the glucose utilization of a given tissue and many investigators have noted the affinity of FDG for active inflammatory and infectious disorders such as inflammatory bowel disease or vasculitis.[7,8,9,10]

We have analyzed the existing PET data from this population by using methodologies we will utilize in this protocol. The study group included 22 patients, 7 males and 15 females, whose age ranged from 20 to 69 years (average of 36.9). The duration of the disease ranged from 0 to 32 years, with an average of 8.71. Endoscopy was performed in every patient and was reviewed by blinded experts, who qualitatively assessed five different segments of colon (ileum, ascending, transverse, descending, and rectum) and graded the severity of each with a number scale from 0 to 4. There were 48 segments with a score of 0, 16 segments with a score of 1, 18 segments with a score of 2, 7 segments with a score of 3, and 7 segments with a score of 4. The average score among all segments studied and graded by endoscopy was 1.052.

The PET scan data were analyzed with Region of interest Visualization, Evaluation, and Image Registration (ROVER) image analysis software, which we plan to utilize for examining data to be generated by the proposed research. Clinical/laboratory disease assessment indices (CDAI, CRP, calprotectin) were correlated with PET quantification data, and statistical analysis was performed. Of the results generated from global disease assessment, statistically significant correlations (P-value < 0.05) were noted between mean SUV and CRP (correlation coefficient of 0.62 and 0.68 when corrected for partial volume), and between MVP and CDAI value (coefficient of 0.60 and 0.64 when PV-corrected). Importantly, we noted that the correlation between CDAI and calprotectin was statistically insignificant (P-value = 0.29).

With regard to regional disease assessment, CDEIS was strongly correlated with SUVmean and cSUVmean (coefficients 0.62 and 0.69, P-values <0.001 and <0.0001, respectively). Correlation with MVP was not statistically significant. A logistic regression model was created to analyze the probability of detecting a severe (type 3 or 4) endoscopic lesion. Of the PET quantification data measured, partial volume corrected SUV mean was the most statistically significant, with an odds ratio of 1.82 and a P-value of 0.02. Area under the ROC-curve for cSUVmean was 0.6897. These preliminary data clearly shows a promising role for the approaches that we have proposed. This further strengthens our belief that novel image based quantification paradigms are necessary for optimal examination of this complicated disorder.

Our group has obtained similar FDG PET data in patients with inflammatory bowel disease using the same software proposed in the current study. This Region of Interest

Visualization, Evaluation, and Image Registration (ROVER) image analysis software found an excellent correlation between regional disease assessment and metabolic uptake on the PET scan (correlation coefficient of ~0.65, $p < 0.001$). Thus, this technique can provide important diagnostic information in patients with IBS. Combining this information with other data from stool analyses and laboratory studies will be essential for managing patients and evaluating the response of IBS to this integrative approach.

2.0 OBJECTIVES

AIM #1. To evaluate the ability of FDG PET-MRI to detect inflammation in the GI tract in patients with IBS.
AIM #2. To correlate FDG PET-MRI findings with various physiological and clinical parameters at baseline.
AIM #3. To evaluate the utility of FDG PET-MRI for assessing reductions in inflammation in patients with IBS managed with an integrative medicine approach based on diet and nutritional counselling.

3.0 STUDY PLAN

3.1 Subject Recruitment for IBS treatments

Subjects will be recruited if they are already presenting to the Marcus Institute of Integrative Health for clinical care of their IBS. Subjects may be pre-screened by telephone using a standardized script and screening form. Verbal consent and HIPAA Authorization to obtain the prescreening information will be obtained from subjects prior to the prescreening interview. If subjects are prescreened in person, a signed consent and HIPAA Authorization to obtain prescreening information will be obtained. Information collected during pre-screening will be incorporated into the research records as source documentation for subjects included in the study. If subjects are not eligible to participate in the study they will be asked if the information provided in during prescreening maybe retained for consideration in other studies. Prescreening information will be retained for an indefinite period on an official screening form that will be kept in a secure locked area that will only be used by persons involved with research with this research Study.

The proposed study will use FDG PET-MRI to explore the physiological effects of inflammation in IBS. We will plan to study 50 patients with known IBS over a two year period (25 per year) but may consent up to 60 patients in order to meet enrollment. The diagnosis of IBS will be based on the presence of appropriate GI symptoms. All subjects will be evaluated both clinically and physiologically (i.e. laboratory studies). All subjects will then have an initial visit #1 (pre-treatment) that will include an FDG PET-MRI that will quantify the level of GI tract inflammation at baseline. Subjects will then be provided a detailed and individualized integrative medicine program based diet and nutritional counseling (see below for additional detail). Subjects will be contacted by phone at one month and will also be given the option for an in office meeting if desired to review progress and answer any additional questions. After approximately 2 months of integrative therapy, subjects will have post treatment physiological measures along with a repeat FDG PET-MRI. This will represent visit #2 (post-treatment).

FDG PET scans will be performed using the PET-MR scanner at the Marcus Institute of Integrative Health in order to obtain simultaneous PET and fMRI data. Patients will be treated according to our integrative medicine program which allows for a standardized, but individualized approach towards the patient based on diet and nutritional counseling. The goal of the diet and nutritional approach it to develop an anti-inflammatory diet program focused on plant based foods and the reduction of inflammatory foods (i.e. dairy or gluten products) which have been shown to be beneficial in IBS. Patients will undergo an initial one hour dietary and nutritional counseling. They will be contacted a minimum of once a month for 2 months to make sure they are following the diet and also to answer any questions. It is our clinical experience that this level of counseling is highly effective in helping patients maintain the diet and improve clinical symptoms. They will be scanned initially and then after undergoing the Integrative Medicine program for 2 months. Referring physicians will be provided the results of the diagnostic studies in order to potentially help with determining additional treatment options.

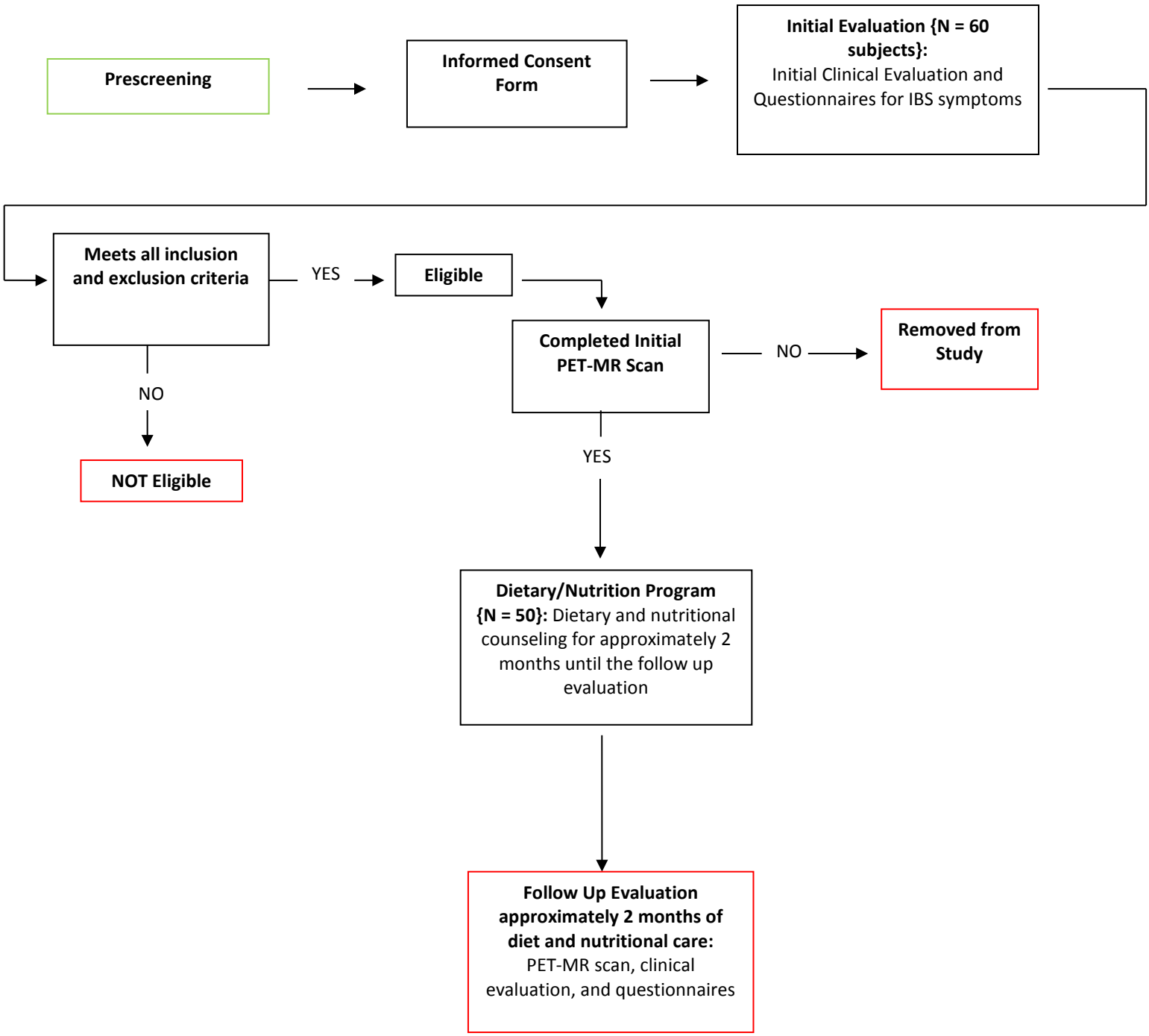
At the conclusion of the study, a thorough evaluation will be performed on understanding which diagnostic tests revealed clinically important abnormalities and how such findings predicted outcome and response to the dietary and nutritional counseling.

3.1.1 Subject Recruitment for healthy controls

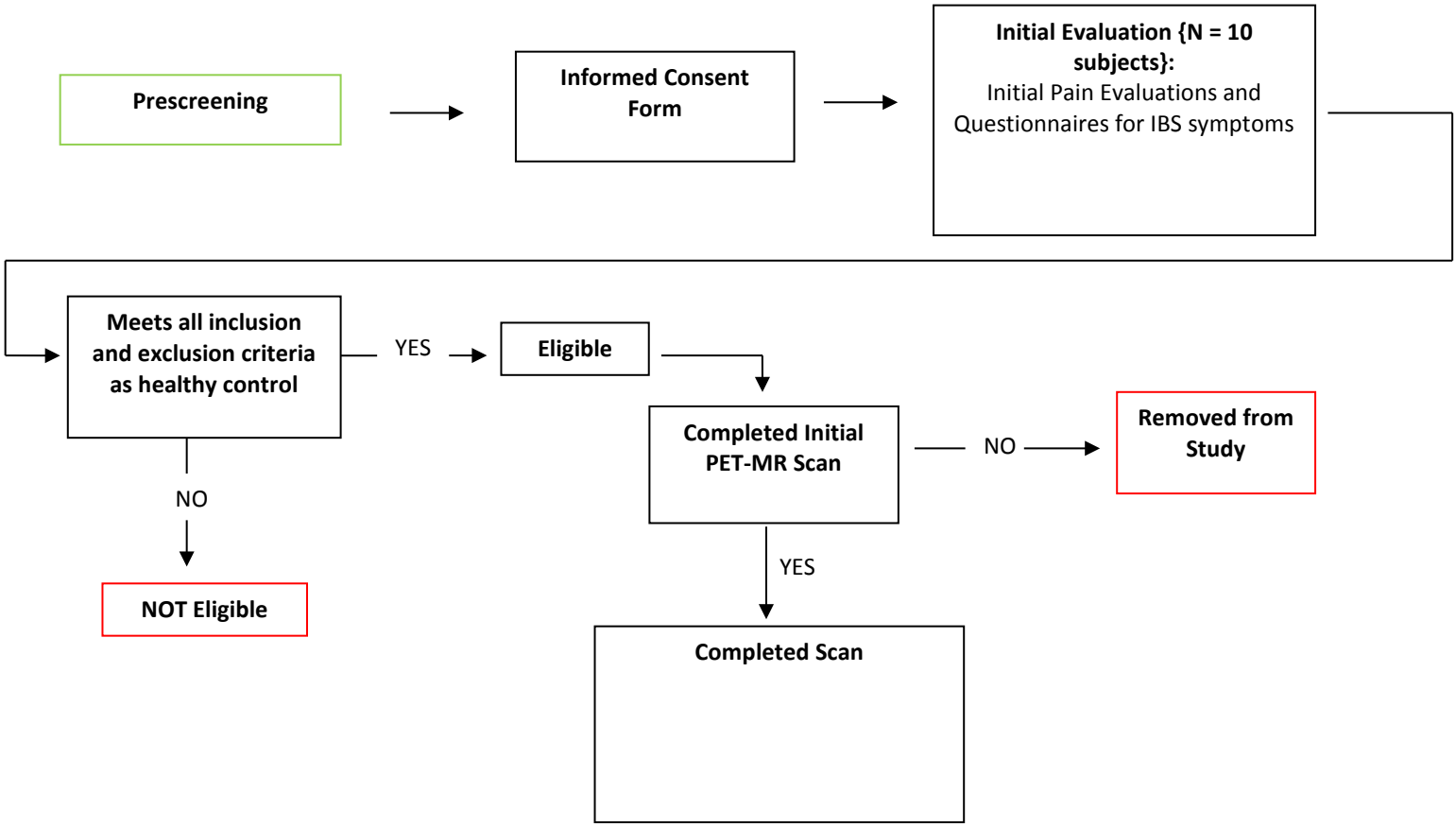
Up to 10 healthy controls will be recruited for a single PET-MR scan using the same imaging protocol as for the patients with IBS. The scan data will be necessary to better compare the results from the IBS patients to a normal database.

3.1.1 Flow Chart

3.1.3 Flow chart for IBS patients



3.1.3 Flow chart for healthy controls



3.1.4 Inclusion criteria for IBS patients

1. Age greater than 18 years old.
2. Meets the Rome III criteria for IBS: Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following: 1) Improvement with defecation; 2) Onset associated with a change in frequency of stool; 3) Onset associated with a change in form (appearance) of stool.
3. Patients have no other pre-existing and active significant gastrointestinal medical, neurological, or psychological disorders as per review by the PI
4. Minor, stable health problems that should have no substantial effect on cerebral blood flow will be allowed (i.e. controlled hypertension, medication controlled diabetes) as per review by the PI.
5. Patients will be allowed to be taking medications or supplements at the initial intake, but they must be on a stable dose regimen for at least 1 month.
6. Able to give informed consent and willing to complete the study.

3.1.5 Inclusion criteria for healthy controls

1. No significant current active medical conditions.
2. Stable medical conditions as determined by the PI are allowed.
3. No brain or body abnormalities that would affect the acquisition or analysis of the scan.

3.1.6 Exclusion criteria for IBS patients and healthy controls

1. Previous abdominal (bowel) surgery.
2. Not continuously taking antioxidants or anti-inflammatory medications (to be reviewed by the PI.
3. No other active medical conditions potentially requiring changes in treatment regimen during the study duration.
4. Not pregnant or breast feeding
5. Enrollment in active clinical trial/ experimental therapy within the prior 30 days.
6. Subject is unable or unwilling to lie still in the scanner (i.e. due to claustrophobia or weight > 350 pounds)
7. Subject has metal in their body or other reason that they cannot undergo magnetic resonance imaging.

3.2 Registration Guidelines and Recruitment

Study subjects initially will be recruited by referral from the Jefferson University Practices physicians, the Marcus Institute of Integrative Health, and self-referrals. If any recruitment materials are developed, they will not be distributed without IRB approval.

The subject population is derived from the greater Philadelphia area, which represents a racially and economically diverse population. We will make efforts for this protocol to be widely accessible, including offering the procedures protocol without charge to the subject.

3.3 Treatment Plan:

3.3.1 Informed consent will be obtained from all subjects before protocol specific activities are carried out. The subject will be informed about the limited data on the use of the Integrative Medicine program for IBS, possible risks and benefits, and possible adverse events. Informed consent will be documented by use of written consent form approved by the Institutional Review Board at Thomas Jefferson University and signed by the subject. History, physical examination, and initial diagnostic procedures (see below) will begin within 14 days of the informed consent process. Once patients are enrolled, a full set of laboratory values will be obtained including measures of inflammation such as CRP. Clinical symptoms and quality of life measures will be obtained as well.[11] Patients will undergo a FDG PET-MRI whole body scan including the abdomen and pelvis to evaluate for areas of GI tract inflammation. For the scan, patients will present to the Marcus Institute of Integrative Health Imaging Facility. They will be requested to fast for 8 hours prior to scanning. Patients will be brought into an injection room and will receive an intravenous catheter. Subjects will then receive the standard 6-12mCi of FDG through the IV. Patients will rest quietly for approximately 45 minutes and then will undergo scanning on the Siemens mMR PET-MRI scanner for approximately 60 minutes. During that time, PET images of the FDG in the GI tract will be obtained along with MRI scans to assess structural signs of inflammation. The FDG PET scan will be analyzed according to the Region of Interest, Evaluation, and Image Registration (ROVER) program.[12] This provides a Global Disease Activity score based on the activity level and overall volume of affected regions. The combination of the PET-MR system allows for this unique global quantitation of inflammation. After three months of receiving their integrative treatment program or standard of care, patients will undergo a follow up evaluation of the same clinical and physiological/laboratory measures obtained initially. Clinical symptoms and quality of life measures will be obtained as well. Patients will also undergo a follow up FDG PET-MRI scan to evaluate changes in inflammation in the GI tract.

3.3.2 The goal of this pilot study will be to assess the effect of our standard therapeutic diet plan provided at our Marcus Institute of Integrative Health for patients with IBS symptoms. The dietary and nutrition program will entail obtaining an extensive dietary history with the goal of determining foods in the patient's diet that are causing symptoms, particularly those foods that are pro-inflammatory such as dairy, gluten, and processed foods. Depending on the patient's presenting diet, a new diet will be discussed that will limit pro-inflammatory foods. The goal will be to develop a plant based diet with healthy fats and proteins and limited carbohydrates. This is the standard therapeutic diet plan provided at our Marcus Institute of Integrative Health. When necessary, we may also recommend nutritional supplements to support gut health such as basic vitamins and nutrients.

3.4 Criteria for Removal from / Cessation of Protocol

3.4.1 Measuring Endpoints: Endpoints will be measured after receiving either 2 months of the Integrative Medicine program. Any serious adverse events also will result in immediate discontinuation of the subject from the study.

3.4.2 Subject Withdrawal: The subject may withdraw from the study at any time for any reason.

3.4.3 Assessing Compliance: Patients will be contacted at one month to assess progress with following the program and answer any additional questions. As per the PI, if the patient is not following the diet/nutrition program, they may be withdrawn from the study.

All reasons for discontinuation of procedure will be documented in study flow sheets.

3.5 Adverse Events

The OHRP defines an adverse event as "any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research." Adverse events can additionally be classified as an unanticipated problem, meaning it was not expected to occur during the course of the research. If an unexpected adverse event were to occur, it then needs to be determined whether or not it is due to the research being conducted. If the event is a result of the research procedures, most likely the event is directly connected to the subject's participation in the research. It is also vital to determine whether an adverse event is serious. The OHRP defines a serious adverse event as one that a) results in death, b) is life-threatening, c) results in patient hospitalization or prolongation of existing hospitalization, d) results in persistent or significant disability/incapacity, e) results in congenital anomaly, or f) jeopardizes the subject's health to the point where they may need medical or surgical intervention. If the adverse event is unexpected, related to the research, and serious (where it is causing harm to subjects), then it is also classified as an unanticipated problem and must be reported to the Thomas Jefferson University Hospital IRB. All adverse events will be reported in accordance with Jefferson IRB Adverse Events Report. The IRB shall be notified in a written safety report if any serious and unexpected adverse experience associated with the use of the oral or intravenous nutritional supplements occurs.

3.6 Data Collection and Submission Schedule

3.6.1 Data Submission: Data must be submitted according to the protocol requirements for all subjects registered, whether or not assigned treatment is administered.

3.6.2 Master files, such as case report forms and progress reports, are prepared, and updated, by the investigator, study coordinator or designated staff. Case report forms will include eligibility checklist, demographic data, baseline history and physical laboratory results, adverse events, and off-study document. These will be completed by the study coordinator under the supervision of the principal investigator.

3.7 Measurement of Effect of the Nutritional Supplements

3.7.1 Clinical Response

Subjects will be evaluated initially and then at the approximate 2 month time point. All subjects will be administered the SF-36 for general health, the IBS Quality of Life questionnaire and the modified International Foundation for Functional Gastrointestinal Disorders (IFFGD) Personal Daily Diary. In addition, subjects will be given the Speilberger State Trait Anxiety Inventory (STAI) and The Profile of Moods Scale (POMS) will be administered. The Beck Depression Inventory is a standard 21 item questionnaire probing cognitive and somatic symptoms of depression.

3.7.2 PET Imaging Procedure

(a) Subject Preparation - An indwelling catheter needle will be inserted into an antecubital vein. FDG will be administered through the indwelling line as per standard protocol.

(b) FDG PET Imaging Procedure – Subjects will receive a standard of care FDG PET scan initially. Subjects will be asked to arrive at the Marcus Institute of Integrative Health in the morning on the day of the study. A signed informed consent form will be documented after all questions have been answered. Women of childbearing potential must have had a negative pregnancy test within 48 hours before proceeding with the PET study. The intravenous catheter will be inserted and capped. FDG (6-12 mCi) will be injected intravenously. After injection of the FDG, the venous catheter will be removed, and then the subject will be asked to sit comfortably in a chair in a dimly lit room for approximately 30 minutes to allow for the uptake of the FDG. Subjects will receive an MRI to assist with anatomic delineation.

(c) Image Acquisition and Processing – The FDG PET brain scan component will be obtained over approximately 20 minutes on the Siemens mMR PET-MRI scanner. This will allow for simultaneous acquisition of both the FDG PET data and MRI data. The FDG PET scan will enable us to obtain quantitative regional metabolic values in the brain as determined by a commercially available software program called MIM neuro that quantifies uptake and compares the results to a normative database. Immediately following the brain scan, PET-MRI of the abdomen and pelvis will be performed over approximately 30 minutes to evaluate activity in the bowel. Abdominal and pelvic PET images will be independently analyzed on a dedicated computer workstation. Automated computer software may also be used to aid in regional and global assessment of disease on PET images. Quantitative metabolic analysis will be performed in a manner similar to that described by Louis et al.[89] The degree of FDG uptake in the bowel will be measured by assessing the maximum and mean SUVs in different disease sites as well as segments of bowel on each examination (esophagus, stomach, proximal small bowel, distal small bowel, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum). Bowel SUVs in each subject will be summed to obtain a single value that accounts for the disease activity of the entire bowel, and bowel SUVs over multiple bowel segments in each subject will be averaged to obtain a single average bowel SUV value as an alternative marker for disease activity in the entire bowel. Similar calculations using ratios of bowel segment SUVs to either

liver SUV or to local background SUV may be performed as well. Summation and average measurements over the entire bowel per subject will be averaged over all subjects in each disease group cohort, and compared. Both SUVs and ratios calculated will be correlated with pathologic and endoscopic findings to assess sensitivity and specificity.

We have substantial expertise in examining abdominal structures, as previously we have examined data from a large number of normal subjects and published these results.[95] The data from healthy controls will be analyzed as follows: a region of interest will be assigned to the entire small bowel based on CT scans acquired along with PET in this population. An attempt will be made to separate jejunal from ileal small bowel in this population. Colonic activity will be measured in the following segments: ascending, transverse, descending, sigmoid and rectum. Mean and maximum SUVs will be measured in coronal planes by assigning at least 5 slices to the structures to be examined. We will use new ROVER analysis software (ABX, Radeberg, Germany) that will allow us to perform the PET measurements. This experimental image analysis software will be used to assess regional and global bowel SUV, while taking into account partial volume effects, and to calculate the metabolic volumetric product (MVP) of bowel, which we define as the product of bowel SUV and bowel wall volume. This novel approach will substantially improve our ability to calculate the disease burden by taking into consideration both volumetric and metabolic aspects of disease activity rather than relying on these parameters independently.

For the MRI, we will explore small bowel water content, transverse colon volumes, and also bowel movement with cine-MRI, all of which have been shown to be altered in patients with IBS.[13,14]

3.7.3 Statistical Considerations

Pre and post measures will be compared to determine the ability of the integrative program to reduce inflammation in the GI tract with a concomitant reduction in clinical symptoms. Data will be evaluated to assess the specific aims described above. The initial analyses of the data will be descriptive in nature. The results from each physiological and clinical measure will be described for each time point before and after patients have undergone the integrative health management program using means, standard deviations, median, and range. Graphical methods, such as plots of measurements over time, histograms, and boxplots are important tools for understanding the quality of the data, and assessing assumptions underlying statistical models (such as normality). Plots of all of the measured variables over time will be important to assess longitudinal patterns of change.

To evaluate if the integrative medicine program reduced inflammation, pre and post program physiological measures of inflammation will be compared, as will measures of FDG uptake in the GI tract on the PET-MRI scan, and measures of small bowel water content, colonic volume and bowel movement. These measures will be compared initially with paired t-tests followed by a more detailed comparison with a repeated measures analysis of variance. To accommodate the longitudinal nature of the data, we will also utilize a Heterogeneous Random Coefficients Model which will be fit for the measures in each clinical and physiological test. This model can also account for both between and within subject heterogeneity and will accommodate modeling potentially nonlinear therapeutic effects over time. The random coefficients model may be more flexible in terms of modeling the changes in clinical and physiological measures over time than repeated measures analyses of variance. The random coefficients model also has

fewer restrictions on the correlation structure between multiple measures within subjects. To determine if there is a correlation between changes in physiological and clinical measures, Pearson product-moment correlations will be computed unless the normality assumption is violated, in which case the Spearman rank correlation will be computed.

3.7.4 Power Analysis: Power is determined based upon the potential therapeutic response to the integrative intervention and the ability of the PET-MR imaging technique to determine abnormal metabolic activity in patients with IBS. Studies of integrative diet techniques, along with other clinical studies generally shows a clinical response of symptomatic improvement greater than 50% in approximately 50% of patients. We will have the goal of trying to have a greater than 75% response rate in patients as the result of our more detailed and individualized diagnostic and therapeutic approach. Assuming a power of 0.8 and α of 0.05 for a comparison between two equal size groups, the sample size will need to be 21 per group. Regarding PET imaging, we have used the results from preliminary data described briefly above. Based on this study, the average of SUVmean of severe lesions was 4.09 (SD 2.11, 95% CI 2.74 - 5.44) and the average of SUVmean of non-severe lesions was 2.67 (SD 0.97, 95% CI 2.30 - 3.04). Assuming reductions in inflammation in response to integrative medicine treatment similar to these values, then given these data and assuming power of 0.8 and α of 0.05 for two-sample comparison means, the estimated sample size will be n = 25 which will be able to detect an effect size of 0.8 (Stata sample size calculation). Based on these estimates, we will include 25 subjects in each group.

4.0 RISKS

4.1 Integrative Dietary and Nutritional Counseling: The diet is a healthful diet that provides all the essential dietary requirements. Anytime a diet is changed, gastrointestinal discomfort or symptoms may occur.

4.3 Potential Risks of FDG PET Scan: The FDG is a commercially available radioactive tracer that will be used according to its dose, route, and indication, but results in some exposure to ionizing radiation. The amount is acceptable for the research subjects who will directly benefit by receiving full clinical reads of these scans that their referring physician can utilize for determination of prognosis and treatment planning. Subjects will be required to lie still on the imaging table for 30-60 minutes, which can be uncomfortable. Subjects may feel hungry, dizzy or light-headed from fasting prior to the FDG scan.

4.5 Risks of venous cannulation: Venous cannulation is a routine clinical procedure that carries minimal risks when performed by trained personnel. It is possible that bruising could occur in some subjects. There is a theoretical risk of phlebitis or infection, which is very remote.

4.6 Magnetic Resonance Imaging: The MRI scanner requires a very strong magnetic field. MRI can be dangerous if a person has metal or metallic objects in their body. Subjects will be thoroughly screened to ensure that they have no metal in their body. Because of the magnetic field, metallic objects can move into the scanner and potentially injure the patient. All

precautions are taken to ensure that no such metallic objects are in the scanning room that could result in an injury. The MRI requires the patient to lie still for approximately 1 hour, which can be uncomfortable, or be claustrophobic

4.7 Risk of Discovering Incidental Findings

The results of these scan will be reported in a clinical report by a trained specialist. If an unknown abnormality (also called an incidental finding) is discovered on the FDG PET or MRI scans. The study participants who have an incidental finding will be thoroughly counseled by the study doctor and will have an opportunity to ask any questions. Such a finding may make the participant feel anxious of depressed. The information and scans for incidental findings may be made available to the study participant's PCP or health care provider in order to manage the finding as quickly and effectively as possible

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