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TITLE PAGE

Keeping Weight Off: Brain Changes Associated with Healthy Behaviors: Study Protocol of a Randomized Controlled Trial

Carl Fulwiler[1], Julia A. Siegel[2], Jeroan Allison[3], Milagros C. Rosal[4], Judson Brewer[1], Jean A. King[5]

[1] University of Massachusetts Medical School, Departments of Psychiatry and Medicine and Center for Mindfulness
[2] University of Massachusetts Medical School
[3] University of Massachusetts Medical School, Department of Quantitative Health Sciences
[4] University of Massachusetts Medical School, Department of Medicine
[5] University of Massachusetts Medical School, Departments of Psychiatry, Neurology and Radiology

Corresponding Author (Primary Sponsor):
Carl Fulwiler, MD, PhD
Center for Mindfulness
University of Massachusetts Medical School
222 Maple Avenue
Shrewsbury, MA 01545
Email: carl.fulwiler@umassmed.edu
Phone: +1 508-856-8389
Fax: +1 508-856-1977

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ABSTRACT (300 words)

Introduction:

Obesity is a growing epidemic fueled by unhealthy behaviors and associated with significant comorbidities and financial costs. Weight loss is vital to mitigate these burdens but, while behavioral interventions produce clinically meaningful weight loss, weight loss maintenance is challenging. This may partially be due to failure of interventions to target stress and emotional reactivity and their potential impact on relapse to unhealthy behaviors. Mindfulness-Based Stress Reduction (MBSR), a psycho-educational program that teaches emotional and physical self-care, effectively reduces stress and emotional reactivity and may be a useful tool for behavior change maintenance. This study seeks to provide a mechanistic understanding for clinical trials of the benefits of MBSR for weight loss maintenance by examining changes in functional connectivity in an emotion regulation circuit and the association of these changes with clinical outcomes.

Methods and analysis:

Community-dwelling individuals (n=80) who intentionally lost ≥5% of their body weight in the past year will be recruited and randomized to an MBSR program or educational control. Functional connectivity (FC) using resting state functional MRI (fMRI) will be measured at baseline and 8 weeks. Psychological factors, health behaviors, body mass index (BMI), and waist circumference will be measured at baseline, 8 weeks, and 6 months post-intervention. A 12-month telephone follow-up will assess self-reported weight. Analyses will characterize FC changes in response to MBSR in comparison to a control condition, assess the relationship between baseline FC status and pre-post MBSR changes in FC, and investigate the association of FC change with changes in psychological factors and weight loss maintenance.

Ethics and dissemination:

The University of Massachusetts Medical School Institutional Review Board has approved this study, Declaration of Helsinki protocols are being followed, and patients will give written informed consent. The Independent Monitoring Committee will monitor protocol adherence.

Trial registration number: NCT02189187 (http://clinicaltrials.gov).

ARTICLE SUMMARY

Article focus

- How does MBSR affect functional connectivity (FC) in emotion regulation circuits and are specific changes in FC related to improved ability to maintain weight loss?
- Can we identify a stable change in brain circuitry (a biomarker) that corresponds with lasting effects of MBSR?
- Can we use this biomarker to monitor fidelity of intervention delivery, adherence, and dose-response in future clinical trials?

Key messages

- Many tools are effective for *initiating* health behavior change such as weight loss, but study results may suggest that MBSR could be effective for *maintenance* of health behavior change, which would be instrumental in decreasing rates of obesity and associated comorbidities.
- If successful, this study will demonstrate that MBSR alters resting state connectivity in emotional regulation circuitry, and that these changes can serve as a valuable biomarker and predictor of long-term maintenance of healthy behaviors.
- This biomarker may allow future studies to identify which components of the mindfulness intervention are most active, and which individuals are most responsive, and may enable development of a more compact and potent intervention that can be tailored toward response optimization based on individual differences.

Strengths and limitations of this study

- This is a timely and innovative study that will advance the field of mindfulness research and increase understanding of its mechanisms of action, setting the stage for a comprehensive clinical trial.
- The intervention is low-risk, highly accessible, low-cost, and is implemented in a real world clinical population and community setting. The control course was specifically designed to serve as an attention control for MBSR.
- The cost of a neuroimaging biomarker could be considered a limitation for large-scale clinical trials, but the insights about neural mechanisms of change cannot be obtained with other methods.

INTRODUCTION

Unhealthy behaviors such as overeating and sedentary lifestyles are major contributors to cardiovascular disease, cancer, type 2 diabetes and other chronic conditions. They have produced a rapid rise in obesity that threatens to reverse recent gains in life expectancy[1] and accounts for a large percentage of premature deaths in the U.S.[2] The number of obese adults in the U.S. is expected to rise by 65 million from 2010 to 2030, resulting in a predicted additional 6–8 million cases of diabetes, 5–6.8 million cases of heart disease and stroke, and over 400,000 cancer cases.[3] For each 5kg/m^2 increase in BMI, the risks of esophageal cancer and colon cancer in men increase by 52% and 24%, respectively, and the risks of endometrial cancer, gall bladder cancer, and breast cancer in women increase by 59%, 59%, and 12%, respectively.[4]

In addition to significant morbidity, obesity has a substantial financial impact due to both health care costs and decreased productivity. Obesity-related U.S. health care costs were $2.5 trillion in 2009 and are predicted to rise by at least $22 billion/year by 2020 and $48 billion/year by 2030.[3]

Weight loss is vital for reducing these extensive health and economic burdens; and even minimal weight loss has a meaningful impact. In an overweight and obese population in Ireland, a 1kg/m^2 decrease in BMI led to 26 fewer cases of chronic disease per 1,000 men and 28 fewer cases per 1,000 women.[5] Similarly, a 1% decrease in BMI across the U.S. population (1kg weight loss for the average adult) is predicted to prevent 2.1–2.4 million cases of diabetes, 1.4–1.7 million cases of cardiovascular disease, and 73,000–127,000 cancer cases; and would only require reducing caloric intake by 20 kcal per day for 3 years.[3]

Current obesity treatments include lifestyle modification, pharmacotherapy, and surgical options. A systematic review of various approaches to weight loss maintenance found that behavioral interventions involving both food intake and physical activity led to significant, albeit small, improvements in weight loss maintenance at 12 months after the intervention.[6] Exercise programs alone, however, may be most effective in the adoption phase.[7] Similarly, certain medications such as orlistat and sibutramine facilitate weight loss but commonly only work short-term when used alone, and may have unfavorable side effects.[8] Bariatric surgery can be effective long-term, but it can be associated with perioperative surgical risks and weight regain is common.[8] Also, many patients are unwilling or ineligible to undergo surgery.

Many interventions are effective for initiating weight loss and other health behavior changes, but they have shown only limited ability to affect significant, long-term behavior change in the majority of adults.[7,9–11] In part this may be attributable to a failure of existing interventions to adequately address the effects of stress and emotional reactivity on relapse to unhealthy behaviors and failure to maintain long-term behavior change. Perceived stress and symptoms of emotional reactivity (depression, anxiety, anger) are linked to unhealthy lifestyle behaviors[12–15] and predict worse outcomes in maintenance studies.[16–18] Indeed, studies of health behavior change have demonstrated that perceived stress[19–21] and indices of emotional reactivity such as anxiety,[22–24] depression, and anger[25–27] are associated with poor outcomes. In contrast, positive affect is associated with improved outcomes.[28,29]

Mindfulness, defined as paying attention to one's inner and outer experiences in a non-judgmental manner from moment to moment,[30] has been associated with healthy behaviors. Dispositional mindfulness in obese patients awaiting bariatric surgery was found to be positively associated with a restrained eating style (using restrictive control over food to lose weight) but negatively associated with emotional (eating in response to emotional states) and external eating behaviors (eating in response to external cues). Mindfulness may discourage external eating by increasing sensitivity to hunger and satiety such that these internal cues guide behavior instead. In addition, mindfulness may prevent emotional eating by encouraging acceptance of negative feelings, lowering stress, and thus promoting distinction between emotion and hunger. Finally, mindfulness has been shown to decrease impulsivity which may reduce unhealthy eating behaviors.[31]

Several mindfulness-based or mindfulness-associated practices are promising agents of behavior change, but we need to understand their neural mechanisms in order to optimize their use. Mindfulness-Based Stress Reduction (MBSR) is a psycho-educational program that teaches emotional and physical self-care. Participants receive training in formal and informal mindfulness practices and learn about the role of good nutrition, rest, and exercise, as well as the role played by thoughts and emotions in physical and emotional health. They are taught how to cultivate a non-reactive awareness of mental and physical experience in an effort to increase self-efficacy and reduced emotional reactivity—leading to healthier lifestyle practices. A recent comparative effectiveness review found moderately strong evidence for mindfulness meditation programs, particularly MBSR, for anxiety, depression and pain compared to nonspecific active controls, and weaker evidence for stress and health-related quality of life.[32] Evidence is mixed regarding the effectiveness of mindfulness-based interventions on weight loss, at least with relatively short follow-up periods.[33] Whether MBSR can support maintenance of weight loss following successful initiation of health behavior change warrants investigation based on its ability to lower emotional and behavioral reactivity to stress and negative emotions, risk risk factors for relapse to unhealthy behaviors. Importantly, an understanding of neural targets and mechanisms of change is necessary for specifying for whom mindfulness is likely to work and for optimizing the intervention for maximal effectiveness. Mindfulness may work better in specific subpopulations, as seen in a group of women with specific endogenous opiodergic activity who were found to be more receptive to mindfulness training in an effort to decrease pleasure eating.[34] Additionally, efficacy of mindfulness-based therapy has been strongly positively associated with dispositional mindfulness of participants and therapists.[35] Neuroimaging, specifically resting state functional MRI (fMRI), is a powerful approach to identifying mechanisms of change for MBSR involving the role of emotion regulation in maintenance of health behavior change.

Neuroimaging studies report an association between MBSR and changes in functional connectivity (FC) that may reflect improved attention, sensory processing, and reflective awareness of sensory experience.[36,37] Mindfulness has also been shown to alter resting state FC of the amygdala, a region involved in physiological stress response. A randomized controlled trial found that a three-day intensive mindfulness training reversed the effects of stress on the amygdala-subgenual anterior cingulate cortex in a group of stressed unemployed adults in the community.[38] This mindfulness training was also shown to increase resting state FC between the default mode network and the left dorsolateral prefrontal cortex, an area involved in top-down

executive control.[39] However, no previous studies have examined how mindfulness training affects the neural circuitry of emotion regulation in a weight loss sample and little is known about mechanisms of behavior change in people undergoing mindfulness training.

Gaps in knowledge

Emerging evidence suggests that mindfulness may be helpful for changing behaviors such as overeating[40] but the mechanistic knowledge of how mindfulness facilitates behavior change is not known. Efforts to fill this gap could enhance our ability to identify likely "responders" and thus optimize intervention efforts, consistent with current trends towards personalized medicine approaches. Specifically, we are lacking knowledge of specific neural targets of mindfulness training to inform clinical trials of health behavior change and maintenance of change. In addition, data on long-term outcomes of mindfulness training is lacking.

Understanding the neural mechanisms that link MBSR to changes in emotional regulation and behavior are a critical next step in tapping the potential of MBSR as an intervention for behavior change and maintenance. A validated biomarker will allow investigators to monitor fidelity of intervention delivery, adherence, and dose-response in clinical trials. If validated as a biomarker, changes in FC will allow future studies to determine characteristics of individuals who are most responsive to MBSR and which components of the mindfulness intervention are most active, and may enable development of a more compact and potent intervention. FC may also help identify subsets of high-risk patients that would benefit from specific tailoring of the intervention. It is worth noting that if clinical trials prove that MBSR prevents weight regain, MRIs would not be required in a larger dissemination study or as the intervention is deployed in a large-scale public health approach.

Study aims and hypotheses

To characterize FC, psychological, behavioral, and anthropometric changes in response to MBSR and the comparison condition, we will randomize a sample of 80 participants who have intentionally lost ≥ 5% of their body weight during the previous year to MBSR or an attention control specifically designed to be structurally equivalent to MBSR. Study aims and hypotheses are as follows.

Our first primary aim is to characterize FC changes in response to MBSR and the comparison condition. We hypothesize that participants randomized to the MBSR condition will experience greater increases in FC from baseline to post-intervention (Hypothesis 1); and participants with higher baseline FC will show less change in response to MBSR (Hypothesis 2).

Our second primary aim is to investigate the association of FC change with changes in psychological factors and maintenance of weight loss at 8 weeks and 6-month follow-up. We hypothesize that increases in FC will be associated with improvement in depressive symptoms (Hypothesis 3) and inversely related to decreased weight (BMI) and total waist circumference (Hypothesis 4).

Our third primary aim is to assess **changes in BMI at 6 & 12 months to obtain preliminary measures of effect size and variability by study group for future clinical trials.**

As secondary aims, we will use mediation analysis to determine how change in FC is explained by 1) class attendance, 2) self-reported time in homework practice, 3) self-reported time for each specific component of the multifaceted training program, and 4) trait mindfulness. An exploratory aim is to examine correlations of change in FC with changes in additional psychological factors (perceived stress, trait anger, trait anxiety, positive affect) and health behaviors (healthy eating, physical activity, sleep quality).

METHODS

Study design

The "Keeping Weight Off" study is a randomized, prospective, two-armed, controlled trial. A sample of 80 participants from the community, who have intentionally lost at least 5% of their body weight during the previous year, will be equally randomized into two groups: an MBSR program and a Healthy Living Course (HLC)—an attention control specifically designed to be structurally equivalent to MBSR.[41] The HLC uses the same format of 8-weekly classes lasting 2 1/2 hours, and controls for attention and other nonspecific factors including staff interactions, psychoeducation about health and stress management, classroom format, homework, group process, and data collection.[41] Our main outcome measures are resting-state FC, depression symptoms, BMI, and waist circumference. FC, psychological factors, health behaviors, BMI, and waist circumference will be measured at baseline and 8 weeks. Psychological factors, health behaviors, BMI, and waist circumference will also be measured at 6 months. In addition, a telephone follow-up will be attempted on participants at 12 months to assess weight.

Total planned enrollment is 80 participants. Screening for eligibility criteria, baseline visits, and follow-up visits will take place at University of Massachusetts Medical School (UMMS), Worcester, Massachusetts. All MBSR classes will be conducted at the UMMS Center for Mindfulness in Shrewsbury, Massachusetts.

Study participants

We will recruit participants who range in age from 25 to 60 (chosen to minimize age-related changes in FC), have intentionally lost $\geq$ 5% of their body weight during the previous year, and are motivated to maintain this weight loss. Individuals will be excluded if they have participated in an MBSR course, regular meditation practice, or any other form of meditative practice (such as yoga, Tai Chi or contemplative prayer), for more than an average of 20 minutes per week within the past 2 years. Full inclusion and exclusion criteria are listed in Table 1.

Eligible participants will proceed with the baseline visit prior to randomization, including collection of demographic information about age, education, marital status, occupation, and current employment status, followed by questionnaires and fMRI scan. All participants will provide informed consent. This process will be conducted by the study coordinator in person prior to the baseline visit, following the protocol established by the University of Massachusetts Institutional Review Board (IRB). Study staff will keep in touch with participants regarding attendance and homework completion and provide support and encouragement to continue with the intervention if participants express dissatisfaction. Participants who drop out of the intervention will be asked to return for all follow-up visits to complete all outcome data collection.

Study recruitment

Recruitment will be conducted using advertising in the community (internet, flyers and social media) as well as a two-stage process to recruit outpatients from the UMass Memorial Medical Center using the electronic medical record. First, with a HIPAA waiver authorization a search query will be conducted with basic eligibility criteria, and secondly identified records will be reviewed to exclude causes of weight loss such as serious illness or weight loss medications. Web-based and telephone screening will determine whether they meet inclusion criteria. Further screening will be done in person to gather a medical history and complete the Structured Clinical Interview for DSM-IV (SCID) to exclude participants with a serious psychiatric, cognitive or medical disorder or a history of alcohol or substance abuse or dependence in the past 6 months.

Randomization and study blinding

Study participants will be equally randomized to either the MBSR intervention arm or HLC arm based on a permuted blocks randomization scheme. In this procedure, treatment allocations will be made within blocks so that the numbers assigned to each arm are equal after each block has been filled. Blocks of various sizes (2, 4, 6) will be used in random order, to facilitate allocation concealment, that is, to make it nearly impossible to determine the treatment assignment based on a pattern of previous treatment allocations. Randomization will be implemented by the study coordinator using sealed envelopes.

To address the possibility that an imbalanced distribution of baseline FC could mask important findings, we will employ a non-stratified permuted-block randomized design with an interim analysis of the distribution of baseline FC. If important imbalances are found, we will implement recruitment strategies to increase enrollment of participants who have baseline FC with a specified range combined with covariate-adaptive randomization techniques. Residual imbalances will be addressed with post-hoc statistical adjustment.

Assessments

Resting state functional connectivity

All MRI's will be acquired on the 3T scanner (Philips Achieva) in the UMMS Advanced MRI Center. 3D high-resolution structural T1-weighted MR images will be obtained to provide anatomical landmarks. Following the structural imaging, resting-state fMRI data will be collected. Participants will be instructed to remain relaxed with eye closed as fMRI images are continuously collected for 10 mins. The duration of the entire MRI procedure will be 30 min.

Psychological symptoms

The Center for Epidemiologic Studies Depression Scale (CES-D)[50] depression symptom score is a primary outcome. Additional outcomes include perceived stress, anxiety, anger, positive affect, and emotion regulation, which will be assessed using the following measures respectively: the Perceived Stress Scale (PSS-14),[51] the State-Trait Anxiety Inventory – trait version (STAI-T),[52] the State-Trait Anger Expression Inventory (STAXI-II) trait anger subscale,[53] the Satisfaction with Life Scale[54] and the Emotion Regulation Questionnaire.[55]

Health behaviors

Health behaviors will be assessed using the Eating Behavior Inventory,[56] the Internal Disinhibition Subscale of the Eating Inventory,[57] the Paffenbarger Physical Activity Scale,[58] and the Pittsburgh Sleep Quality Index (PSQI),[59] respectively.

Anthropometrics
Procedures are adapted from the CDC's Anthropometry Procedures Manual.[60] For the measurement of height and weight, the Seca 213 Portable stadiometer and the TANITA, BWB-800 electronic scale will be used and measurements will be taken twice and averaged to assure reliability. Measurement of waist circumference will be taken directly on the skin using measuring tape placed just above top of the iliac crest on each side.

Potential mediators and confounds
Intervention engagement will be assessed with class attendance and a home practice log. Treatment expectancy and credibility will be assessed with the Credibility/Expectancy Questionnaire CEQ[61] modified slightly to substitute the word "Class" for "Therapy" in the instructions. Secondary analyses will examine how change in FC is explained by 1) class attendance, 2) self-reported time in homework practice, 3) self-reported time for each specific component of the multifaceted training program, and 4) trait mindfulness as measured by the Five Facet Mindfulness Questionnaire (FFMQ).[62]

Interventions
Experimental Condition: Mindfulness-Based Stress Reduction (MBSR)
MBSR, described above, is taught in eight weekly classes and one all-day retreat. Homework assignments include formal meditation practices and informal practices during daily life. Classroom activities teach formal meditation practices including sitting meditation, body scan, mindful yoga, walking meditation). Participants also learn to bring awareness in the present moment to aspects of daily life and apply this practice to stressful experiences in order to avoid reflexive or conditioned reactions. The goal of MBSR is to provide participants with these skills for lifelong self-management.

The MBSR classes are taught by certified teachers from the UMass Center for Mindfulness. All teachers have completed the rigorous training and certification for MBSR through the Center for Mindfulness. To further assure fidelity each class will be reviewed in weekly sessions with a co-investigator. In addition, the principal investigators will routinely convene the entire clinical research team to monitor the overall fidelity of the MBSR intervention.

Attention control: Healthy Living Course
The Healthy Living Course (HLC) was specifically designed to serve as a control condition for MBSR.[41] HLC consists of 8 weekly 2-hour classes. Sessions consist of lectures and discussion on the following topics: healthy living, healthy eating, physical activity and health, sleep and health, stress management, time management, and unhealthy behaviors (smoking, drinking). The HLC is designed to control for attention and other nonspecific factors including staff interactions, psychoeducation about health and stress management, classroom format, homework, group process, and data collection.[41]

Data collection

Electronic data capture (EDC, REDCap™) will be used for all data collection except imaging. Surveys for psychological symptoms, health behaviors, and potential mediators and confounds are programmed into the EDC system. During research visits, participants will enter survey responses directly into this system and research staff will enter screening and anthropometric data with periodic checks for quality assurance. All data will be maintained in a secure location accessible only to study personnel. For MRI measures, data will be analyzed blind to intervention group by two fMRI experts who perform cross-validity checks.

Data analysis and sample size considerations

We based the study sample size on Hypothesis 1, powered to detect an effect size of 0.32 standard deviations. This moderate Cohen effect size[63] represents differential over-time change for the intervention versus comparison group cast in standard deviation units. The study design calls for a baseline measurement and two follow-up measurements. In addition, we assumed a two-tailed alpha error of 0.05, and a within-person correlation for over-time measurement of 0.8.[64] With these assumptions, 40 participants in each group are needed for 80% power. We will enroll 100 participants (50 randomized to each arm) and allow for up to 20% loss to follow up, for an effective sample size of 80.

Statistical analysis will begin with univariate summaries of data distributions and examination of longitudinal trends with graphic displays. Bivariate associations will then be examined using the chi-square test, ANOVA, and the Spearman correlation test. Hypotheses 1 and 2 focus on over-time differences between the two study groups, while Hypotheses 2 and 3 focus on over-time differences for the combined sample. Hypotheses will be formally tested using generalized linear mixed models that represent the clustering of observations within participants as a random intercept, adopt an appropriate link and distribution for the specific outcome, and parameterize the intervention effect as a group-time intervention, when appropriate.[65] To preserve the power of randomization, hypothesis testing will be performed on an intent-to-treat basis. As a secondary aim, mediation analysis will determine how change in FC is explained by markers of intervention adherence using techniques as described by MacKinnon.[66,67] Sensitivity analyses with multiple imputation with chained equations will address missing data.

Imaging data is preprocessed using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, London, UK) running under the MATLAB environment (Mathworks, Inc., Sherborn, MA). The data is initially corrected for motion (threshold of 2 mm). Further pre-processing of the data includes a) slice scan time correction, b) spatial smoothing using a 3D Gaussian filter (4-mm FWHM), and c) voxel-wise linear detrending and 0.01-0.08Hz band-pass filtering. Structural and functional data of each participant is then be transformed to standard stereotaxic space[68] to facilitate group analysis.

Following the preprocessing steps, FC will be generated using correlational analysis. Left and right amygdala are used as separate seed regions of interest (ROI). FC maps from each individual seed will then be calculated for each individual subject using Resting-State fMRI Data Analysis Toolkit (REST, http://www.restfmri.net). Each seed ROI will be evaluated using two-way repeated measures ANOVA on a voxel-by-voxel basis (factors: group and imaging day) at the threshold of $p < 0.05$ after accounting for multiple comparisons using the criteria of false discovery rate (FDR).[69] Voxels with significantly changed FC within each ROI will then be

averaged to generate the FC change for the ROI. This procedure will yield a single value of amygdala-orbitofrontal FC for each participant at each point in time. All ROI definitions are based on Automated Anatomical Labeling (AAL)[70] built in the MarsBAR toolbox of SPM8. Image analysis will be done blind to group membership.

As a secondary analysis, we will explore FC changes in other brain networks following MBSR using other seed regions. For example, other cortical regions that have been implicated in modulation of limbic reactivity (e.g. anterior cingulate) will examined using a hypothesis-driven approach.

Ethical considerations

This study is approved by the University of Massachusetts Medical School IRB and registered as a national clinical trial (NCT02189187), Declaration of Helsinki protocols are being followed, and patients will give written informed consent. Protocol adherence will be monitored by the Independent Monitoring Committee.

AUTHORS' CONTRIBUTIONS

CF conceptualized the study, and JAK, JA, MR and JB participated in the study design. CF, JAK, and JAS collected data. CF and JAS wrote and all authors revised the article and approved the final version to be published.

COMPETING INTERESTS

All authors declare no conflicts of interest.

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TABLES

Table 1. Eligibility criteria

Inclusion criteria:	Exclusion criteria:
• Males and females • Right or left handed • Ages 25-60 • Intentionally lost ≥5% of body weight during the previous year • Intending to maintain weight loss • BMI > 25 kg/m2 in the past 2 years and greater than 20.5 kg/m2 at time of study entry • Under the care of a primary care physician for at least the last year prior to screening • Able to communicate by telephone with research staff • Have a healthcare provider, personal trainer or weight-loss counselor who can complete and sign a form indicating the amount and timing of their weight loss OR have a dated photograph or weight loss diary.[71]	• Weight >300lbs (limitation of MRI scanner) • Prior participation in an MBSR course • Regular meditation practice (or any other form of meditative practice, such as yoga, Tai Chi, or contemplative prayer) for more than an average of 20 min/week within the past 2 years • Serious psychiatric, cognitive, or medical disorder • Alcohol/substance abuse or dependence in past 6 months • Any conditions that are incompatible with MRI • Structural brain damage as determined by an independent neuroradiologist, based on T1W 3D TFE sagittal and T1W FFE axial images • History of an eating disorder, diabetes mellitus or medications for diabetes mellitus • Medication that affects weight (weight loss medications, corticosteroids, antipsychotics) • History of weight loss surgery • Participation in another weight management research study • Regain of >3% of total body weight in the 2 months prior to study entry • Childbirth in the past 6 months • Claustrophobia, or any MRI incompatible implants • Pregnant or planning to become pregnant • Unable to consent

Table 2. Study schedule of recruitment, treatment, and assessments as a function of time-points (according to the SPIRIT 2013 figure guidelines)

	DURATION OF THE STUDY				
	Recruitment	**Baseline**	**Post-treatment (8 weeks)**	**Follow-up (6 months)**	**Follow-up (12 months)**
TIME-POINT	t_0	t_1	t_2	t_3	t_4
RECRUITMENT					
Screening for inclusion/exclusion criteria	X				
Informed consent		X			
Assignment to treatment arms	X				
TREATMENT					
MBSR		X	X		
HLC		X	X		
ASSESSMENT					
SCID-IV	X				
fMRI		X	X		
Weight		X	X	X	X
Height (and BMI)		X	X	X	
Waist Circumference		X	X	X	
CES-D		X	X	X	
PSS-14		X	X	X	
STAI-T		X	X	X	
STAXI-II		X	X	X	
Satisfaction with Life		X	X	X	
Emotion Regulation Questionnaire		X	X	X	
Eating Behavior Inventory		X	X	X	
Internal Disinhibition Subscale of the Eating Inventory		X	X	X	
Paffenbarger Physical Activity Scale		X	X	X	
Pittsburgh Sleep Quality Index		X	X	X	

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APPENDIX

World Health Organization Trial Registration Data Set information

1. Primary Registry and Trial Identifying Number: NCT02189187 (http://clinicaltrials.gov).
2. Date of Registration in Primary Registry: June 24, 2014
3. Secondary Identifying Numbers: n/a
4. Source(s) of Monetary or Material Support: see page 12
5. Primary Sponsor: Carl Fulwiler (see page 1)
6. Secondary Sponsor(s): n/a
7. Contact for Public Queries: Carl Fulwiler (see page 1)
8. Contact for Scientific Queries: Carl Fulwiler (see page 1)
9. Public Title: "Keeping Weight Off: Brain Changes Associated With Healthy Behaviors"
10. Scientific Title: "Mind and health: developing a neural marker for mindfulness, a pathway to health"
11. Countries of Recruitment: United States
12. Health Condition(s) or Problem(s) Studied: see Introduction section
13. Intervention(s): see Interventions section of Methods
14. Key Inclusion and Exclusion Criteria: see Table 1
15. Study Type: Randomized controlled trial with evenly distributed arms
16. Date of First Enrollment: January 8, 2015
17. Target Sample Size: 80 (see page 10)
18. Recruitment Status: Recruiting
19. Primary Outcome(s): see Assessments and Data Analysis sections
20. Key Secondary Outcomes: see Assessments and Data Analysis sections

Other items from SPIRIT Checklist

3. Protocol version: 8; last modified July 1, 2015

21a, 22. The funding agency has determined that a full Data Safety Monitoring Board is not necessary for this study. Instead, any unexpected, serious, or intervention-related i.e. Serious Adverse Event (SAEs) will be reported to an Independent Monitoring Committee composed 3 scientists not involved in the study. This includes a senior biostatistician, an obesity research expert and clinician, and a senior neuroimaging researcher. Adverse events include possible health related risks such as MRI discomfort, psychological distress during the Interventions, imminent subject's risk during SCID interview or detecting structural brain image at baseline. Anticipated or unrelated AEs will be reported to the Independent Monitoring Committee, the IRB, and the NIH in accordance with their requirements. In the semi-annual SAE summary, the Independent Monitoring Committee will provide a review of each SAE, including relevant information forwarded by the study team, and verify that he has reviewed all serious adverse event reports.

23. The funding agency conducts annual on-site reviews of study procedures and progress.

31c. We will provide supplemental access to the requisite data, workflows and results, as well as provide maximum data availability to reuse in future meta-analyses and data pooling efforts. In addition, we will make all data available at the end of the award period via a NIH-funded NITRC (Neuroimaging Informatics Tools and Resources Clearinghouse - nitrc.org) project. We will release the data under the Creative Commons, Attribution-NonCommercial-Share Alike License.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	___Appendix___
Protocol version	3	Date and version identifier	___Appendix___
Funding	4	Sources and types of financial, material, and other support	_____12_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1, 11____
	5b	Name and contact information for the trial sponsor	_____1_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____11, 12___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____n/a_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-7
	6b	Explanation for choice of comparators	6, 7
Objectives	7	Specific objectives or hypotheses	6, 7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7, 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7, 8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, 8, 13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7, 8, 13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____8_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____8_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___8, 10, 11____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____8-10_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____7_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____10_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____10, 11____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____10, 11_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____10_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__Appendix__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___n/a_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___Appendix__
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Appendix__
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____11_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____n/a_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____7_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____n/a_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____10_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____11_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____n/a_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____n/a_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____11_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____11_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Appendix___
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____n/a_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Keeping Weight Off: Study Protocol of a RCT to Investigate Brain Changes Associated with Mindfulness-Based Stress Reduction

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Secondary Subject Heading:	Medical management
Keywords:	mindfulness, weight loss, behavior change maintenance, neuroimaging

TITLE PAGE

Keeping Weight Off: Study Protocol of a RCT to Investigate Brain Changes Associated with Mindfulness-Based Stress Reduction

Carl Fulwiler[1], Julia A. Siegel[2], Jeroan Allison[3], Milagros C. Rosal[4], Judson Brewer[1], Jean A. King[5]

[1] University of Massachusetts Medical School, Departments of Psychiatry and Medicine and Center for Mindfulness
[2] University of Massachusetts Medical School
[3] University of Massachusetts Medical School, Department of Quantitative Health Sciences
[4] University of Massachusetts Medical School, Department of Medicine
[5] University of Massachusetts Medical School, Departments of Psychiatry, Neurology and Radiology

Corresponding Author (Primary Sponsor):
Carl Fulwiler, MD, PhD
Center for Mindfulness
University of Massachusetts Medical School
222 Maple Avenue
Shrewsbury, MA 01545
Email: carl.fulwiler@umassmed.edu
Phone: +1 508-856-8389
Fax: +1 508-856-1977

Keywords:
mindfulness; Mindfulness Based Stress Reduction; weight loss; behavior change maintenance; resting state functional connectivity; neuroimaging

ABSTRACT

Introduction:
Obesity is a growing epidemic fueled by unhealthy behaviors and associated with significant comorbidities and financial costs. While behavioral interventions produce clinically meaningful weight loss, weight loss maintenance is challenging. This may partially be due to failure to target stress and emotional reactivity. Mindfulness-Based Stress Reduction (MBSR) reduces stress and emotional reactivity and may be a useful tool for behavior change maintenance. This study seeks to provide a mechanistic understanding for clinical trials of the benefits of MBSR for weight loss maintenance by examining changes in functional connectivity and the association of these changes with clinical outcomes.

Methods and analysis:
Community-dwelling individuals (n=80) who intentionally lost ≥5% of their body weight in the past year will be recruited and randomized to an MBSR program or educational control. Functional connectivity (FC) using resting state functional MRI (fMRI) will be measured at baseline and 8 weeks. Psychological factors, health behaviors, body mass index (BMI), and waist circumference will be measured at baseline, 8 weeks, and 6 months post-intervention. A 12-month telephone follow-up will assess self-reported weight. Analyses will characterize FC changes in response to MBSR in comparison to a control condition, assess the relationship between baseline FC status and pre-post MBSR changes in FC, and investigate the association of FC change with changes in psychological factors and weight loss maintenance.

Ethics and dissemination:
The University of Massachusetts Medical School Institutional Review Board has approved this study, Declaration of Helsinki protocols are being followed, and patients will give written informed consent. The Independent Monitoring Committee will monitor protocol adherence. Results from the study will be disseminated to the medical community at conferences and submitted for publication in peer-reviewed journals when the last patient included has been followed up for 12 months.

Trial registration number: NCT02189187 (http://clinicaltrials.gov).

ARTICLE SUMMARY

Strengths and limitations of this study

- This is a timely and innovative study that will advance the field of mindfulness research and increase understanding of its mechanisms of action, setting the stage for a comprehensive clinical trial.
- The intervention is low-risk, highly accessible, low-cost, and is implemented in a real world clinical population and community setting. The control course was specifically designed to serve as an attention control for MBSR.
- The cost of a neuroimaging biomarker could be considered a limitation for large-scale clinical trials, but the insights about neural mechanisms of change cannot be obtained with other methods.

INTRODUCTION

Unhealthy behaviors such as overeating and sedentary lifestyles are major contributors to cardiovascular disease, cancer, type 2 diabetes and other chronic conditions. They have produced a rapid rise in obesity that threatens to reverse recent gains in life expectancy[1] and accounts for a large percentage of premature deaths in the U.S.[2] The number of obese adults in the U.S. is expected to rise by 65 million from 2010 to 2030, resulting in a predicted additional 6–8 million cases of diabetes, 5–6.8 million cases of heart disease and stroke, and over 400,000 cancer cases.[3] For each 5kg/m^2 increase in BMI, the risks of esophageal cancer and colon cancer in men increase by 52% and 24%, respectively, and the risks of endometrial cancer, gall bladder cancer, and breast cancer in women increase by 59%, 59%, and 12%, respectively.[4]

In addition to significant morbidity, obesity has a substantial financial impact due to both health care costs and decreased productivity. Obesity-related U.S. health care costs were $2.5 trillion in 2009 and are predicted to rise by at least $22 billion/year by 2020 and $48 billion/year by 2030.[3]

Weight loss is vital for reducing these extensive health and economic burdens; and even minimal weight loss has a meaningful impact. In an overweight and obese population in Ireland, a 1kg/m^2 decrease in BMI led to 26 fewer cases of chronic disease per 1,000 men and 28 fewer cases per 1,000 women.[5] Similarly, a 1% decrease in BMI across the U.S. population (1kg weight loss for the average adult) is predicted to prevent 2.1–2.4 million cases of diabetes, 1.4–1.7 million cases of cardiovascular disease, and 73,000–127,000 cancer cases; and would only require reducing caloric intake by 20 kcal per day for 3 years.[3]

Current obesity treatments include lifestyle modification, pharmacotherapy, and surgical options. A systematic review of various approaches to weight loss maintenance found that behavioral interventions involving both food intake and physical activity led to significant, albeit small, improvements in weight loss maintenance at 12 months after the intervention.[6] Exercise programs alone, however, may be most effective in the adoption phase.[7] Similarly, certain medications such as orlistat and sibutramine facilitate weight loss but commonly only work short-term when used alone, and may have unfavorable side effects.[8] Bariatric surgery can be effective long-term, but it can be associated with perioperative surgical risks and weight regain is common.[8] Also, many patients are unwilling or ineligible to undergo surgery.

Many interventions are effective for initiating weight loss and other health behavior changes, but they have shown only limited ability to affect significant, long-term behavior change in the majority of adults.[7,9–11] In part this may be attributable to a failure of existing interventions to adequately address the effects of stress and emotional reactivity on relapse to unhealthy behaviors and failure to maintain long-term behavior change. Perceived stress and symptoms of emotional reactivity (depression, anxiety, anger) are linked to unhealthy lifestyle behaviors[12–15] and predict worse outcomes in maintenance studies.[16–18] Indeed, studies of health behavior change have demonstrated that perceived stress[19–21] and indices of emotional reactivity such as anxiety,[22–24] depression, and anger[25–27] are associated with poor outcomes. In contrast, positive affect is associated with improved outcomes.[28,29]

Mindfulness, defined as paying attention to one's inner and outer experiences in a non-judgmental manner from moment to moment,[30] has been associated with healthy behaviors. Dispositional mindfulness in obese patients awaiting bariatric surgery was found to be positively associated with a restrained eating style (using restrictive control over food to lose weight) but negatively associated with emotional (eating in response to emotional states) and external eating behaviors (eating in response to external cues). Mindfulness may discourage external eating by increasing sensitivity to hunger and satiety such that these internal cues guide behavior instead. In addition, mindfulness may prevent emotional eating by encouraging acceptance of negative feelings, lowering stress, and thus promoting distinction between emotion and hunger. Finally, mindfulness has been shown to decrease impulsivity which may reduce unhealthy eating behaviors.[31]

Several mindfulness-based or mindfulness-associated practices are promising agents of behavior change, but we need to understand their neural mechanisms in order to optimize their use. Mindfulness-Based Stress Reduction (MBSR) is a psycho-educational program that teaches emotional and physical self-care. Participants receive training in formal and informal mindfulness practices and learn about the role of good nutrition, rest, and exercise, as well as the role played by thoughts and emotions in physical and emotional health. They are taught how to cultivate a non-reactive awareness of mental and physical experience in an effort to increase self-efficacy and reduced emotional reactivity—leading to healthier lifestyle practices. A recent comparative effectiveness review found moderately strong evidence for mindfulness meditation programs, particularly MBSR, for anxiety, depression and pain compared to nonspecific active controls, and weaker evidence for stress and health-related quality of life.[32] Evidence is mixed regarding the effectiveness of mindfulness-based interventions on weight loss, at least with relatively short follow-up periods.[33] Whether MBSR can support maintenance of weight loss following successful initiation of health behavior change warrants investigation based on its ability to lower emotional and behavioral reactivity to stress and negative emotions, risk risk factors for relapse to unhealthy behaviors. Importantly, an understanding of neural targets and mechanisms of change is necessary for specifying for whom mindfulness is likely to work and for optimizing the intervention for maximal effectiveness. Mindfulness may work better in specific subpopulations, as seen in a group of women with specific endogenous opiodergic activity who were found to be more receptive to mindfulness training in an effort to decrease pleasure eating.[34] Additionally, efficacy of mindfulness-based therapy has been strongly positively associated with dispositional mindfulness of participants and therapists.[35] Neuroimaging, specifically resting state functional MRI (fMRI), is a powerful approach to identifying mechanisms of change for MBSR involving the role of emotion regulation in maintenance of health behavior change.

Neuroimaging studies report an association between MBSR and changes in functional connectivity (FC) that may reflect improved attention, sensory processing, and reflective awareness of sensory experience.[36,37] Mindfulness has also been shown to alter resting state FC of the amygdala, a region involved in physiological stress response. A randomized controlled trial found that a three-day intensive mindfulness training reversed the effects of stress on the amygdala-subgenual anterior cingulate cortex in a group of stressed unemployed adults in the community.[38] This mindfulness training was also shown to increase resting state FC between the default mode network and the left dorsolateral prefrontal cortex, an area involved in top-down

executive control.[39] However, no previous studies have examined how mindfulness training affects the neural circuitry of emotion regulation in a weight loss sample and little is known about mechanisms of behavior change in people undergoing mindfulness training.

Gaps in knowledge

Emerging evidence suggests that mindfulness may be helpful for changing behaviors such as overeating[40] but the mechanistic knowledge of how mindfulness facilitates behavior change is not known. Efforts to fill this gap could enhance our ability to identify likely "responders" and thus optimize intervention efforts, consistent with current trends towards personalized medicine approaches. Specifically, we are lacking knowledge of specific neural targets of mindfulness training to inform clinical trials of health behavior change and maintenance of change. In addition, data on long-term outcomes of mindfulness training is lacking.

Understanding the neural mechanisms that link MBSR to changes in emotional regulation and behavior are a critical next step in tapping the potential of MBSR as an intervention for behavior change and maintenance. A validated biomarker will allow investigators to monitor fidelity of intervention delivery, adherence, and dose-response in clinical trials. If validated as a biomarker, changes in FC will allow future studies to determine characteristics of individuals who are most responsive to MBSR and which components of the mindfulness intervention are most active, and may enable development of a more compact and potent intervention. FC may also help identify subsets of high-risk patients that would benefit from specific tailoring of the intervention. It is worth noting that if clinical trials prove that MBSR prevents weight regain, MRIs would not be required in a larger dissemination study or as the intervention is deployed in a large-scale public health approach.

Study aims and hypotheses

To characterize FC, psychological, behavioral, and anthropometric changes in response to MBSR and the comparison condition, we will randomize a sample of 80 participants who have intentionally lost ≥ 5% of their body weight during the previous year to MBSR or an attention control specifically designed to be structurally equivalent to MBSR. Study aims and hypotheses are as follows.

Our first primary aim is to characterize FC changes in response to MBSR and the comparison condition. We hypothesize that participants randomized to the MBSR condition will experience greater increases in FC from baseline to post-intervention (Hypothesis 1); and participants with higher baseline FC will show less change in response to MBSR (Hypothesis 2).

Our second primary aim is to investigate the association of FC change with changes in psychological factors and maintenance of weight loss at 8 weeks and 6-month follow-up. We hypothesize that increases in FC will be associated with improvement in depressive symptoms (Hypothesis 3) and inversely related to decreased weight (BMI) and total waist circumference (Hypothesis 4).

Our third primary aim is to assess **changes in BMI at 6 & 12 months to obtain preliminary measures of effect size and variability by study group for future clinical trials.**

As secondary aims, we will use mediation analysis to determine how change in FC is explained by 1) class attendance, 2) self-reported time in homework practice, 3) self-reported time for each specific component of the multifaceted training program, and 4) trait mindfulness. An exploratory aim is to examine correlations of change in FC with changes in additional psychological factors (perceived stress, trait anger, trait anxiety, positive affect) and health behaviors (healthy eating, physical activity, sleep quality).

METHODS

Study design

The "Keeping Weight Off" study is a randomized, prospective, two-armed, controlled trial. A sample of 80 participants from the community, who have intentionally lost at least 5% of their body weight during the previous year, will be equally randomized into two groups: an MBSR program and a Healthy Living Course (HLC)—an attention control specifically designed to be structurally equivalent to MBSR.[41] The HLC uses the same format of 8-weekly classes lasting 2 1/2 hours, and controls for attention and other nonspecific factors including staff interactions, psychoeducation about health and stress management, classroom format, homework, group process, and data collection.[41] Our main outcome measures are resting-state FC, depression symptoms, BMI, and waist circumference. FC, psychological factors, health behaviors, BMI, and waist circumference will be measured at baseline and 8 weeks. Psychological factors, health behaviors, BMI, and waist circumference will also be measured at 6 months. In addition, a telephone follow-up will be attempted on participants at 12 months to assess weight.

Total planned enrollment is 80 participants. Screening for eligibility criteria, baseline visits, and follow-up visits will take place at University of Massachusetts Medical School (UMMS), Worcester, Massachusetts. All MBSR classes will be conducted at the UMMS Center for Mindfulness in Shrewsbury, Massachusetts.

Study participants

We will recruit participants who range in age from 25 to 60 (chosen to minimize age-related changes in FC), have intentionally lost $\geq$ 5% of their body weight during the previous year, and are motivated to maintain this weight loss. Individuals will be excluded if they have participated in an MBSR course, regular meditation practice, or any other form of meditative practice (such as yoga, Tai Chi or contemplative prayer), for more than an average of 20 minutes per week within the past 2 years. Full inclusion and exclusion criteria are listed in Table 1.

Eligible participants will proceed with the baseline visit prior to randomization, including collection of demographic information about age, education, marital status, occupation, and current employment status, followed by questionnaires and fMRI scan. The full study schedule of recruitment, treatment, and assessments is described in Table 2. All participants will provide informed consent. This process will be conducted by the study coordinator in person prior to the baseline visit, following the protocol established by the University of Massachusetts Institutional Review Board (IRB). Study staff will keep in touch with participants regarding attendance and homework completion and provide support and encouragement to continue with the intervention if participants express dissatisfaction. Participants who drop out of the intervention will be asked to return for all follow-up visits to complete all outcome data collection.

Study recruitment

Recruitment will be conducted using advertising in the community (internet, flyers and social media) of Worcester County, which has a population of over 800,000, as well as a two-stage process to recruit outpatients from the UMass Memorial Medical Center using the electronic medical record. The largest health care system in Central and Western Massachusetts, the medical center has a large population from which to draw, with nearly 70,000 patient visits for primary care alone, and a Weight Center sees that sees nearly 1000 new patients per year. Our team has an excellent record of recruitment and retention in our previous of overweight/obese subjects using these methods.

First, with a HIPAA waiver authorization a search query will be conducted with basic eligibility criteria, and secondly identified records will be reviewed to exclude causes of weight loss such as serious illness or weight loss medications. Web-based and telephone screening will determine whether they meet inclusion criteria. Further screening will be done in person to gather a medical history and complete the Structured Clinical Interview for DSM-IV (SCID) to exclude participants with a serious psychiatric, cognitive or medical disorder or a history of alcohol or substance abuse or dependence in the past 6 months.

Randomization and study blinding

Study participants will be equally randomized to either the MBSR intervention arm or HLC arm based on a permuted blocks randomization scheme. In this procedure, treatment allocations will be made within blocks so that the numbers assigned to each arm are equal after each block has been filled. Blocks of various sizes (2, 4, 6) will be used in random order, to facilitate allocation concealment, that is, to make it nearly impossible to determine the treatment assignment based on a pattern of previous treatment allocations. Randomization will be implemented using sealed envelopes by the study coordinator who will be the only member of the research team who is not blind to treatment assignment. A unique identification number will help to endure that blindness is maintained throughout the study. All members of the research team involved in data analysis will be blind to treatment assignment.

To address the possibility that an imbalanced distribution of baseline FC could mask important findings, we will employ a non-stratified permuted-block randomized design with an interim analysis of the distribution of baseline FC. If important imbalances are found, we will implement recruitment strategies to increase enrollment of participants who have baseline FC with a specified range combined with covariate-adaptive randomization techniques. Residual imbalances will be addressed with post-hoc statistical adjustment.

Assessments

Resting state functional connectivity

In contrast to task-evoked functional and effective connectivity studies, resting-state fMRI enables examination of the brain's intrinsic functional connections in the absence of externally controlled stimuli or tasks.[42,43] FC is responsive to changing levels of stress,[44] intense training on a task,[45] and recently, meditation practice including MBSR.[46,47] FC has been shown to have remarkable consistency and moderate to high test-test reliability over periods of months to a year as well.[48,49] All MRI's will be acquired on the 3T scanner (Philips Achieva) in the UMMS

Advanced MRI Center. 3D high-resolution structural T1-weighted MR images will be obtained to provide anatomical landmarks. Following the structural imaging, resting-state fMRI data will be collected. Participants will be instructed to remain relaxed with eye closed as fMRI images are continuously collected for 10 mins. The duration of the entire MRI procedure will be 30 min.

Psychological symptoms
The Center for Epidemiologic Studies Depression Scale (CES-D)[50] depression symptom score is a primary outcome. Additional outcomes include perceived stress, anxiety, anger, positive affect, and emotion regulation, which will be assessed using the following measures respectively: the Perceived Stress Scale (PSS-14),[51] the State-Trait Anxiety Inventory – trait version (STAI-T),[52] the State-Trait Anger Expression Inventory (STAXI-II) trait anger subscale,[53] the Satisfaction with Life Scale[54] and the Emotion Regulation Questionnaire.[55]

Health behaviors
Health behaviors will be assessed using the Eating Behavior Inventory,[56] the Internal Disinhibition Subscale of the Eating Inventory,[57] the Paffenbarger Physical Activity Scale,[58] and the Pittsburgh Sleep Quality Index (PSQI),[59] respectively.

Anthropometrics
Procedures are adapted from the CDC's Anthropometry Procedures Manual.[60] For the measurement of height and weight, the Seca 213 Portable stadiometer and the TANITA, BWB-800 electronic scale will be used and measurements will be taken twice and averaged to assure reliability. Measurement of waist circumference will be taken directly on the skin using measuring tape placed just above top of the iliac crest on each side.

Potential mediators and confounds
Intervention engagement will be assessed with class attendance and a home practice log. Treatment expectancy and credibility will be assessed with the Credibility/Expectancy Questionnaire CEQ[61] modified slightly to substitute the word "Class" for "Therapy" in the instructions. Secondary analyses will examine how change in FC is explained by 1) class attendance, 2) self-reported time in homework practice, 3) self-reported time for each specific component of the multifaceted training program, and 4) trait mindfulness as measured by the Five Facet Mindfulness Questionnaire (FFMQ).[62]

Interventions
Experimental Condition: Mindfulness-Based Stress Reduction (MBSR)
MBSR, described above, is taught in eight weekly classes and one all-day retreat. Homework assignments include formal meditation practices and informal practices during daily life. Classroom activities teach formal meditation practices including sitting meditation, body scan, mindful yoga, walking meditation). Participants also learn to bring awareness in the present moment to aspects of daily life and apply this practice to stressful experiences in order to avoid reflexive or conditioned reactions. The goal of MBSR is to provide participants with these skills for lifelong self-management.

The MBSR classes are taught by certified teachers from the UMass Center for Mindfulness. All teachers have completed the rigorous training and certification for MBSR through the Center for

Mindfulness. To further assure fidelity each class will be reviewed in weekly sessions with a co-investigator. In addition, the principal investigators will routinely convene the entire clinical research team to monitor the overall fidelity of the MBSR intervention.

Attention control: Healthy Living Course

The Healthy Living Course (HLC) was specifically designed to serve as a control condition for MBSR.[41] HLC consists of 8 weekly 2-hour classes. Sessions consist of lectures and discussion on the following topics: healthy living, healthy eating, physical activity and health, sleep and health, stress management, time management, and unhealthy behaviors (smoking, drinking). The HLC is designed to control for attention and other nonspecific factors including staff interactions, psychoeducation about health and stress management, classroom format, homework, group process, and data collection.[41]

Data collection

Electronic data capture (EDC, REDCap™) will be used for all data collection except imaging. Surveys for psychological symptoms, health behaviors, and potential mediators and confounds are programmed into the EDC system. During research visits, participants will enter survey responses directly into this system and research staff will enter screening and anthropometric data with periodic checks for quality assurance. All data will be maintained in a secure location accessible only to study personnel. For MRI measures, data will be analyzed blind to intervention group by two fMRI experts who perform cross-validity checks.

Data analysis and sample size considerations

We based the study sample size on Hypothesis 1, powered to detect an effect size of 0.32 standard deviations. This moderate Cohen effect size[63] represents differential over-time change for the intervention versus comparison group cast in standard deviation units. The study design calls for a baseline measurement and two follow-up measurements. In addition, we assumed a two-tailed alpha error of 0.05, and a within-person correlation for over-time measurement of 0.8.[64] With these assumptions, 40 participants in each group are needed for 80% power. We will enroll 100 participants (50 randomized to each arm) and allow for up to 20% loss to follow up, for an effective sample size of 80.

Statistical analysis will begin with univariate summaries of data distributions and examination of longitudinal trends with graphic displays. Bivariate associations will then be examined using the chi-square test, ANOVA, and the Spearman correlation test. Hypotheses 1 and 2 focus on over-time differences between the two study groups, while Hypotheses 2 and 3 focus on over-time differences for the combined sample. Hypotheses will be formally tested using generalized linear mixed models that represent the clustering of observations within participants as a random intercept, adopt an appropriate link and distribution for the specific outcome, and parameterize the intervention effect as a group-time intervention, when appropriate.[65] To preserve the power of randomization, hypothesis testing will be performed on an intent-to-treat basis. As a secondary aim, mediation analysis will determine how change in FC is explained by markers of intervention adherence using techniques as described by MacKinnon.[66,67] Sensitivity analyses with multiple imputation with chained equations will address missing data.

Imaging data is preprocessed using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, London, UK) running under the MATLAB environment (Mathworks, Inc., Sherborn, MA). The data is initially corrected for motion (threshold of 2 mm). Further pre-processing of the data includes a) slice scan time correction, b) spatial smoothing using a 3D Gaussian filter (4-mm FWHM), and c) voxel-wise linear detrending and 0.01-0.08Hz band-pass filtering. Structural and functional data of each participant is then be transformed to standard stereotaxic space[68] to facilitate group analysis.

Following the preprocessing steps, FC will be generated using correlational analysis. Left and right amygdala are used as separate seed regions of interest (ROI). FC maps from each individual seed will then be calculated for each individual subject using Resting-State fMRI Data Analysis Toolkit (REST, http://www.restfmri.net). Each seed ROI will be evaluated using two-way repeated measures ANOVA on a voxel-by-voxel basis (factors: group and imaging day) at the threshold of $p < 0.05$ after accounting for multiple comparisons using the criteria of false discovery rate (FDR).[69] Voxels with significantly changed FC within each ROI will then be averaged to generate the FC change for the ROI. This procedure will yield a single value of amygdala-orbitofrontal FC for each participant at each point in time. All ROI definitions are based on Automated Anatomical Labeling (AAL)[70] built in the MarsBAR toolbox of SPM8. Image analysis will be done blind to group membership.

As a secondary analysis, we will explore FC changes in other brain networks following MBSR using other seed regions. For example, other cortical regions that have been implicated in modulation of limbic reactivity (e.g. anterior cingulate) will examined using a hypothesis-driven approach.

Ethical considerations and dissemination plans

This study is approved by the University of Massachusetts Medical School IRB and registered as a national clinical trial (NCT02189187), Declaration of Helsinki protocols are being followed, and patients will give written informed consent. Protocol adherence will be monitored by the Independent Monitoring Committee (for for full WHO Trial Registration Data Set information see Appendix). Results from the study will be disseminated to the medical community at conferences and submitted for publication in peer-reviewed journals when the last patient included has been followed up for 12 months. Negative and inconclusive as well as positive results will be published or made publicly available through the study website www.umassmed.edu/keepingweightoff.

AUTHORS' CONTRIBUTIONS

CF conceptualized the study, and JAK, JA, MR and JB participated in the study design. CF, JAK, and JAS collected data. CF and JAS wrote and all authors revised the article and approved the final version to be published.

COMPETING INTERESTS

All authors declare no conflicts of interest.

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TABLES

Table 1. Eligibility criteria

Inclusion criteria:	Exclusion criteria:
• Males and females • Right or left handed • Ages 25-60 • Intentionally lost ≥5% of body weight during the previous year • Intending to maintain weight loss • BMI > 25 kg/m2 in the past 2 years and greater than 20.5 kg/m2 at time of study entry • Under the care of a primary care physician for at least the last year prior to screening • Able to communicate by telephone with research staff • Have a healthcare provider, personal trainer or weight-loss counselor who can complete and sign a form indicating the amount and timing of their weight loss OR have a dated photograph or weight loss diary.[71]	• Weight >300lbs (limitation of MRI scanner) • Prior participation in an MBSR course • Regular meditation practice (or any other form of meditative practice, such as yoga, Tai Chi, or contemplative prayer) for more than an average of 20 min/week within the past 2 years • Serious psychiatric, cognitive, or medical disorder • Alcohol/substance abuse or dependence in past 6 months • Any conditions that are incompatible with MRI • Structural brain damage as determined by an independent neuroradiologist, based on T1W 3D TFE sagittal and T1W FFE axial images • History of an eating disorder, diabetes mellitus or medications for diabetes mellitus • Medication that affects weight (weight loss medications, corticosteroids, antipsychotics) • History of weight loss surgery • Participation in another weight management research study • Regain of >3% of total body weight in the 2 months prior to study entry • Childbirth in the past 6 months • Claustrophobia, or any MRI incompatible implants • Pregnant or planning to become pregnant • Unable to consent

Table 2. Study schedule of recruitment, treatment, and assessments as a function of time-points (according to the SPIRIT 2013 figure guidelines)

	DURATION OF THE STUDY				
	Recruitment	**Baseline**	**Post-treatment (8 weeks)**	**Follow-up (6 months)**	**Follow-up (12 months)**
TIME-POINT	t_0	t_1	t_2	t_3	t_4
RECRUITMENT					
Screening for inclusion/exclusion criteria	X				
Informed consent		X			
Assignment to treatment arms	X				
TREATMENT					
MBSR		X	X		
HLC		X	X		
ASSESSMENT					
SCID-IV	X				
fMRI		X	X		
Weight		X	X	X	X
Height (and BMI)		X	X	X	
Waist Circumference		X	X	X	
CES-D		X	X	X	
PSS-14		X	X	X	
STAI-T		X	X	X	
STAXI-II		X	X	X	
Satisfaction with Life		X	X	X	
Emotion Regulation Questionnaire		X	X	X	
Eating Behavior Inventory		X	X	X	
Internal Disinhibition Subscale of the Eating Inventory		X	X	X	
Paffenbarger Physical Activity Scale		X	X	X	
Pittsburgh Sleep Quality Index		X	X	X	

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APPENDIX

World Health Organization Trial Registration Data Set information

1. Primary Registry and Trial Identifying Number: NCT02189187 (http://clinicaltrials.gov).
2. Date of Registration in Primary Registry: June 24, 2014
3. Secondary Identifying Numbers: n/a
4. Source(s) of Monetary or Material Support: see page 12
5. Primary Sponsor: Carl Fulwiler (see page 1)
6. Secondary Sponsor(s): n/a
7. Contact for Public Queries: Carl Fulwiler (see page 1)
8. Contact for Scientific Queries: Carl Fulwiler (see page 1)
9. Public Title: "Keeping Weight Off: Brain Changes Associated With Healthy Behaviors"
10. Scientific Title: "Mind and health: developing a neural marker for mindfulness, a pathway to health"
11. Countries of Recruitment: United States
12. Health Condition(s) or Problem(s) Studied: see Introduction section
13. Intervention(s): see Interventions section of Methods
14. Key Inclusion and Exclusion Criteria: see Table 1
15. Study Type: Randomized controlled trial with evenly distributed arms
16. Date of First Enrollment: January 8, 2015
17. Target Sample Size: 80 (see page 10)
18. Recruitment Status: Recruiting
19. Primary Outcome(s): see Assessments and Data Analysis sections
20. Key Secondary Outcomes: see Assessments and Data Analysis sections

Other items from SPIRIT Checklist

3. Protocol version: 8; last modified July 1, 2015

21a, 22. The funding agency has determined that a full Data Safety Monitoring Board is not necessary for this study. Instead, any unexpected, serious, or intervention-related i.e. Serious Adverse Event (SAEs) will be reported to an Independent Monitoring Committee composed 3 scientists not involved in the study. This includes a senior biostatistician, an obesity research expert and clinician, and a senior neuroimaging researcher. Adverse events include possible health related risks such as MRI discomfort, psychological distress during the Interventions, imminent subject's risk during SCID interview or detecting structural brain image at baseline. Anticipated or unrelated AEs will be reported to the Independent Monitoring Committee, the IRB, and the NIH in accordance with their requirements. In the semi-annual SAE summary, the Independent Monitoring Committee will provide a review of each SAE, including relevant information forwarded by the study team, and verify that he has reviewed all serious adverse event reports.

23. The funding agency conducts annual on-site reviews of study procedures and progress.

31c. We will provide supplemental access to the requisite data, workflows and results, as well as provide maximum data availability to reuse in future meta-analyses and data pooling efforts. In addition, we will make all data available at the end of the award period via a NIH-funded NITRC (Neuroimaging Informatics Tools and Resources Clearinghouse - nitrc.org) project. We will release the data under the Creative Commons, Attribution-NonCommercial-Share Alike License.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Appendix
Protocol version	3	Date and version identifier	Appendix
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 11
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11, 12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-7
	6b	Explanation for choice of comparators	6, 7
Objectives	7	Specific objectives or hypotheses	6, 7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7, 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7, 8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, 8, 13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7, 8, 13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____8_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____8_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___8, 10, 11____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____8-10_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____7_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____10_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____10, 11____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____10, 11_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____10_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__Appendix__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___n/a_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___Appendix__
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Appendix__
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____11_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____n/a_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____7_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____n/a_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____10_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____11_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____n/a_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____n/a_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____11_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____11_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Appendix___
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____n/a_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.