HRP-503B – BIOMEDICAL RESEARCH PROTOCOL

Protocol Title: Mindfulness Based Stress Reduction for Older Couples with Metabolic Syndrome

Principal Investigator: Joan Monin, PhD

Version Date: 7/19/17

(*If applicable***) Clinicaltrials.gov Registration #:** Click or tap here to enter text.

INSTRUCTIONS

This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:**

1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library.

2. If a section or question does not apply to your research study, type "Not Applicable" underneath.

3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

1. **Probable Duration of Project: 2 years**

2. Does this study have a Clinical Trials Agreement (CTA)?
   Yes☐ **No☒**
   a. If so, does it require compliance with ICH GCP (E6)?
   Yes☐ **No☐**

3. Will this study have a billable service? **Yes ☐** **No☒**

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

4. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? **Yes ☐** **No ☒**

If Yes, please answer questions a through c and note instructions below.
a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes ☐** **No ☐**
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **Yes ☐** **No ☐**
c. Will a novel approach using existing equipment be applied? **Yes ☐** **No ☐**

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

SECTION I: RESEARCH PLAN

1. Statement of Purpose:

A promising intervention likely to benefit older couples with metabolic syndrome is Mindfulness Based Stress Reduction (MBSR)(Kabat-Zinn, 2013). MBSR is a standardized 8-week manualized program in which a trained clinician teaches participants to engage in mindful meditation in their daily lives to reduce stress. A growing number of MBSR studies show psychological and physical health benefits across multiple health contexts (Grossman, Niemann, Schmidt, & Walach, 2004). The overarching goal of this study is to adapt MBSR to older couples with metabolic syndrome to maximize stress reduction effects on both partners' psychological and physical health. The specific aims of this project are:

1. **To determine the feasibility of Mindfulness Based Stress Reduction (MBSR) for older cohabiting, intimate couples in which one, or both partners, has metabolic syndrome.** We will (a) monitor recruitment, (b) adherence, and (c) missing data for the intervention. We will explore how being a couple impacts the MBSR experience, assessing (a) the prevalence of both partners having metabolic syndrome versus one partner, (b) shared decision making about participation and adherence, (c) how MBSR can be tailored to the needs of older couples, and (d) the impact on relationship quality and shared health behaviors.

2. **To determine whether MBSR improves self-reported physical health status (SF-36) (Ware Jr & Sherbourne, 1992) for each partner.** Hypothesis 1: The intervention group will have a significantly greater score on the SF-12 scale than does the control group.

3. **To determine if MBSR reduces perceived stress (Perceived Stress Scale (Roberti, Harrington, & Storch, 2006)) and increases mindfulness (Kentucky Inventory of Mindfulness Skills (Baer, Smith, & Allen, 2004)).** Hypothesis 2: Perceived stress will be reduced and mindfulness will increase for the MBSR group compared to the control group.

4. **Exploratory aim: To determine if an MBSR intervention is associated with decreases in the composite measure of metabolic syndrome (blood pressure, waist circumference, glucose levels, cholesterol, triglycerides) for each partner.** Hypothesis 3: The metabolic syndrome composite score for partners will be smaller at the end of the study in the MBSR group compared to the control group.

2. Background:

Metabolic syndrome is a common multifactorial disorder that increases risk for cardiovascular disease and diabetes and affects a substantial proportion of older adults(Eckel, Grundy, & Zimmet). Between 23 and 55% of older adults meet metabolic syndrome criteria, which consists of having three of the following: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, high blood pressure, and high fasting glucose (Denys et al., 2009). Although this is a common syndrome, there are few preventive interventions targeting metabolic syndrome (Dunkley et al., 2012). This is despite the fact that the NHLBI suggests that treatment start with lifestyle changes including diet, exercise, maintaining healthy weight, and stress reduction, with medications as a secondary treatment. With the increasing number of medications that older adults take (Charlesworth, Smit, Lee, Alramadhan, & Odden, 2015), lifestyle interventions are becoming even more important. To date, most lifestyle interventions target diet and exercise without explicitly addressing stress reduction. As stress is related to overall psychological and physical health as well as each metabolic syndrome biomarker (Matthews & Kuller, 2002), research on the efficacy of stress reduction interventions for older adults is critical.

Lifestyle interventions that target older couples may be more effective than lifestyle interventions that target older individuals. The majority of older adults (especially men) are in close, committed relationships (US Census Bureau). Within close relationships, especially older intimate cohabiting couples, partners' characteristics and environments make them similar not only in terms of stress, but also health behaviors and mental and physical health (Hoppmann, Michalowski, & Gerstorf, 2016). Partners also have important positive and negative influences on each other. By targeting both partners within a couple, lifestyle interventions have the capability of maximizing the positive influences and minimizing the negative influences. There is some preliminary evidence that this is the case, as multiple weight control interventions show added benefit of involving relationship partners in their programs (Black, Gleser, & Kooyers, 1990).

A promising intervention likely to benefit older couples with metabolic syndrome is Mindfulness Based Stress Reduction (MBSR). MBSR is a standardized 8 week manualized program in which a trained clinician teaches participants to engage in mindful meditation in their daily lives to reduce stress (Kabat-Zinn, 2013). MBSR shows robust psychological (Gu, Strauss, Bond, & Cavanagh, 2015) and physical (Grossman et al., 2004) health benefits across multiple health contexts. MBSR reduces blood pressure (Nyklíček, Mommersteeg, Van Beugen, Ramakers, & Van Boxtel, 2013), helps obese individuals lose weight (Olson & Emery, 2015), and improves glycemic control (Rosenzweig, Reibel, Greeson, & Edman, 2007). MBSR has also been shown to reduce loneliness and pro-inflammatory gene expression in older adults (Creswell et al., 2012).

Aim 1 (Feasibility of addressing couples): Emerging studies are showing the benefits of simultaneous participation of couple members. There a few pilot studies using MBSR with couples, namely cancer patients and their spouses (Birnie, Garland, & Carlson, 2010) and frail elders and their caregivers (McBee, 2003). MBSR is a standardized and well-known intervention beginning to be adopted and covered by healthcare plans and employers. If MBSR proves to be beneficial for older couples, this intervention can be easily disseminated to the increasingly large population of older American couples. It is important to note that because of the standardization that makes MBSR easy to disseminate, research is needed to test its efficacy in different disease contexts, with different populations, and on multiple health outcomes, without substantially changing the intervention itself. This is why our adaptation to the context of couples dealing with metabolic syndrome will include minimal changes that can be easily incorporated into the existing MBSR manual. This approach has been taken by other researchers who have applied MBSR to couples, for instance with cancer(Birnie et al., 2010), in which couples participated simultaneously in MBSR but the MBSR curriculum was not changed to focus on relational issues. Qualitative findings from this couples MBSR cancer pilot study showed that partners supported each other with attendance and adherence to home practice and experienced improvements in relationship quality.

Aim 2 (Hypothesis 1): Self-reported physical health will improve for each partner in the MBSR intervention group compared to a wait-list control group. Our primary outcome will be improvement of self-reported physical health status. We chose to focus on self-reported physical health as measured by the SF-12, which captures functional ability, specific health symptoms, and overall assessment of health, as it is a patient-oriented outcome that has been shown to relate to having metabolic syndrome(Jahangiry, Shojaeezadeh, Montazeri, Najafi, & Mohammad, 2016). In addition, studies show that individual components of metabolic syndrome, for example waist circumference, are related to overall physical functioning and specific health symptoms (e.g. impaired sleep)(Jennings, Muldoon, & Hall, 2007).

Aim 3 (Hypothesis 2): MBSR will reduce each partner's self-reported stress score and increase their mindfulness score. A great deal of MBSR research supports this hypothesis in both individually focused and couple focused studies in multiple health contexts (Grossman et al., 2004) using the Perceived Stress Scale (Roberti et al., 2006) and the Kentucky Inventory of Mindfulness Skills (Baer et al., 2004). Our aim is to replicate these findings in older couples with metabolic syndrome.

Aim 4 (Hypothesis 3): The metabolic syndrome composite score for partners will be smaller at the end of the study in the MBSR group compared to the control group. There is some existing

evidence that individual factors that constitute metabolic syndrome such as glycemic control (Rosenzweig et al., 2007), blood pressure (Carlson, Speca, Faris, & Patel, 2007), and weight (Katterman, Kleinman, Hood, Nackers, & Corsica, 2014) may be affected by MBSR. Although it may be difficult to achieve changes in biomarkers in such a short time frame, these changes are thought to occur after a person has incorporated mindfulness practice into their daily lives (Carlson et al., 2007). By examining potential changes in these biomarkers, this will provide preliminary data and effect sizes for longer term studies of the impact of MBSR for older couples with metabolic syndrome.

Importantly, we will explore the dyadic effects of couple members' simultaneous engagement in the MBSR intervention. In addition to using proper statistical techniques to understand the effects of MBSR on each partner's outcomes, we will examine partner influences. For each primary hypothesis, we will examine the secondary hypothesis that each partner's improvement in each health outcome (self-report physical health, stress, mindfulness, and metabolic syndrome composite biomarker score) will be associated with improvement in the other partner's health outcome. In addition, we will examine the effects of the intervention on both partners' relationship satisfaction. Showing that relationship satisfaction can be enhanced is an important goal on its own, but we may also find that health outcomes improve when relationship quality improves.

3. **Research Plan:**

Procedures

Forty couples (N=80) will participate in a baseline visit to have blood drawn, BMI and BP measured, and to complete questionnaires assessing demographics, contextual factors, and baseline primary outcomes. Couples will be randomized to the MBSR condition (n=20 couples/ 40 individuals) or the wait list control condition (n=20 couples). The baseline blood draws and survey administration will take place at the CSRU, with the HRU as back up as needed. The blood analysis will be done by the YCCI Core lab. All participants will receive an informational sheet about metabolic syndrome.

Participants will be randomized to the intervention or wait-list group after informed consent is obtained, the initial blood is drawn and survey baseline is completed at the CSRU. A random digit generator will be used that assigns a condition (in this case, intervention or wait list) to each couple ID number.

MBSR condition: MBSR is a standardized protocol consisting of 8-weekly 2.5 hour sessions, homework consisting of 30-45 minutes of mindfulness meditation practice six days per week and a one-time half-day (4-6 hour) retreat. This will be offered at the Social Gerontology and Health lab, Suite 801, 55 Church street, New Haven, CT Our MBSR intervention is based upon the standard regimen taught at the University of Massachusetts.(Kabat-Zinn, 2013) Participants will attend weekly group sessions at the Yale Stress Center at the Yale School of Medicine taught by an experienced MBSR instructor (Anne Dutton MA MSW) who collaborates closely with Co-I Dr. Ali. Each weekly session will consist of an instructor-led mindfulness meditation, followed by a discussion of the meditation and its application into participants' everyday life. Formal meditations that will be led and discussed include eating meditation, body scan, sitting meditation, Hatha Yoga, and walking meditation. Participants will take their partners blood pressure reading with an automated Carescaoe cuff at each MSBR class. In addition, informal mindfulness practices of awareness of pleasant and unpleasant events and awareness of routine events will be discussed. Participants will be recording their daily mindfulness practice minutes on attached form.

Wait list condition: After the MBSR condition groups have completed their sessions, the participants in the Wait List group may choose to participate in the 8-week MBSR class. Participants will be provided with a coupon to participate starting July 2018. In the meantime, participants in the Wait list group will complete the same measures at the same time points as participants enrolled in Cohort 1 and Cohort 2 of the MBSR conditions.

Accounting for simultaneous participation of couple members in MBSR for manual development. Prior to recruitment, the team will meet with Ms. Dutton, the MBSR instructor to adapt the MBSR manual so that it accounts for couples participating in the classes. Although the MBSR curriculum will not be substantially altered from its validated form, Ms. Dutton will provide suggestions about how each practice and assignment in the program can acknowledge the partner's presence. We will maintain the standard MBSR program so that is can be easily disseminated to the public in later phases of this research. We are not developing a new relationship oriented MBSR. Rather, we will provide instruction about how each assignment should be carried out knowing that the partner is also in the program at the same time. Upon completion of the study, we will obtain interventionist feedback about how couple participation may have altered the MBSR program. Ms. Dutton will keep notes about the influence of couple dynamics in her classes throughout the study and summarize them in a team meeting with the PI, Co-Is, and Project manager every 4 weeks and at the end of the study.

Measurement Schedule

	# of items	Variable type	Recruit	Baseline assess	8-week assess
Recruitment					
Referral or chart review: Potential participant has 3 of the following? (a) Abdominal obesity: waist circumference >102 cm in men, >88 cm in women; (b) Hypertriglyceridemia: ≥150 mg/dL (1.69 mmol/L); (c) Low high-density lipoprotein (HDL) cholesterol: <40 mg/dL (1.04 mmol/L) in men, <50 mg/dL (1.29 mmol/L) in women; (d) High blood pressure (BP): ≥130/85 mm Hg and/or taking BP medication; (e) High fasting glucose: ≥110 mg/dL (≥6.1 mmol/L).	1	Inclusion criteria	X		
Participant is 60 or over.	1	Inclusion criteria	X		
Participant married or in romantic relationship?	1	Inclusion criteria	X		
Are they living together?	1	Inclusion criteria	X		
Participant's partner interested in being in the study?	1	Inclusion criteria	X		
Both partners age 60 or over?	1	Inclusion criteria	X		
Either partner non-English speaking?	1	Exclusion criteria	X		
Either partner practice mind-body therapies more than once/week (yoga, meditation)?	1	Exclusion criteria	X		
Either partner taking psychiatric medications?	1	Exclusion criteria	X		
Random assignment to intervention or waitlist control group	1	Intervention/ control status			

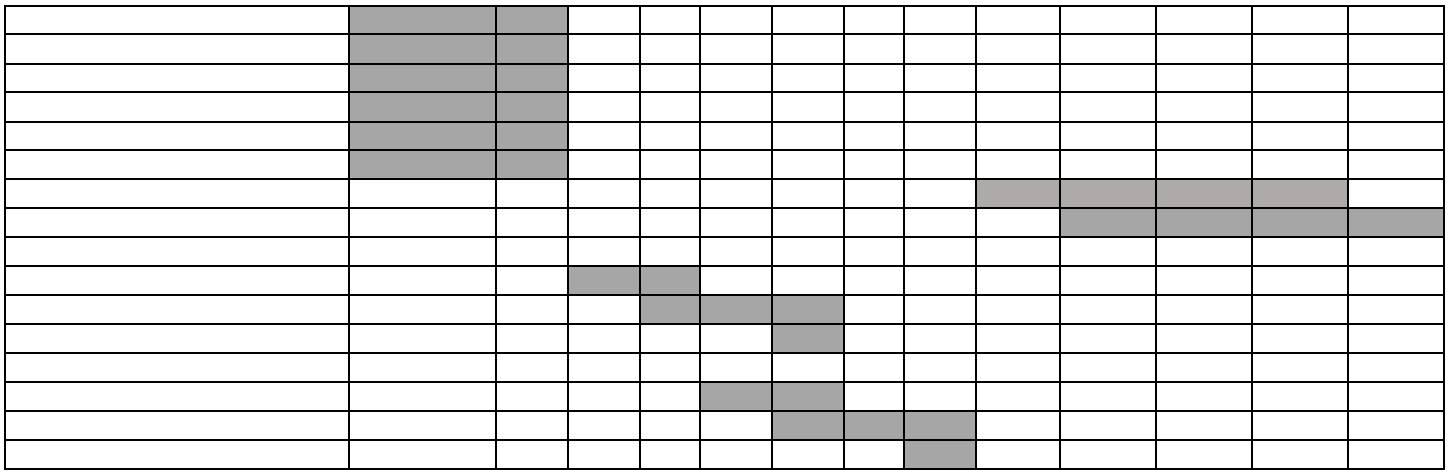
Self-report Measures (Both partners)					
Socio demographics: age, gender, education, income	4	Covariates		X	X
Physical health symptoms (SF-12)	12	Primary outcome		X	X
Perceived stress scale (Roberti et al., 2006)	10	Primary outcome		X	X
Kentucky Inventory of Mindfulness Skills (Baer et al., 2004)	39	Primary outcome		X	X
Relationship Assessment Scale (Hendrick, 1988)	7	Secondary outcome		X	X
Health behavior questionnaire (sleep, physical activity, eating behavior, medication adherence (Schulz et al., 1997))	22	Secondary outcome		X	X
Couples' decision making in participation and adherence: 1) How was your partner involved in your decision to first participate in the intervention? (Responses: a. encouraged you, b. discouraged you, c. neither) 2) How was your partner involved in your decision to continue with each class? (Responses: a. encouraged you, b. discouraged you, c. neither) 3) Open ended question: Describe how participating with your partner influenced your experience with the intervention.	3	Exploring couple dynamics			X
Biological Measures (Both partners)					
Blood draw: to assess hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol and high fasting glucose	3	Secondary outcome		X	X
Abdominal obesity- waist circumference per WHO protocol (2011)	1	Secondary outcome		X	X
Blood pressure (automated Carescape cuff)	1	Secondary outcome		X	X
Do both partners, only the husband, or only the wife have metabolic syndrome at baseline?	1	Exploring couple dynamics			
Feasibility Measures (Both partners)					
Percent of couples who screen versus enroll (Project manager keeps a record.)	1	Feasibility outcome	X		
# of MBSR sessions attended (Interventionist takes attendance.)	1	Feasibility outcome			X
Total minutes of home MBSR practice (Participants keep a daily record.)	1	Feasibility outcome			X

Recruitment, Data management plan, and Retention. We will use the OnCore Clinical Research Management System for recruitment and data management. Dr. Ali and his team have extensive experience using OnCore in a variety of clinical trials. The OnCore product suite includes integrated patient registries, biospecimen management, billing compliance, paperless committee management, data management, and EDC functionality. Patient identifiers and demographics tracked in the standard OnCore form are stored independently of analysis data. All data within OnCore is stored within an Oracle RDBMS database server. EPIC's Registry tool allows consistent identification of subsets of patients with conditions which will allow for advanced subject recruitment. In addition, we will use MyChart and the Yale Center of Clinical Investigation's Help Us Discover database, as well as the Joint Data Analytics Team (JDAT), a unified Yale School of Medicine and Yale-New Haven Health Systems team, to identify potential participants. We will also be accepting physician referrals for participants. The YCCI will send email blasts to area endocrinologists and primary care physicians to identify patients. The Program on Aging Field core, led by Joanne McGloin, will work with the YCCI and JDAT to help our team identify participants. Participants who are identified but are not in the epic system may receive a pre-screening consent phone call.. Specifically, a trained nurse familiar with the EPIC system, Kathleen Williams RN, project coordinator, will efficiently identify patients based on chart reviews. We will also place an ad in the Senior Blue Book and consult with the POA Community Advisory Board. Co-I Dr. Jastreboff will also recruit participants through her clinic. Kathleen Williams, Project manager, will contact and screen potential subjects.

The baseline, 8-week, and 3-month visits will entail data collection using validated questionnaires and self-report paper forms at the CSRU. The eight week visit will take place between five to eleven weeks after enrollment. The three month visit will occur from 10 to 14 weeks after enrollment. At the 8-week visit participants will be asked to complete a qualitative interview in addition to the paper surveys. Responses will be recorded on a cell phone and we will use transcription plus LLC https://www.transcriptionplus.net transcription services. Participants will complete the forms themselves, and they will be entered into the OnCore system by the project manager. These forms will be kept in paper form in each study participant's record and will be kept in a locked file cabinet at the Yale Center for Clinical Investigation. Only the PI and project manager will have access to the participant's records. Forms will be coded with subject number; no personally identifiable information will be associated with these forms. Blood will be drawn by staff at the Church Street Research Unit and sent to the YCCI Core Lab for processing of the glucose, cholesterol, and triglyceride markers. The biomarker information will then be linked to our study on OnCore. The OnCore database will be supported by the Yale Center for Clinical Investigation/ CTSA. Incomplete or missing data prompts follow-up calls or electronic queries in OnCore. Our OnCore database will be checked for completeness in real-time from internal checks; while the PI and project manager will perform weekly audits for complete data.

The project manager will use a study cell phone for the purposes of recruitment, and reminder texts for participants.The project manager will make routine follow-up calls to remind study subjects of their appointments. Attrition will be minimized and data collection optimized with a relatively short intervention duration together with a $150 individual participant remuneration..Payment will be made through the ONCORE bank of America gift card program with renumeration to be as follows. ($50 dollars at baseline,$50 dollars at eight weekfollow-up and $50 dollars at three month follow- up) In Dr. Ali's ongoing studies in fibromyalgia and Irritable Bowel Syndrome patients (n=108), he has achieved complete (no missing data) datasets based on robust data collection, retention, and follow-up procedures in collaboration with the YCCI.

Timeline.



July-Aug 2017: finalize study materials, MBSR manual, train staff, build Oncore database, recruit

September 2017- March 2018: Cohort 1 (baseline, intervention, 8-week follow-up, 3 month follow up)

January 2017-June 2018: Cohort 2 (baseline, intervention, 8-week follow-up, 3 month follow up)

4. Genetic Testing N/A ☒

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

   Older married couples in which both partners are 60 years or older and one or both partners have metabolic syndrome.

6. **Subject classification:** N/A

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? **Yes ☐ No ☒**

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

   Eligibility criteria. (1) The couple is in a cohabiting, committed, intimate relationship (sexual minority couples not excluded). (2) Both partners are age 60 or older. (3) One or both partners have 3 of the following: (a) Abdominal obesity: waist circumference >102 cm in men, >88 cm in women; (b) Hypertriglyceridemia: ≥150 mg/dL (1.69 mmol/L); (c) Low high-density lipoprotein (HDL) cholesterol: <40 mg/dL (1.04 mmol/L) in men, <50 mg/dL (1.29 mmol/L) in women; (d) High blood pressure

(BP): ≥130/85 mm Hg and/or taking BP medication; (e) High fasting glucose: ≥110 mg/dL (≥6.1 mmol/L).

Exclusion criteria. Non-English speaking, practicing mind–body therapies more than once/week (e.g., meditation, yoga), taking psychiatric medications, substance abusers, persons with suicidal ideation, or severe psychopathology.

8. How will **eligibility** be determined, and by whom?

Preliminary eligibility will be determined by the Project Manager based on responses to questions on telephone screening. Final eligibility will be determined by Dr. Jastreboff based on corroborating the diagnosis of metabolic syndrome from their medical chart.

9. Risks:

Mindfulness-based stress reduction has been studied in a number of clinical trials for many conditions. There are no known side effects of mindfulness-based stress reduction. There are potential risks of increased symptoms because mindfulness training can increase awareness of body sensations. As the mindfulness-based stress reduction program incorporates yoga, there is also a risk of physical injury, such as pulled or strained muscles.There are theoretical risks of meditation programs including increased psychological distress in persons with unstable psychological conditions or that are suicidal. However, persons with these conditions will not be allowed to participate in this study.

Other risks from participating in the study include the breach of confidentiality about subject's health status and participation in the study. This is very unlikely to occur, as all study investigators are trained and certified in research privacy.

The risks involved in drawing blood from a vein may include, but are not limited to, momentary discomfort at the site of the blood draw, possible bruising, redness, and swelling around the site, bleeding at the site, feeling of lightheadedness when the blood is drawn, and rarely, an infection at the site of the blood draw. There are no major risks associated with these procedures.

There is a risk of breach of confidentiality.

Dobkin notes possible risks noted in other types of meditation programs including increases in anxiety, panic, tension, less motivation in life, boredom, pain, impaired reality testing, confusion and disorientation, feeling 'spaced out', depression, increased negativity, being more judgmental and feeling 'addicted to meditation.' (Dobkin, Irving, & Amar, 2012)

Dobkin also notes a case report where mania was precipitated by meditation as well as transient meditation-induced psychosis (Dobkin et al., 2012). Our MBSR teacher (Ms. Dutton) notes contraindications in active substance abusers, persons with suicidal ideation, or severe psychopathology

10. **Minimizing Risks:**

a. Recruitment and Informed Consent

For patients who have indicated interest through the YCCI, patients identified and referred for screening will be contacted by the Project Manager by telephone. Yale EPIC electronic medical records will also be reviewed to assess eligibility. Interested patients/partners will be informed about the study using IRB/HIC-approved screening scripts in order to determine preliminary eligibility. All screening, recruitment, and data capture will take place in OnCore, the YCCI's Clinical Trials Management System

At the baseline visit, consent will be obtained by the PI or research assistant Consent forms will include information about the procedures and the risk and benefits involved in the study. All subjects will be informed of the option of not participating, or of stopping at any time during the study. In addition to the consent forms, participants will complete a Commitment Agreement that outlines the activities conducted during the study. Consent forms will be kept in a locked file cabinet.

Prior to signing the consent documents, the PI or research assistant will provide subjects with additional information about the study and review the consent forms and other study-related documentation. All subjects participating in the study will provide written consent. All subjects will be informed of the option of not participating, or of stopping at any time during study. The ability and capacity to consent will be determined by the Principal Investigator or research assistant by thorough questioning during the process of consent. Potential subjects will be asked, "Could you explain to me what we are going to ask you to do in this study? This will help me be to be sure that you understand the research," as well as, "What more would you like to know about this study?"

Protections against risk

Safety and tolerability will be assessed through participant self-report of symptoms or changes in symptoms since baseline (obtained from adverse event logs and direct query at the sessions and at the 8 week and 3 month follow up visits) until completion of the study. Comparison of tabulated safety events by grade (mild, moderate, severe) between intervention and control groups will help identify any unforeseen consequences of the treatment regimen. Based on the safety profile of MBSR, there is minimal risk of adverse events. Should any subjects experience adverse effects related to the intervention, these will be reported using a standard form to the Yale Human Research Protection Program. All subjects will have direct (phone and email) access to the Principal Investigator. If any adverse events occur requiring immediate medical attention, the PI will guide and advise subjects in the medical management of acute and/or emergent reactions. In most cases, this will entail calling '911' and an immediate emergency department referral.

In recent systematic reviews of MBSR for a variety of conditions, no adverse effects were reported (Cramer, Haller, Lauche, & Dobos, 2012; Katterman, Kleinman, Hood, Nackers, & Corsica, 2014). There are, however, theoretical risks of MBSR, including increased symptomology resulting from awareness training (Fjorback, Arendt, Ornbol, Fink, & Walach, 2011), as well as using mindfulness interventions instead of more effective treatments (Marchand, 2013).

Dobkin notes possible risks noted in other types of meditation programs including increases in anxiety, panic, tension, less motivation in life, boredom, pain, impaired reality testing, confusion and disorientation, feeling 'spaced out', depression, increased negativity, being more judgmental and feeling 'addicted to meditation.' (Dobkin, Irving, & Amar, 2012)

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psychopathology.

Data and Safety Monitoring Plan:

11. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? n/s
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

12.

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency [*monthly*]. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator and the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular study meetings and via email as they are reviewed by the principal investigator.

13. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Feasibility outcomes will be observed, recorded, and qualitatively evaluated. Descriptive characteristics of the cohort will be summarized with means and standard deviations and counts and percentages according to intervention group. Although this pilot study will not be powered to test all outcomes for statistical significance, the primary quantitative outcomes are expected to have continuous Gaussian distributions making possible the comparison of intervention and control group results with linear mixed effects regression models that can accommodate the clustering of outcome results within couples. Finally, in anticipation of future studies of the metabolic syndrome outcome,

selected analyses will be conducted to compare the utility of the composite metabolic syndrome outcome and with a version of this outcome yielded by a measurement model in a structural equation modeling context.

Hypothesis 1: Self-reported physical health will be greater on average for participants in the MBSR intervention group compared to a wait-list control group. A multivariable linear mixed effects model will be used to assess whether self-reported physical health is greater in the intervention group than in the control group. A random effect will be used to account for the clustering of outcome values within couples. A pre-specified set of covariates will be entered into the regression model including baseline self-reported physical health and demographics and contextual factors that differ significantly across intervention and control groups. Model goodness of fit will be assessed with residual analysis, influence statistics, and goodness-of-fit statistics.

Hypothesis 2: MBSR will reduce each partner's self-reported stress and increase their mindfulness. The analyses for these two secondary outcomes will proceed according to the same procedures as cited for Hypothesis 1 above.

Hypothesis 3: The metabolic syndrome composite score for participants will be smaller at the end of the study in the MBSR group compared to the control group. Given the exploratory nature of this hypothesis and the lack of consensus as to how to code a variable for metabolic syndrome, this Hypothesis 3 will be analyzed in three different ways: 1) with the outcome as a binary indicator variable indicating the occurrence of 3 or more of the 5 syndrome components; 2) with the outcome as a continuous variable obtained from the summation of Z-score transformations of the 5 syndrome components; and 3) as continuous latent factor or principal component construct obtained from a factor analytic measurement model. Performing these three analyses will provide invaluable insights for determining how the metabolic syndrome outcome will be coded in future studies using older samples.

We will explore the dyadic effects of couple members' simultaneous engagement in the MBSR intervention. In addition to the above analyses, we will use SPSS mixed models for analyzing repeated measures in couples. In this analytic approach, reports of health (primary outcome) (Level 1) are nested within time-invariant individual and couple variables (i.e., background variables, intervention condition (primary predictor), and moderators) at Level 2. The program allows for the analysis of intercepts and slopes of the hypothesized associations between Level 1 variables (i.e., within-couple relations between each partner's health) across all assessment points (baseline, 8 weeks, and 3 months), as well as interactions between Level 2 variables and Level 1 intercepts and slopes. In other words, we will assess whether the intervention was successful at the couple level by looking at the overall intervention effect, as well examine, for heterosexual couples, differential effects for husbands and wives by looking at the role (husband or wife) X intervention interaction.

How quantitative and qualitative data will be combined to understand outcomes. Qualitative data will be analyzed using Atlas.ti software and themes will be identified regarding partner influence on study experience. Key demographic characteristics and results from quantitative questions regarding decision making in participation and adherence will be entered into the software as coded attributes. Queries will be conducted to investigate the relationships between identified themes and coded attributes. Finally, the results of this qualitative analysis will be used to formulate hypotheses about the meanings and mechanisms underlying the quantitative results for Hypotheses 1 and 2, and especially, for the results of dyadic analyses of couple members' simultaneous engagement in the MBSR intervention.

Power: The sample size procedure in PASS shows that in anticipation of loss-to-follow-up, and with recognition of dependency in results from couples, the effective sample size is estimated to be 70, a reduction of 10 from the enrollment of 80 study participants. Assuming power of 80%, an outcome standard deviation of 10, and equal assignments to the intervention and control groups, this effective sample size will allow for detection of a difference between intervention and control groups mean values for the SF-12 outcome of 6.43 or more at the two-sided level of significance of 0.05. The sample size procedure in PASS was performed.

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects: 80 participants

a. Targeted for enrollment at Yale for this protocol: 80
b. If this is a multi-site study, give the total number of subjects targeted across all sites: N/A

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

- ☐ Flyers
- ☐ Posters
- ☐ Letter
- ☒ Medical Record Review*
- ☐ Departmental/Center Newsletters
- ☒ YCCI Recruitment database
- ☐ Other (describe):
- ☐ Internet/Web Postings
- ☐ Mass E-mail Solicitation
- ☐ Departmental/Center Website
- ☐ Departmental/Center Research Boards
- ☐ Web-Based Clinical Trial Registries
- ☐ Clinicaltrials.gov Registry (do not send materials to HIC)
- ☐ Radio
- ☐ Telephone
- ☐ Television
- ☐ Newspaper

*** Requests for medical records should be made through JDAT as described at**
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Endocrinologist and Co-I, Dr. Ania Jastreboff, MD at Yale is eager to refer patients for this study. Dr. Jastreboff will provide study information to potentially eligible patients.

We can also recruit from Yale-affiliated community practices and other relevant sources through our local networks. The investigators have active referral networks through primary care and general pediatric specialty clinics throughout Connecticut.

We will also work with the Program on Aging field core, YCCI recruitment specialists, and JDAT to identify participants. We will be using the staff at the YCCI Recruitment call center as well.

b. Describe how potential subjects are contacted.

Patients identified for screening through YCCI will be referred to the Project Manager via phone. Interested patients/partners will be informed about the study using IRB/HIC-approved screening scripts in order to determine preliminary eligibility. The phone screening will entail a review of the eligibility criteria and verbal and written description of the intervention procedures. We will collect eligibility/exclusion criteria information (except for the biological indicators of metabolic syndrome) which includes marital/ couple status, age, whether they practice mindfulness, whether they take psychiatric medication, whether they have a substance abuse problem. All screening, recruitment, and data capture will take place in OnCore, the YCCI's Clinical Trials Management System.

c. Who is recruiting potential subjects?

Dr. Monin (Principal Investigator), co-investigators (Drs. Jastreboff and Dr. Ali), and the study project manager (Kathleen Williams) will recruit participants. The Yale Center for Clinical

Investigation (YCCI) will also be used for study recruitment, which includes dedicated recruitment staff, community outreach personnel, and the use of YCCI's Clinical Research at Yale website, www.yalestudies.org. The Program on Aging will also help with recruitment.

4. **Assessment of Current Health Provider Relationship for HIPAA Consideration:**
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?
☐ Yes, all subjects
☒ Yes, some of the subjects
☐ No

If yes, describe the nature of this relationship.

Some of the participants may be patients of Dr. Jastreboff.

5. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:
☐ For entire study
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

With waiver of HIPAA authorization, databases can be accessed identify patients to contact about the study. Without the waiver, this rich source of potential subjects would not be available.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data:

N/A

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name,

purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

At the baseline visit at Yale School of Medicine, prior to signing the consent/assent document, the Principal Investigator or research assistant will provide subjects with additional information about the study and review the consent forms and other study-related documentation. All subjects participating in the study will provide written consent. All subjects will be informed of the option of not participating, or of stopping at any time during the interview.

7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

The ability and capacity to consent/assent will be determined by the Principal Investigator or research assistant by thorough questioning during the process of consent. Potential subjects will be asked, "Could you explain to me what we are going to ask you to do in this study? This will help me be to be sure that you understand the research," as well as, "What more would you like to know about this study?"

8. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

Non-English speaking is part of the exclusion criteria for this study.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐**Not Requesting any consent waivers**

☐**Requesting a waiver of <u>signed</u> consent:**

☐ **Recruitment/Screening only**

☐ **Entire Study (**Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? **YES** ☐ **NO** ☐
- Does a breach of confidentiality constitute the principal risk to subjects? **YES** ☐ **NO** ☐

OR

- Does the research pose greater than minimal risk? **YES** ☐ **NO**☐
- Does the research include any activities that would require signed consent in a non-research context? **YES** ☐ **NO** ☐

☒ **Requesting a waiver of consent:**

☒ **<u>Recruitment/Screening</u> only**

☐ **<u>Entire Study</u>**

For a waiver of consent, please address the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***
  ☒ No
- Will the waiver adversely affect subjects' rights and welfare? **YES** ☐ **NO**☒
- Why would the research be impracticable to conduct without the waiver? We will need to view medical records to determine eligibility before we call potential subjects
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? na

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Name, date of birth, telephone number, address, email address, sex, metabolic syndrome status, medications, other diagnoses. Only the PI and research assistant will have access to PHI.

b. How will the research data be collected, recorded and stored?

The baseline, 8-week, and 3 month visits will entail data collection using validated questionnaires and self-report forms. These forms will be kept in paper form in each study participant's record and will be kept in a locked file cabinet at the Yale Center for Clinical Investigation. Only the PI and study assistant will have access to the participant's records. Forms will be coded with subject number; no personally identifiable information will be associated with these forms. Data will be entered to a secure OnCore database hosted at Yale University. OnCore is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The OnCore database will be supported by the Yale Center for Clinical Investigation/CTSA.

Incomplete or missing data prompts follow-up calls or electronic queries in OnCore. Our OnCore database will be checked for completeness in real-time from internal checks; while the PI and project manager will perform weekly audits for complete data.

We work closely with the Yale Program on Aging and the biostatistics core director, Dr. Peter Van Ness, an expert in the design and analysis of clinical trials with older adults.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☐ Laptop Computer ☐ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

All documents and subject information will be strictly maintained according to HIC and HIPAA regulations to ensure confidentiality at all times. Access to subject information will be limited to a "need to know" basis and all data will be coded to maintain confidentiality. Only those investigators with appropriate Human Subjects training will have access to subject data. All electronic files are encrypted and password protected; paper files are kept in locked file cabinets. All data will be managed to assure strict confidentiality of subjects at all times.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information

Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Data will be kept for five years after the study ends. Data will then be de-identified using a "Safe Harbor" (45CFR164.514(b)(2)) approach consistent with the HIPAA Privacy rule. De-identified data will be certified by a statistician that there is a very small risk that use of the protected health information could lead to a subject being identified. The principal investigator (Dr. Monin) is responsible for the implementation of data de-identification.

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB and the OHRP.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

Only the principal investigator and research team will have access to PHI.

g. If appropriate, has a Certificate of Confidentiality been obtained?

A Certificate of Confidentiality is not needed and therefore has not been obtained.

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

No.

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

The potential improved patient satisfaction, functional status, and quality of life for older adults with metabolic syndrome can have far reaching implications, including greater receptivity to the benefits of interventions, superior adherence, and enhanced resiliency to the inevitable variations in chronic disease presentation. Adding MBSR to metabolic syndrome treatment regimens could provide tremendous benefit to the many older adults, in addition to relieving a sub-optimal and overburdened healthcare system. The relative risk to subjects participating in this pilot study is negligible. The greatest risk may be

that subjects are involved in alternative treatment that ultimately proves to be no more effective than the usual care they have already received. Thus, the risk-benefit ratio strongly favors the study participant.

The identification of a practical stress reduction regimen of that can produce symptomatic and psychological relief has the potential to help alleviate the suffering of patients with metabolic syndrome and improve public health. Results obtained from this initial line of inquiry will be the first step in developing a graduated, stepwise integrative medicine algorithm for the treatment of metabolic syndrome in older adults. The long-term intention is to expand this approach to a larger sample and to older couples with other types of medical risk factors.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   Alternatives to participating in the study would be to continue with their usual medical care, often involving pharmacotherapy.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   All payments will be made in the form of Visa® prepaid debit cards. As a thank you for their time, each participant will receive $50 after completing the baseline assessment, $50 after completing the 8-week assessment, and $50 at 3 month follow-up, for a total of $150.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   Subjects will not incur any costs associated with participation in the research besides transportation fees. Parking stubs for the Doctor's Building parking lot are validated at each office visit and parking will be provided at the Social and Gerontology Health Laboratory at 55 Church Street. The MBSR intervention is provided at no cost to the subject.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   This research does not involve more than minimal risk. There are no known risks associated with MBSR. Numerous clinical trials of MBSR have not reported significant adverse effects related to the intervention.

   b. Will medical treatment be available if research-related injury occurs?

   The YCCI CSRU will provide this service.

c. Where and from whom may treatment be obtained?
The YCCI CSRU.

d. Are there any limits to the treatment being provided?

No.

e. Who will pay for this treatment?

The YCCI has liability for these circumstances.

f. How will the medical treatment be accessed by subjects?

The YCCI CSRU treatment will be available immediately if there is an injury.

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