Study Protocol

Title: Use Of A Weight Loss Aid In A Population Exposed To Polybrominated Biphenyl (Pbb)

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USE OF A WEIGHT LOSS AID IN A POPULATION EXPOSED TO POLYBROMINATED BIPHENYL (PBB)

Principal Investigator: Michele Marcus, PhD, MPH

Professor of Epidemiology, Rollins School of Public Health

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EXTERNAL COLLABORATORS

Jennifer Morse, MD, Medical Director, Mid-Michigan District Health Department. The Mid-Michigan District Health Department does not have an IRB and a reliance agreement has been executed.

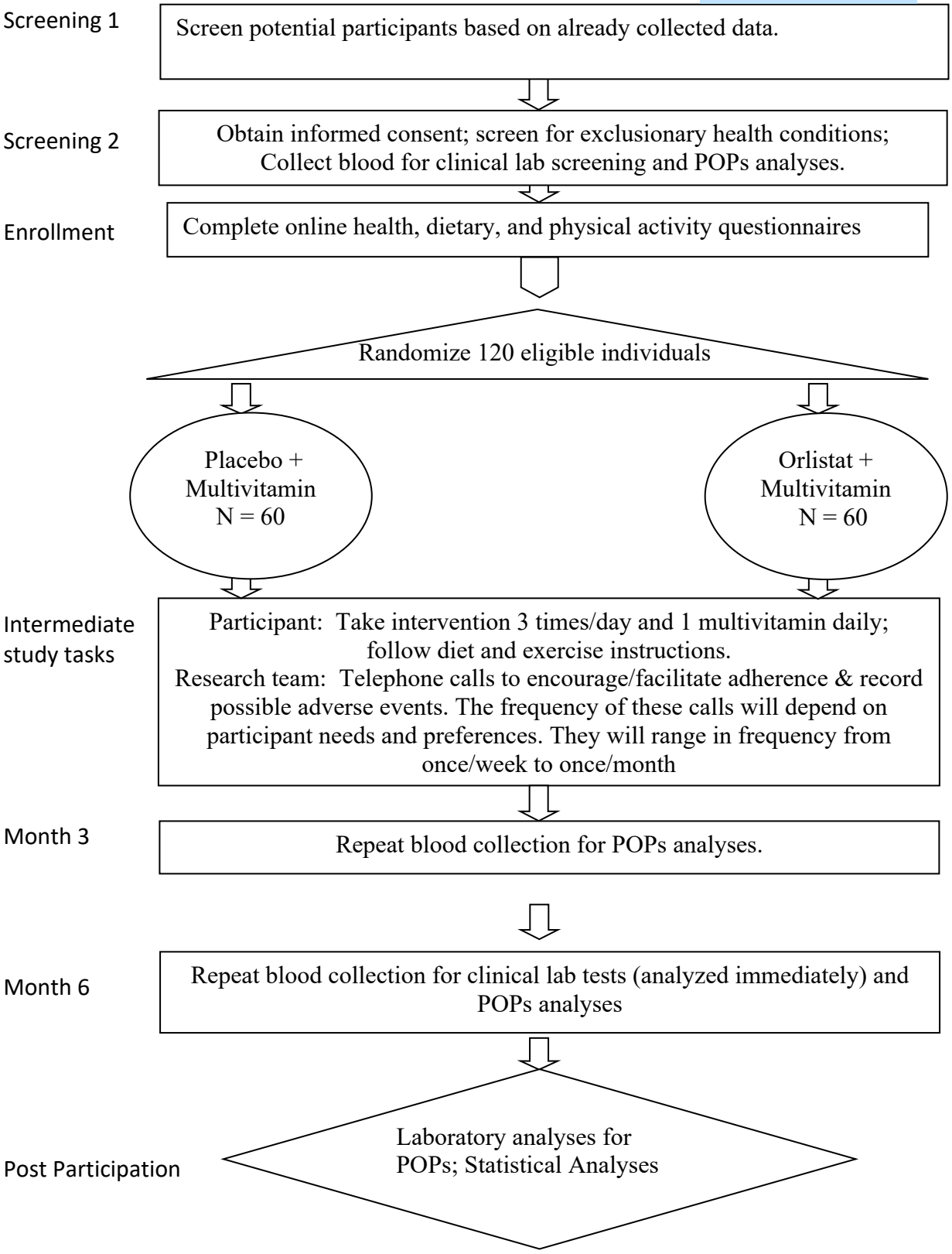
ABSTRACT

Millions of people living in Michigan were exposed to brominated flame retardants (Polybrominated biphenyls or PBB) as a result of the largest agricultural disaster in US history. Over the past six years, Emory researchers have tested nearly 900 Michigan residents and determined that 60% still had PBB in their bodies from that disaster. PBB is stored in body fat and we have been asked by community members if weight loss might reduce their body burdens of PBB and other lipophilic chemicals. In an effort to understand how PBB and other persistent organic pollutants (POPs) are eliminated, we have proposed (and funding has been approved for) a randomized trial of Orlistat vs. placebo. The Notice of Award will be issued when we receive IRB approval for the trial.

Orlistat is an over-the-counter product approved by the FDA for weight loss and works by increasing excretion of fat into the stool. Since PBB is stored in body fat, we hypothesized that Orlistat may reduce the body burden of PBB and other POPs. The proposed study is a randomized, placebo-controlled trial of Orlistat (at the dose available over-the-counter) plus diet and exercise for 6 months in a population with elevated PBB levels. Participants will be healthy overweight adults and Orlistat will be taken as directed for the approved indication (weight loss). We will follow all FDA-approved eligibility criteria and not enroll anyone with contra-indications to taking the drug. In addition, we will screen individuals for liver, kidney, or thyroid abnormalities, excluding anyone with abnormal values. We will repeat clinical laboratory tests at the conclusion of the trial (at 6 months). The primary outcome is weight loss and the secondary outcomes are blood levels of PBBs and other POPs. Sixty individuals will be included in each arm, with the aim of fifty participants completing 6 months of participation in each arm (100 total).

PROTOCOL SUMMARY

Figure 1: Schema



INTRODUCTION & BACKGROUND

In 1973, the Michigan Chemical Company accidentally shipped FireMaster, a brominated flame retardant mixture in place of a nutritional supplement for livestock feed. This introduced polybrominated biphenyls (PBB) into the Michigan food chain, ultimately exposing millions of Michigan residents, and resulted in one of the largest chemical exposure incidents in US history. To evaluate long-term health effects of exposure, the Michigan PBB Research Registry was established in 1976. The Registry is a multigenerational cohort with over 7,000 individuals ever enrolled, and includes those exposed during the contamination incident as well as subsequent generations, as PBB can be transferred from mother to child in the womb and through breastfeeding. Health-related research has been ongoing with this cohort for almost forty years and evidence to date of adverse health outcomes associated with PBB exposure includes increased risk of breast cancer, lymphoma, earlier age at menarche, increased miscarriages and lower estrogen levels among females, and more urogenital problems among males. Increased risks of thyroid dysfunction have also been found among men and women.

PBB is a Persistent Organic Pollutant (POP). POPs are characterized by a very long half-life and storage in adipose (fat) tissue. Approximately 60% of 867 Registry participants recently tested still have elevated blood levels of PBB (above the 95%ile of NHANES, random sample of the US population) in their blood. PBB Research Registry participants have repeatedly asked whether weight loss could reduce their body burdens of PBB and if there was a way to speed elimination of PBBs. Orlistat is a reversible inhibitor of gastric and pancreatic lipases (enzymes that break down dietary fats for absorption in the intestines), thus inhibiting absorption of dietary fats by approximately 30% [1] and increasing excretion of fat into feces [2]. Orlistat was approved by FDA in 2007 as an over-the-counter aid to weight loss for overweight individuals. Although the weight loss attributed to Orlistat (compared to diet and exercise alone), is modest, the loss of body fat is much greater with Orlistat than diet and exercise alone.

We hypothesized that weight loss due to Orlistat, because it preferentially results in loss of adipose tissue, may also reduce blood levels of PBB and other POPs. There is biologic evidence that supports this hypothesis [3] and in a pilot study using a rodent model [4], Orlistat was shown to safely reduce body burden of lipophilic chemicals. In addition, the study suggested that the rate of toxicant elimination increases with a higher dose of Orlistat. A recent review of detoxification regimens noted the absence of randomized controlled trials and the need for such trials [5]. We proposed such a randomized controlled trial of Orlistat to provide some evidence of whether weight loss due to Orlistat may also reduce serum levels of POPs in a highly exposed community. The study was approved for funding by NIH/NIEHS.

OBJECTIVES

- The primary objective is to determine if the use of Orlistat results in weight loss that is accompanied by a reduction in the body burdens of PBB and other POPs.
- The primary endpoint is the change in weight and BMI in the Orlistat group compared to the placebo.
- The secondary endpoint is the change in serum concentrations of PBBs, PCBs, DDE, and PBDE in the Orlistat group compared to placebo.

STUDY DESIGN & METHODS

Study Overview

Title:	Use of a Weight Loss Aid in a population exposed to PBBs.
Study Description:	Orlistat is an over-the-counter weight-loss aid that preferentially reduces body fat compared to diet and exercise alone. Our primary outcome is weight loss. Our secondary outcome is the change in concentration of chemicals that are stored in body fat (POPs). We hypothesize that the Orlistat group will lose more weight than the placebo group and because Orlistat preferentially reduces fat, that the weight loss in the Orlistat group will be accompanied by a reduction in serum levels of fat-soluble chemicals (POPs). Eligible individuals (using stricter criteria than recommended by FDA), will be randomized to Orlistat or placebo taken 3x daily with food. Both groups will receive multivitamins and a program of diet and exercise for six months.
Objectives:	To explore whether weight loss associated with Orlistat has a secondary effect of reducing blood levels of PBB and other POPs
Endpoints:	Primary Endpoint: Weight loss Secondary Endpoint: Change in serum concentrations of PBBs, PCBs, DDE, and PBDE.
Study Population:	We will conduct this study among individuals exposed to polybrominated biphenyls (PBB) as the result of an industrial accident. We estimate we will need to enroll approximately 120 individuals into the trial to have 100 complete the 6-month trial duration. Healthy men and women, aged ≧18 with a BMI ≥ 25 and at high risk for a PBB level ≥ 1 part-per-billion or a recently measured PBB level ≥ 1 part-per-billion will be screened for additional health-related eligibility criteria. We will NOT enroll individuals with contra-indications for Orlistat and will have more stringent inclusion criteria than recommended by the FDA for Orlistat.
Description of Sites/Facilities Enrolling Participants:	Participants will be enrolled by telephone from Emory University or enrolled in-person by Emory staff in Michigan.
Description of Study Intervention:	Random assignment to Orlistat at the over-the-counter dose (60 mg capsule, up to three times daily with fat-containing meals) or placebo capsule. Diet and exercise plus a daily multivitamin will also be recommended and monitored for both groups.
Study Duration:	Approximately three years.
Participant Duration:	Six months

Figure 2: Schedule of Activities

STUDY CALENDAR					
Procedures	Screening		Time (months) ± 2 weeks		
	1	2	Enrollment	3	6
Review previously collected data for provisional eligibility	X				
Informed Consent		X			
Telephone screen for additional eligibility criteria		X			
Online comprehensive health questionnaire (CHQ) or update of previous health questionnaire		X			
Blood draw for clinical function blood tests (liver, kidney, thyroid); review for eligibility and return results to individuals		X			X
Anthropometry (weight, height, waist circumference)		X		X	X
Blood draw for serum POPs concentrations		X		X	X
Analyses of serum POPs concentrations (baseline, 3 mo., 6 mo.)	After all samples collected				
Randomization			X		
Dietary Assessments			X	X	X
Physical activity assessments			X	X	X
Pill count to check adherence			Months 3, 6		
Compensation				$40	$60
Initiate a weekly telephone call – to answer questions, encourage adherence and determine any adverse events or new health problems – then reduce frequency of calls depending on each patient's needs and preference.			Months 1 -6		
Medication dispensed (Orlistat or placebo)			Enrollment: 3 mo. supply Month 3: 3 mo. supply		
Multivitamins dispensed (200ct)			X		
Post-study follow-up telephone calls			One week and one month after completion		

Study Design Overview: A randomized, double-blind, placebo-controlled 6-month trial will be conducted among selected participants from the PBB Registry. Signed informed consent will be obtained, in person or online, after discussion with study staff and an opportunity to ask questions. Potential participants will be screened for eligibility by self-report of health information and clinical laboratory tests. Study participants will be randomized into one of two groups: the Orlistat (intervention) group or the control (placebo) group. Both groups will be prescribed the same diet and exercise regimen.

Anthropometry measurements (weight, height, waist circumference) will be obtained at enrollment and serum levels of PBB, PCB, DDT/DDE and PBDE (POPs) will be measured at enrollment, at 3 months and at 6 months (all chemical analyses will be done at the conclusion of the trial). We will determine if body weight and serum concentrations of POPs have changed over time in each group. Subgroup analyses by amount of weight loss, enrollment PBB concentration, and gender will be undertaken as well. Data will be analyzed to see if the Orlistat group experiences greater weight loss than placebo and secondarily, whether the Orlistat group experiences a greater reduction in serum POPs over the course of the trial.

Intervention: Orlistat is the active ingredient while the inactive ingredients include microcrystalline cellulose, povidone, sodium lauryl sulfate, and xylitol. Store at 20-25 °C (68-77°F.) FDA has approved a 60mg dose 3x daily with meals for over-the-counter sale. This is the lowest dose available of Orlistat. Higher doses require a prescription. The dosage will not change during the course of the trial (6 months for each participant). Upon enrollment we will dispense a three-month supply of Orlistat or placebo. At the end of month three they will receive a three-month supply.

Alli (trade name) or Orlistat is a weight loss aid for overweight adults, 18 years and older. It is recommended that Alli be accompanied by a reduced-calorie and low-fat diet and exercise program until weight loss goal is reached. Most weight loss occurs in the first 6 months, hence the 6-month duration of the trial. Participants will be instructed to take 1 capsule (60mg) with each meal containing fat, and not to take more than 3 capsules daily. These are the FDA-approved instructions provided in over-the-counter Alli. Orlistat may decrease absorption of fat soluble vitamins and thus a multivitamin will be provided for all participants to be taken once a day, at bedtime.

Study Procedures: Individuals will undergo two levels of screening before randomization (see details in section "9. Participant Selection" below). Briefly, we will identify those likely to be eligible using information they provided to the PBB Research Registry previously. This includes age ≥ 18, BMI ≥ 25 likely PBB serum level ≥ 1 part-per-billion, indicated from recent PBB level data or as a part of a high-risk sub-group, and no contra-indicated medical conditions such as, have type 1 diabetes, had an organ transplant, are pregnant or lactating, current use of weight-loss medications, oral steroids, Coumadin, warfarin or Cyclosporine, have a diagnosed problem absorbing food, or have an eating disorder, a history of bariatric surgery, pancreatitis, kidney stones, a gall bladder disorder or a serious chronic disease (e.g. uncontrolled diabetes, congestive heart failure, chronic kidney disease) or allergies to any ingredients of the Orlistat OTC capsules. Ingredients including Orlistat, microcrystalline cellulose, povidone, sodium lauryl sulfate, and xylitol. Those who are provisionally eligible will be interviewed over the telephone to update those characteristics. Informed consent will be obtained in person or online. The participant will be asked to get a blood sample drawn at a local health department or medical facility for additional screening for liver, kidney, and thyroid levels. Additional blood will be collected for later chemical analyses. They will also be weighed and measured. Their clinical test results and medical history will be reviewed by Dr. Jennifer Morse to determine final eligibility. Anyone with abnormal clinical test results will be ineligible.

Randomization: Dr. Amita Manatunga, Professor of Biostatistics at RSPH will perform the randomization. Because background characteristics may affect PBB elimination rates, assignments to the study groups (Orlistat or placebo), will be stratified by gender and BMI and a randomization plan will be generated using a pseudo-random-number generator with randomly permuted blocks. This method serves to balance the group assignments over the course of the study and to ensure that the desired number of

participants will be allocated to each of the study groups at any time point during the randomization period. Permuted block sizes will not be disclosed to the blinded study personnel to minimize the likelihood of their being able to predict the next randomization assignment in the series. These assignments will be stored in a backend database table that will be password protected with restricted access to designated study personnel. Dr. Michael Collins, Director of the Healthway Compounding Pharmacy will also have access to the participant assignments in order to dispense the appropriate capsules.

After random assignment, the first installment of study supplies will be sent to participants (multivitamins for all participants and three-month supply of Orlistat or placebo, according to participant's study group assignment) and instructions for dietary modification and exercise recommendations. Study participants must familiarize themselves with the material before beginning their regimen. Intervention will arrive ready in pill-form for the participant to ingest.

The study intervention and control product will be prescribed by Jennifer Morse, MD and provided by Healthway Compounding Pharmacy in Michigan by Michael E. Collins, R.Ph, by mail to participants' homes.

Jennifer Morse, MD, is Medical Director for three local public health departments covering a 19-county area in Central and Northern Michigan, which covers the area the most highly exposed participants live. She is trained and Board Certified in Family Medicine and Board Certified in Obesity Medicine. She has experience prescribing and monitoring Orlistat in clinical practice and will be the prescribing physician for the clinical trial.

Michael E. Collins R.Ph., FIACP is Director of Healthway Compounding Pharmacy in central Michigan where many of the most highly exposed participants live. He was selected as the Professional Compounding Centers of America 2015 Pharmacist of the year and has many years of experience dispensing medications as part of randomized clinical trials. Healthway Compounding Pharmacy was the first pharmacy in Michigan to be accredited by the National PCAB (Pharmacy Compounding Accreditation Board).

Participants will be contacted upon expected receipt of study materials. Contact will be established weekly, then reduced as the study proceeds. The frequency of contact will depend on the individual needs/preferences of each participant until the conclusion of the trial at 6 months. Adherence will be monitored by these telephone calls and intervals of compensation. All participants will be asked to report pill counts to measure adherence at 3 and 6-month time points. Participants will also be asked at each study phone call whether they are experiencing any adverse symptoms potentially related to the medication or other aspects of the study.

Weight Management Intervention: The weight management intervention, dietary assessments, and physical activity assessments will be supervised by Terry Hartman, PhD, MPH, RD, Professor of Epidemiology. Prior to relocating to Emory in 2013, Dr. Hartman was Professor of Nutrition and Director of the Diet Assessment Center at The Pennsylvania State University. As a nutrition epidemiologist and a registered dietitian, she has approximately 20 years of experience exploring associations between

nutritional exposures and chronic disease outcomes and has designed and collaborated on multi-disciplinary trials of diet, exercise and other interventions to improve health.

Participants in both arms will follow the same study schedule with approximately equal contact time. Any contacts (e.g., in person, phone, e-mail) with the study staff will be logged to assess total contact time. We will provide weight loss and management guidance and support primarily via telephone interactions and online resources focusing on dietary and physical activity weight loss and management strategies. Participant interactions will begin weekly then adjusted based on participant needs and preferences. This plan allows the participants to implement strategies to gradually alter their food intake to promote weight loss and maintenance. Weight loss and management strategies for both study arms will be consistent with the Orlistat recommendations of limiting overall fat intake to 30% of daily energy with energy intake altered to lose 1-2 lbs. /wk.

Participants in both arms will receive nutrition and activity information emphasizing weight loss management including instruction on reading food labels, determining appropriate portion sizes, lowering overall dietary fat content, replacing higher energy dense foods with intakes of satiating, low energy dense foods like fruits, vegetables and whole grains, and increasing physical activity. We will encourage intake of foods high in soluble fiber (e.g., legumes, oats, barley, flax, nuts, selected fruits (oranges, apricots, apples, pears) and vegetables. In addition, information will be provided on managing energy intake when snacking, dining out, when traveling, and on special occasions. We will encourage light/moderate physical activity (e.g., walking). All information will be provided as behaviorally-based strategies similar to those used in the Diabetes Prevention Program (DPP) [6] and Look Action for Health in Diabetes (AHEAD) [7] lifestyle intervention programs [8, 9] which used Social Cognitive Theory (SCT) to guide their interventions [10]. According to SCT, self-efficacy, goal setting and outcome expectations are the three predominant factors thought to influence behavior changes. For example, phone contacts will include skill-building activities to increase self-efficacy. Journaling (e.g., food intake, physical activity) and weekly at-home weigh-ins will be used both to monitor individual progress and promote adherence to the intervention. During the final few months, participants will be contacted monthly by the study staff either by phone, email, or text (depending on individual needs) to continue to reinforce and encourage healthy weight management practices.

Intervention Training and Quality Control

Study staff delivering the intervention will participate in approximately eight hours of training initially with additional training as needed over the course of the study. The training, developed by Dr. Hartman, will include the purpose of the project and will review procedures and materials for use during the study. The PhD student will practice using materials and communicating with others during training. In addition, we will cover confidentiality, listening skills, strategies for coaching (but not directing) and sensitivity to cultural, ethnic, and related issues. During the intervention after obtaining the participants' permission, Dr. Hartman will patch-in on a random sample of 5% of interactions to assure protocol fidelity and to provide comments to increase the effectiveness of the intervention.

Outcome measures

1. Anthropometric measures / Body composition

Body weight, height and waist circumference (WC) will be measured using procedures based on the most recent NHANES Anthropometry Procedures Manual [11] at the local health department or medical facility at the time of the screening blood draw, 3 month and 6 month blood draws. Briefly, participants will have their weight measured in light clothing without shoes on a regularly calibrated digital scale. Height will be measured using a well-mounted stadiometer. Waist circumference will be assessed in duplicate with a measured tape placed horizontally just above the iliac crest, after completion of a respiratory cycle. When available, we will also measure body composition (% body fat measured by bio-impedance scale). We will compare the initial measurements to the 3-month and 6-month weight measurements.

2. Blood measures

Blood samples will be collected at screening and repeated at 3 and 6 months.

Screening blood samples will be used to determine eligibility but will also be processed and stored for analysis of PBB, PCB, DDT/DDE, and PBDE concentrations with the participants' other study time points. Blood samples will be aliquoted into smaller vials and frozen at -70°C and stored for analysis at the completion of the study.

POPs laboratory methods: Samples will be analyzed under the direction the Emory University HERCULES Integrated Health Sciences Core. Dean Jones, PhD directs this core. All chemicals will be analyzed using state-of-the-art laboratory methods after all samples are collected. This will minimize batch-to-batch variability and maximize our ability to detect changes in these chemicals over the course of the trial.

Samples for individual participants will be delivered to the laboratory in random order for analyses and blind quality control samples and duplicates will be included.

3. Diet Assessment

Assessment of dietary intake will be conducted under the supervision of Dr. Terry Hartman, PhD, MPH RD. 24-hour (24-hr) recalls are regarded as the best methodology to measure short-term changes in food intake because they provide high-quality and relatively unbiased dietary data [12]. Subjects will be asked by a trained study staff member to recall their food and beverage intake during the previous 24 hour period, approximately midnight to midnight of the preceding day. During the week prior to randomization, two telephone 24-hour recall interviews will be conducted, one during a weekday and one on a weekend. This process will be repeated again at the 3- and 6-month assessments. At month 3, participants will receive only one call to recount their diet, rather than two. All diet recalls will be collected, processed, and analyzed using the most recent version of the Automated Self-administered 24-hour Recall an interactive web-based system that prompts for food description details and automatically codes and calculates nutrient intakes using a database (USDA Food and Nutrient Database for Dietary Studies – FNDDS). The ASA24 system was developed and validated by researchers at the National Cancer Institute for direct use by respondents. However, if the participant prefers we will use it as an interviewer-administered tool (we have done this successfully in another study)[13]. The system includes a tracking system to monitor study progress but does not collect any identifying data about respondents to protect confidentiality. It provides values for total energy, nutrients and nutrient ratios, foods and food groups, and can be used to calculate the USDA Health Eating Index (HEI) to assess diet quality. Nutrient

data can be reported in a variety of formats and exported to a file for statistical analysis. Of particular interest in this study are dietary intake of total energy, macronutrients and selected food groups (e.g., fruits, vegetables, high-fat snacks). A potential limitation is inaccurate reporting of dietary intake; however, Dr. Hartman has extensive experience in the collection of dietary data and in maximizing the accuracy of this process.

4. Physical activity

We will assess recent usual physical activity and inactivity using the validated form of the Women's Health Initiative Physical Activity Questionnaire (WHI-PAQ) [14, 15] which assesses physical activity for men as well as women, across several domains (leisure, domestic and yard, work and transportation-related activities) and when scored can provide both continuous and categorical indicators of overall activity. This will be measured at enrollment, 3, and 6 month intervals.

Blinding: Due to their roles in assignment of participants to Orlistat or Placebo groups, and dispensing the appropriate medications, Dr. Amita Manatunga and Michael Collins, R.Ph and will not be blinded. All other study staff will be blinded to patient medication assignment to ensure no bias occurs in patient data collection and reporting. This will be maintained through the secure database given access only to those unblinded. All other laboratory and study staff, including the PI will remain blinded. Dr. Jennifer Morse will be notified of adverse effects reported and will be unblinded whenever necessary for patient safety. More information is provided in the Data Safety Monitoring Plan.

Risks to Human Subjects

a. Potential risks:

Potential risks associated with the use of Orlistat include:

- Headache
- Oily rectal discharge
- Urgent need to have a bowel movement
- Inability to control bowel movements
- Oxalate kidney stones/oxalate kidney damage
- Pancreatitis
- Liver injury or failure

Most of these risks are not serious with the exception of the last three, kidney, pancreas or liver injury. We have minimized the likelihood of these serious risks by screening potential participants for a history of kidney, liver or pancreatic abnormalities and blood tests for kidney, thyroid and liver function. These clinical screening tests are an ADDITIONAL LAYER OF PROTECTION against risk. They are not required nor recommended before initiating treatment with Orlistat. In addition, we will ask about symptoms of kidney, pancreatic or liver injury during each telephone contact. Participants will be instructed to consult their health care professional if they are experiencing symptoms of liver, pancreatic, or kidney injury possibly associated with the use of Orlistat. Symptoms of liver injury include loss of appetite, itchy skin, yellowing of the skin or the white part of the eyes, amber colored urine, light-colored

bowel movements (stools), or pain in the upper right portion of the stomach. , Signs and symptoms of pancreatitis include right upper abdominal pain, nausea, vomiting, and loss of appetite. Symptoms of kidney problems include swelling, especially of the legs and feet, little or no urine output, frequent or painful urination, blood in the urine, loss of appetite, nausea, vomiting, or severe pain in the back, belly, or groin. These serious risks are also very rare. In 2010 FDA reported 13 cases of liver failure (12 of them with the prescription dose of Orlistat which is twice the over-the-counter dose). https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213038.htm Because of this report, we will repeat liver and kidney function tests again at the conclusion of the study (at 6 months), to determine if any decline in liver or kidney function occurred during the trial.

Potential risks associated with blood draws include:

- Syncope or lightheadedness
- Hematoma
- Arterial puncture

Adequacy of Protection Against Risks

a. Recruitment and informed Consent

Individuals eligible for the study will be recruited from among those who have participated in PBB observational research. All Registry members that meet the provisional eligibility criteria will be contacted and informed about the trial by mail and telephone. The call will include detailed information about the trial procedures and potential risks of participating. If the individual indicates interest in participating, verbal consent will be obtained and the participant will be instructed to sign the online consent form.

b. Protections Against Risk

All study participant data will be organized and maintained by an assigned study ID number. The results will be published only in aggregate form. All identifying information will be kept in locked cabinets and secure computer files and will only be used by select study personnel for purposes of contacting cohort members, data cleaning and analysis when necessary. Identifying information in electronic form will be kept on a password protected research drive in a folder that is only accessible to the study personnel who need this information. RSPH aligns with the National Institute of Standards and Technology (NIST) special publications (800 series) for identifying, assessing, and managing information security risk within a technology environment. Drawing on federal and industry best practices, RSPH has implemented a series of multi-layered security controls to protect the integrity, reliability, and confidentiality of data. Additional protections

- Venipuncture will be conducted by trained phlebotomists.
- Study participants will report their health status weekly in the first few months and then monthly to the research team via phone. Additionally, participants will be informed to contact the research team in the case of changes in medical status or occurrence of side effects. In the case that a participant experiences a change in medical status or side effects Dr. Jennifer Morse, Co-Investigator will be make recommendations regarding continuation in the trial and physician follow-up.
- Since Orlistat may interfere with absorbance of fat-soluble vitamins, all study participants will receive a multivitamin dietary supplement to take daily during the study period.
- Liver function, thyroid function, and creatinine levels (for kidney function) will be measured prior to enrollment to ensure that the participant is healthy enough to partake in the study. These requirements go beyond the OTC recommendations to provide additional protection.

Potential Benefits of the Proposed Research to Human Subjects and Others

The risks associated with participation in the PBB Registry and the proposed study include that associated with venipuncture, the use of Orlistat at the over the counter approved dose, and the collection of PHI. These risks, along with the proposed protections are reasonable in comparison to the anticipated benefit to individual human subjects, their community and others in similar situations.

Potential Benefits: All participants will be overweight and are likely to lose weight as a consequence of the diet and exercise regimen regardless of whether they are assigned to the Orlistat or placebo interventions. The benefits of weight loss in overweight adults is well-documented. Registry members have shown a high degree of interest in continued health monitoring, as reflected in the most recent study's high participation rate and large number of study-related inquiries. Study findings are also of potential direct benefit to individual participants as knowledge of individual exposure levels can help health care providers understand health risks of their patients and provide appropriate screening and healthcare based on this information. Individuals with high PBB levels may be at increased risk of thyroid dysfunction, breast cancer and other cancers. Relevant findings from investigations have been, and will continue to be, conveyed in lay terms to individuals and to the community through various methods of communication. These findings will also benefit members of other similarly exposed communities.

The potential knowledge to be gained from the proposed study include understanding the disposition of PBB and other POPs in the body, understanding how the body eliminates such chemicals and to understand the relationship between weight loss and blood levels of POPs. The findings could directly benefit the affected community, similarly exposed populations, and public policy. Our community partners strongly support this study and submitted letters of support to NIH with our application for funding (we can provide these upon request).

DISPOSITION OF COLLECTED DATA

After data is collected, analyzed and recorded it will be archived using a secure database, used for all Michigan PBB Research Registry participants. Data collected will be used for future research on this cohort. Biological samples remaining after study-specific analyses will be banked in the PBB biorepository for further research. More information about this is provided in the confidentiality section.

COMMUNITY PARTICIPATION

This community-driven, community-partnered study was developed in direct response to concerns expressed by PBB Registry members at community meetings held across the state between 2010 - 2015. The community meetings were held to share previous PBB research findings with the community and to learn their continuing concerns. Members representing three community partners contributed to the development of the research proposal and design: the Mid-Michigan District Health Department, Pine River Superfund Citizen Task Force, and the PBB Citizens Advisory Board. Two representatives from each of these partner groups meet monthly with the PBB research team to discuss study progress and address study concerns. Partners contribute to study design, outreach, data and specimen collection logistics, development and testing of study materials, logistics for community meetings and partner meetings, and development of educational materials. Individual results (anthropometric measures, blood measures, diet assessments, and physical activity assessments) will be shared individually with each research participant either by email or by mail. Overall study findings will be shared with both individual

research participants in a mailing (or email), in scientific presentations and publications, via traditional and social media, and in-person at community meetings held across the state of Michigan.

PARTICIPANT SELECTION

Population: The Emory research team collected blood samples from nearly 900 individuals during the last few years, and the majority (approximately 60%) were above-background levels for PBB (NHANES 95%ile). We have identified at least 140 individuals that have historically high PBB levels, recent measurements ≥1 part per billion (ppb) or identified to be part of a high-risk sub-group. During the next two years we expect to test an additional 500 individuals. Those who fit the above criteria will be screened for eligibility for the trial. We will enroll 20% more participants than our final target sample size.

Inclusion of Women and Minorities
Participants will be included without regard to sex/gender, race or ethnicity. Currently, the large majority of PBB Registry participants are Non-Hispanic Whites, with a relatively equal distribution of males and females. Individuals expected to be newly enrolled into the PBB Registry will also fall into this category. The lack of representation of diversity of racial or ethnic groups is directly related to the characteristics of the population in the state of Michigan. It is possible that individuals from other racial or ethnic categories will be included.

Justifications for Exclusion of Children
Children under the age of 18 will not be included in the clinical trial. Orlistat will be prescribed in coherence with over the counter indications and is not indicated for anyone under the age of 18.

Recruitment and Informed Consent
Individuals eligible for the study will be recruited from among those who have participated in PBB observational research. All Registry members that meet the provisional eligibility criteria will be contacted and informed about the trial by mail and telephone. The call will include detailed information about the trial procedures and potential risks of participating. If the individual indicates interest in participating, verbal consent will be obtained and the participant will be directed to an online consent form and directed to their local health department for a blood draw for additional screening tests.

Provisional Eligibility: Registry participants will be provisionally eligible if they have a current or recent (within the last five years) PBB level of ≥1ppb, or are a member of a sub-group likely to have high serum PBB (former chemical worker, family member of former chemical worker, lived on a farm with animals that were quarantined because of PBB exposure), are at least 18 years old; currently reside in Michigan; and able to participate in examinations and laboratory tests and to engage in moderate physical activity (e.g. walking). Participants will complete informed consent after a telephone discussion with study staff, complete a health history questionnaire online and have a blood sample drawn at a local health department or other medical health facility for determination of eligibility. The blood tests include a lipid panel, liver panel, thyroid function, and creatinine levels (for determination of kidney function). These tests will also be repeated at the conclusion of the 6 month-trial. Persons eligible for the trial will receive a follow-up telephone call from study staff to review the study protocol and answer questions.

Participants will be EXCLUDED if they have any of the following:
BMI≤25, abnormal liver function, abnormal creatinine levels, abnormal thyroid levels (TSH), have type 1 diabetes , have had an organ transplant, are pregnant or lactating, current use of weight-loss medications, oral steroids, Coumadin, warfarin or Cyclosporine, have a diagnosed problem absorbing food, or have an eating disorder, a history of bariatric surgery, pancreatitis, kidney stones, a gall bladder disorder or a serious chronic disease (e.g. uncontrolled diabetes, congestive heart failure, chronic kidney disease) or allergies to any ingredients of the Orlistat OTC capsules. Ingredients of Orlistat include the active ingredient, Orlistat, and the inactive ingredients, microcrystalline cellulose, povidone, sodium lauryl sulfate, and xylitol. Participants will become ineligible at any point during the study if they begin a medical regimen involving any of the above medications. Participants with undiagnosed abdominal pain or diarrhea, Crohn's disease, Ulcerative Colitis, Celiac Disease, treated diabetes or treated thyroid disorder, will only be eligible following consultation with their primary care provider. Any participant using levothyroxine will be instructed to take their dosage 4 hours before or after Orlistat in order to maintain eligibility. Because Orlistat may impede absorption of lipid-soluble vitamins, all participants will receive a daily multivitamin to be taken at bedtime. **Due to an abundance of caution and a desire to minimize variance in response to Orlistat, these exclusion criteria are more conservative than FDA recommendations.**
We will NOT enroll any individuals with contra-indications for Orlistat as described by the FDA approved "Drug Facts".

Participants will be informed of their clinical test results, if results are abnormal. Abnormal results will disqualify participants from the study. More information is provided in the DSMP. Persons eligible for the trial will receive a follow-up telephone call from study staff to review the study protocol and answer questions.

Final determination of eligibility: Blood tests, along with health questionnaires will be reviewed by the study physician, Dr. Jennifer Morse, for final determination of eligibility. Individuals who do not meet the criteria for participation in this trial (screen failure) because of an abnormal lab result will not be re-screened.

Participant Discontinuation or Withdrawal:
Participants are free to withdraw from participation in the study at any time upon request. Discontinuation from Orlistat does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, Dr. Jennifer Morse will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuing
- Participant will be asked to complete all study procedures including 3 month and 6 month blood draws for POPs determination.

The PI may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive Orlistat

The reason for participant discontinuation or withdrawal from the study will be recorded on a Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced, unless the withdrawal rate exceeds that anticipated (approximately 20%)
A participant will be considered lost to follow-up if he or she is unable to be contacted by the study staff. The following actions will be taken if a participant fails to return for the required 3-month or 6-month blood draw. Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (telephone calls, emails and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study file. Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator or approved team members will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided over the phone in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the consent form and ask questions prior to signing. The participants will also have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. If the participant is unable to save an electronic copy of the consent form, one can be provided via mail. The informed consent process will be conducted and documented in the participant's record, and the form signed electronically, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected.

COMPENSATION

Attrition is a concern for any weight loss intervention; thus, we will use several methods to encourage retention of participants for the duration of the trial. At the beginning of the study we will have frequent telephone contact with participants (at least once/week) followed by reduced frequency as the study

progresses but no less than monthly. These frequent interactions with study participants should encourage retention. We will also contact participants (e-mail or text) to provide encouragement regularly (weekly in months 1-3; at least monthly, but more if needed in months 4-6). Compensation of $100 per participant will be offered to promote retention over the 6-month duration of the study. Participants will be compensated with $40 after the first 3 months of participation and an additional $60 after completion of the 6 months of the trial.

STATISTICAL ANALYSIS

The statistical hypothesis of interest is whether a mean change in weight or serum levels of POPs is detected at six months from the baseline. H_0:δ_I-δ_P=0 vs H_a: δ_I-δ_P>0, testing whether the mean change in weight or serum levels of POPs differs (mean change: δ, between the groups; δ_I, intervention group; δ_P, placebo group). The null hypothesis denotes no mean difference between the groups, and the one-sided alternative hypothesis denotes a difference between the groups, with the intervention group having a greater reduction in weight or serum levels of POPs over the course of the trial.

We plan to recruit and screen PBB registry participants, to enroll 120 participants into the trial. Our goal is to have 100 participants complete the 6-month trial duration. These estimates are based on the power analyses described here:

Power Analysis: The primary objective is to determine if the use of Orlistat results in weight loss in this population. Previous studies have shown an average of 2 to 3 kg weight difference between the intervention and placebo groups [16]. Assumming a standard deviation for weight change of 5 kg, we would have adequate power (80%) to detect a 2-3 kg difference (α=0.05; ρ=0.5) in weight with a sample size of 50 in each group. Power analyses were performed in PASS 13 software [17].

The secondary endpoint is the change in serum concentrations of PBBs, PCBs, DDE, and PBDE at six months from the baseline. For the outcome of change in serum POP levels, we based our sample size estimations on the historical PBB data for PBB registry participants with at least 2 measurements within a year and the pilot data from Jandacek et al [18]. We estimate that the variance of the differences in PBB levels is expected to be between 0.1 and 0.2 log parts per billion (ppb) (σ^2_{diff}). We have used the pooled variances for our power calculations. From our historical data, we expect a 1% reduction in PBB levels due to the natural course of exposure. A sample size of 50 in each group, would provide at least 80% power to detect a mean change in log PBB levels of -0.1 and -0.2 log ppb with a significance level of α=0.05.

After accounting for 20% attrition (based on 18% in Jandacek), our goal is to recruit at least 60 participants per group. The sample size projections are, in large part dependent on the estimated variances. Given the small sample sizes on which we have to estimate the anticipated variance, there is much uncertainty in the sample size needed. However, given the statistically significant findings of increased excretion of PCBs with only 14 individuals in each group consuming potato chips with artificial fat [18], we feel that 50 individuals in each group comparing Orlistat to placebo is reasonable based on all available preliminary data.

Data Management: Analysis variables will be captured from the study measures (anthropometric measures, blood levels, diet assessment, and physical activity assessment). Data will be collected and coded systematically, reviewed periodically for quality control, logical checks, data entry errors, missing or invalid values and logical inconsistencies among related questions will be checked. Plausibility of outliers will be examined. All data related changes, including changes to respective datasets will be documented electronically. Analytic datasets will be created to address specific study aims. Data dictionaries will be created. All data files will be maintained on a password-protected network system. Original and back-up datasets are stored on a secured network server.

Data exploration and will include the following: 1) determining whether the shapes of continuous distributions indicate that transformations are needed, 2) ensuring that the underlying assumptions of statistical analyses are satisfied (normality, linearity and homogeneity of variance), 3) identifying potential collinearity problems, 4) identifying potential outliers that require further investigation, and 5) exploring bivariate and unadjusted associations with the endpoints and reviewing potential confounding variables. These will be considered prior to constructing models to address our study hypothesis. Descriptive statistics will include means, medians, and percentiles as appropriate for each variable of interest.

The health history questionnaire (already approved by IRB for the related study IRB# 45959) and an online version of the WHI-PAQ will be created using REDCap Software and available to participants through an online website. The Automated Self-Administered 24-Hour (ASA24) dietary assessment tool will be used to collect information on food consumption over the past 24 hours. Participants will complete the ASA24 at enrollment, 3 months and 6 months. If the participant prefers, the PhD student or authorized staff member will complete the assessments with the participant by telephone. Data from all questionnaires will be reviewed periodically for quality control, data entry errors, logical checks, and inconsistencies among related questions. Plausibility of outliers will be examined. All data related changes, including changes to the datasets will be documented electronically. Analytic datasets will be created to address specific study aims. Data dictionaries will be created. All data files will be maintained on a password-protected network system. Original and back-up datasets are stored on a secured network server.

Exploratory Analyses: Comparisons between the intervention and placebo groups will be conducted to assess the degree to which comparability of study groups was achieved. From the ASA24, we will calculate mean daily caloric, total fat, and carbohydrate intake. We will examine changes in these measures over the study period. From the WHI-PAQ, we will estimate physical activity intensity. Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline, follow-up, clinical, and exposure data. We will examine longitudinal trends through graphical methods, such as individual profile plots and plots of mean POP levels over time, by group. These plots will be inspected to characterize the within and between subject variations across time.

Statistical Modeling: Data will be analyzed according to the intention to treat (ITT) principle. We will use a repeated measures approach and mixed-effects models [19] where the dependent variable is either body weight in kg or natural-log PBB levels and the primary predictors of interest are the group variable (placebo or intervention) and the measurement time treated as a continuous variable.
The general random-intercept model notation is:

$$Y_{ij} = (\beta_0 + b_i) + (\beta_1 + \beta_2 X_i)t_{ij} + \varepsilon_{ij}$$

where Y_{ij} denotes the weight in kg or the log-transformed serum PBB concentrations measured on participant i at time t_{ij} where $(i = 1,2,...n)$ for participants and $(j = 1,2,...n)$ for measurements within a participant. X_i is an indicator variable which takes the value zero for the placebo group and one for the intervention group. β_0, represents the overall intercept (mean weight in kg or mean log PBB levels) at baseline, independent of group and b_i is the random effect that represents the deviation from the population mean for participant i. This model assumes that the random effect $b_i \sim N(0,\sigma_b^2)$ and the error $\varepsilon_{ij} \sim N(0,\sigma^2)$ are independent. β_1 and $(\beta_1 + \beta_2)$, represent the slopes (or elimination rates of PBB) for the placebo or the intervention group, respectively. The group-by-time interaction parameter $(\beta_2 X_i * t_{ij})$ assesses if the mean change in weight or if the PBB elimination rates vary by group across time. Slopes that vary randomly among participants will also be considered and an appropriate covariance structure will be selected.

Adjustment for relevant baseline variables and subgroup analyses will be performed to assess differences in weight change or PBB elimination rates by relevant covariates (such as age, gender, initial PBB level, or initial BMI). Since, physical activity reduces body weight and BMI, and increases metabolism, both may be associated with reducing PBB body burden. In multivariable models of serum PBB concentrations, we will consider adjusting for intensity of physical activity and change in BMI in order to measure the independent effect of Orlistat on reducing PBB levels. For the ASA24 measures, we will examine possible associations between changes in mean daily caloric, fat, and carbohydrate intake and serum PBB concentrations. Statistical analyses will be performed in SAS 9.4 software, and models will be fit with the Mixed procedure [19].

DATA & SAFETY MONITORING & REPORTING

Data Safety and Monitoring Plan

OVERSIGHT RESPONSIBILITIES

Oversight of the progress and safety of the trial will be provided by the Principal Investigator (PI), Dr. Michele Marcus, and co-investigators Drs. Terry Hartman, Amita Manatunga, and Jennifer Morse along with Ms. Metrecia Terrell, project data manager/biostatistician. Adverse events are not anticipated, but any occurring will be documented and reported according to Emory IRB policies and procedures. Cumulative adverse events and study progress summary will be communicated to the IRB at the time of continuing review

MONITORING PROCEDURES

Dr. Marcus assures that informed consent is obtained prior to performing any research procedures, that all participants meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan. Dr. Morse will also review individual (de-identified) records and laboratory tests to confirm eligibility.

De-identified study data are accessible at all times for the PI and co-investigators to review. The PI and co-investigators review study conduct, including protocol deviations and dropouts, on a monthly basis. The PI and co-investigators review adverse events (AEs) individually in real-time and in aggregate on a monthly basis. The PI and co-investigators review serious adverse events (SAEs) in real-time. Liver

function, thyroid function, and creatinine levels will be measured prior to enrollment to ensure that the participant is healthy enough to partake in the study. Participants with abnormal levels or functions will not be eligible to participate in the study and will be counseled to seek care from their primary care physician. Additionally, participants with chronic kidney disease (defined by a glomerular filtration rate below 60) or kidney stones or gall bladder disorder will be excluded. Participants will be excluded if they are pregnant or lactating, have a diagnosed problem absorbing food, have a history of pancreatitis, bariatric surgery, organ transplantation, a diagnosed eating disorder, or a serious chronic disease as identified by the study doctor. Use of weight-loss medications, Coumadin, warfarin, Cyclosporine, or oral steroids will also exclude participants from the study. Allergies to any ingredients of the Orlistat OTC capsules including the active ingredient, Orlistat, and the inactive ingredients, microcrystalline cellulose, povidone, and xylitol will result in exclusion from the study. Participants will become ineligible at any point during the study if they begin a medical regimen involving any of the above medications. Pancreatitis is a very rare side effect of Orlistat use. Due to the extreme rarity, no routine laboratory tests will be performed. Patients will be counseled about the signs and symptoms of pancreatitis and instructed to report any relevant symptoms to Emory study staff. Liver injury is a very rare possible side effect. We will minimize the risk of liver injury by screening individuals for abnormal liver function and counseling participants about the signs and symptoms of possible liver injury.
The PI ensures that all protocol deviations, AEs, and SAEs are reported to NIEHS and IRB according to applicable regulatory requirements.

COLLECTION AND REPORTING OF SAEs AND AEs
For this study, the following standard AE definitions are used:

Adverse event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

Serious Adverse Event:
Any AE that results in any of the following outcomes:

- Death
- Life-threatening event
- Event requiring inpatient hospitalization
- Persistent or significant disability/incapacity
- An important medical event based upon appropriate medical judgment of Dr. Morse

AEs are graded according to the following scale, based on their impact on the patient:

Mild:
An experience that is transient, and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.

Moderate:
An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

Serious:

An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment, it becomes a serious adverse event.

The study uses the following AE attribution scale to determine the likelihood that they are related to the study intervention:

Not related:
The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
Possibly related:
An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

Related:
The AE is clearly related to the study procedures.

AEs are identified through self-report by participants via follow-up phone calls. At the beginning of the study we will have frequent telephone contact with participants (at least once/week) followed by reduced frequency as the study progresses but no less than monthly. Participants can request more frequent phone calls. Participants will be asked to contact the Emory study staff if additional adverse events occur or if they have any concerns or questions about the protocol.

All AEs are reported according to the Emory IRB AE reporting guidelines.

MANAGEMENT OF RISKS TO SUBJECTS
AEs that may be associated with the use Orlistat include:

- Headache
- Oily rectal discharge
- Urgent need to have a bowel movement
- Being unable to control bowel movements
- Oxalate kidney stones/oxalate kidney damage
- Pancreatitis
- Liver injury or failure

<u>AE Management</u>
AEs are identified through self-report by participants via follow-up phone calls that occur weekly and then are adjusted based on patient's needs and preferences. Participants can request more or less frequent phone calls. Participants will be asked to contact the Emory study staff if additional adverse events occur or if they have any concerns or questions about the protocol.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during interviews of a study participant presenting for medical care, or upon review by a study monitor.

If participants report gastrointestinal issues following Orlistat use, they will be counseled to reduce the fat content of their meals. If symptoms persist or more serious symptoms arise, participants will be told to discontinue the Orlistat regimen but continue with the diet and exercise plan.

The signs and symptoms of severe liver injury include loss of appetite, itchy skin, yellowing of the skin or the white part of the eyes, amber colored urine, light-colored bowel movements (stools), or pain in the upper right portion of the stomach. People who experience these signs and symptoms should contact their healthcare professional immediately.

Signs and symptoms of pancreatitis include right upper abdominal pain, nausea, vomiting, and loss of appetite.

Symptoms of kidney problems include swelling, especially of the legs and feet, little or no urine output, frequent or painful urination, blood in the urine, loss of appetite, nausea, vomiting, or severe pain in the back, belly, or groin

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. After review of reported symptoms and real-time communication with Dr. Morse, she will determine the appropriate action needed on a case-by-case basis. If contact with participant is necessary then Dr. Morse will learn the identity of the individual, their intervention group and contact information. She will contact the participant to discuss management.

SAE REPORTING

SAEs that are unanticipated, and possibly related to the study intervention will be reported to the, IRB, and NIEHS in accordance with requirements. There are no expected SAEs associated with this trial.

PROCEDURES

Study personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. We will call participants one week and one month after the participant completes the study. Any of these findings detected from one or more of our study assessments found by our study personnel will then follow a chain-of-command in a notification scheme provided to study personnel at the beginning of the study. This chain-of-command will lead to the appropriate channels being notified of a possible event.

After each study telephone call, the staff member will inform the PI, Dr. Marcus of the occurrence of AE/SAEs since the last visit. If a further input is necessary Dr. Marcus will request advice from study clinician, Dr. Morse. If, after review, there is a confirmation of an AE/SAE, Dr. Morse, will immediately report to the PI, Dr. Marcus any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Dr. Morse will notify patients individually by phone of AEs and SAEs, and study-related results that are of concern and may need additional management by the patient's health care provider.
The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

DATA QUALITY AND MONITORING PLAN
The PI or study staff will review all data collected on an ongoing basis for data completeness and accuracy as well as protocol compliance. Dropout rates will be monitored but will not affect the study's progress. All SAEs and aggregate AEs will be reviewed.

Research staff will collect information on adherence to protocol through follow-up phone calls abiding by the aforementioned schedule. Adherence of participants will be evaluated by pill counts, completion of Automated Self-Administered 24-Hour Dietary Assessment and the Physical Activity Questionnaire surveys completed by all participants at enrollment, 3 months, and 6 months. The PI, co-investigators and study statistician, will review adherence and drop-outs on a regular basis (probably monthly depending on the rate of accrual of participants).

Safety oversight will be under the direction of a Data and Safety Monitoring Plan (DSMP) composed of a procedure with input from the appropriate expertise, including Dr. Marcus, Dr. Hartman, and Dr. Morse. All deviations will be addressed in study documents. Protocol deviations will be sent to the Institutional Review Board (IRB).

If a pregnancy is reported the patient will be discontinued from the study intervention effective immediately.

UNANTICIPATED PROBLEMS
The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The investigator will report unanticipated problems (UPs) to the Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

CONFIDENTIALITY

PLAN FOR DATA MANAGEMENT AND CONFIDENTIALITY

Confidentiality of participants will be maintained throughout the trial. Only a study ID number will identify participant blood samples and other study data and not their personal identifiable information, such as a name. Any database used to store data from this study will be password protected. Electronic communication with outside collaborators will involve only unidentifiable information. All documents will be maintained electronically and only accessible to the study staff and investigators. AE reports and annual summaries will not include subject- or group-identifiable material. Each report will only include the identification code. Additionally, Emory has obtained a Certificate of Confidentiality from the National Institutes of Health to help protect participant privacy. There are no conflicts of interest among the co-investigators to report.

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