SLEEP AND CIRCADIAN TREATMENTS FOR SHIFTWORKERS

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DETAILED PROTOCOL

I. BACKGROUND AND SIGNIFICANCE

I.a. Historical Background

Difficulty sleeping is one of the most widespread problems affecting night and rotating shift workers (1-3). It not only has immediate impacts on workers' on-shift alertness, performance, and safety, it can have longer-term effects on their health and quality of life. Such problems are more likely to be experienced by older workers. The proposed Field Trial will test, in older shift workers, a sleep strategy that has been shown to be successful with older participants in a simulated shift work study in the laboratory (4-6). The Field Trial is designed to translate our laboratory findings into practice in an operational setting. Our afternoon-evening sleep intervention is based theoretically on the two-process model of human sleep regulation (7, 8); see below. An evening sleep episode results in a shorter duration of wake prior to the night shift, thereby reducing "sleep pressure" (the wake-dependent increase in sleepiness) during night shifts. Our preliminary studies demonstrate that this leads to improved nighttime alertness and performance as well as longer and more consolidated sleep in older adults, similar to previous findings in young adults. If these changes also occur in the Field Trial, when implemented more widely it could not only lead to improved well-being but also a lower risk of occupational error and injury. Furthermore, we have preliminary data showing that cortisol levels are also lower following this intervention, suggesting that it could lead to better long-term health outcomes in shift workers.

The impact of shift work in the US. Shift work has become increasingly common as our 24/7 global society has required more and more workers to do their jobs at night. In fact, workers in food service, retail, and financial services now work at night along with more traditional night workers such as public safety, healthcare, and manufacturing employees. Data from the National Health Interview Survey (NHIS) in 2010 revealed that 28.7% of all employees work some type of alternative shifts (night shifts or rotating shifts)(9).

The negative consequences of shift work. Working at night or on a rotating schedule, thereby frequently shifting the timing of sleep and wakefulness, poses a serious threat to the shift worker's physical, mental, and psychosocial health (10-12). In fact, the disruption caused by shift work is recognized as a circadian rhythm sleep disorder in both the International Classification of Sleep Disorders and the DSM-IV 4, and is called shift work disorder (SWD (13-15)). Even those who choose to work at night because of higher pay or to accommodate childcare or other demands report that working at night negatively influences their health and safety (16, 17). Adverse consequences of shift work include greater complaints of gastrointestinal disorders (13, 18-20), increased risk of accidents while at work and while commuting home (13, 17, 21-23), greater likelihood of depression, increased risk of myocardial infarction and cardiovascular disease (24-26), greater risk for developing certain cancers and metabolic syndrome (27-29), and more sleep complaints (3, 30, 31, 10, 15, 32-34).

The older worker and shift work. Not only have we moved toward a 24-h society, the median age in the US continues to rise (US Census Bureau, 2017). Furthermore, the number of older people in the workforce and the number choosing to remain on the job has increased and represent the fastest-growing segment in the workforce (195). By 2020, an estimated one fourth of American workers (41 million) will be 55 or older, up from 19 percent in 2010 (196). This has resulted in an increasing number of older night and rotating shift workers, estimated at nearly 3 million older night and shift workers in 2001 [US Department of Labor, 2002].

While the same factors that negatively impact the health, safety, and productivity of younger shift workers also affect older workers, field and laboratory studies indicate that working at night impacts older workers to a greater extent (57, 171). A survey study of over 3,000 French workers found that older workers (42-62 years of age) were more likely to report difficulty falling asleep, staying asleep, and returning to sleep after awakening than young workers (172), and this sleep difficulty was reflected in the progressive increase in reported hypnotic (sleep-promoting medication) use with age in those same workers. In addition to experiencing difficulty sleeping during the daytime following night shifts, night workers also report high levels of sleepiness during their work

hours (45, 173). A study of Finnish workers found that up to 37% of older (45-60 years) night and shift workers reported difficulty staying awake during work hours often or very often, and those same night and shift workers reported higher levels of insomnia than their day worker colleagues (173). In a field study of Swedish train engineers whose sleep was recorded at home after both day and night shifts, the workers slept 3 hours less during the day (following night shifts) than they did when sleeping at night, and the older (50-59 years) workers had more wakefulness during sleep, more awakenings, and more sleep stage changes than the young workers, indicating that their sleep was less consolidated and more disrupted (144). A review of the shiftwork-aging literature reported that while older shift workers have fewer occupational injuries, they have more serious injuries (57) including permanent disabilities and fatalities [(145) and reviewed in (57)].

Many of the problems associated with shift work intolerance in older workers are related to circadian challenges. The timing of the circadian rhythms of body temperature, melatonin, and cortisol have been shown to move earlier, or advance, in older adults compared with young adults (176). In addition, there are numerous reports that the amplitude of circadian rhythms, including those of body temperature, melatonin, and other hormones, are reduced in older adults (176). In addition to changes in the timing of physiologic rhythms controlled by the circadian timing system, there are also reports that the relative timing of rhythms with respect to sleep-wake timing change with age (154, 161, 175, 176). This latter finding means that older adults are not only sleeping at different clock times than young adults, they are also sleeping at different biological times. Laboratory studies have shown that the sleep of older adults is much more sensitive to the circadian time at which it occurs than is the sleep of young adults (161), thus making older adults more vulnerable to shift-work disorder (172-174). Studies in which the circadian time of sleep is systematically manipulated have revealed that there may be an age-related reduction in the amplitude of the circadian rhythm of sleep-wake propensity that not only makes it more difficult to sleep at an adverse circadian time but makes consolidation of an extended nighttime sleep episode more difficult (161, 162).

Although older shift workers represent a sizeable and at-risk group, most previous shift work studies were developed using young shift workers. Our studies will extend our laboratory work on sleep-wake regulation in older adults by evaluating the efficacy of a sleep-homeostatic countermeasure for older shift workers.

The impaired ability to remain sleep during the biological daytime**.** Many of the problems associated with shift work intolerance are related to difficulty sleeping during the day (35). Humans typically sleep in one consolidated bout during the nighttime hours and remain awake for an extended period throughout the day. This ability to remain awake or asleep for an extended time is due to a complex interaction of the circadian timing system and the homeostatic sleep-wake system (7). The circadian process contributes a rhythmic variation in sleep-wake propensity and promotes wakefulness during the day and sleep at night. The sleep-wake homeostatic process describes a build-up of sleep pressure with time awake, and that sleep pressure is then dissipated during sleep (7, 8). Sleep is longest and least disturbed when it occurs at the biological times when the circadian system is promoting sleep (36, 37).

In contrast, the night worker must remain awake during the night, a time when the biological clock is promoting sleep, and then attempt to sleep in the day when the biological clock is promoting wakefulness. While most individuals can initiate sleep in the day if they have remained awake all night, the ability to sustain that sleep over 7-9 h is difficult, due to the influence of the biological drive for wakefulness in the daytime. Studies have shown that shift workers obtain substantially less sleep on work days compared to their days off (38) and obtain less sleep on work days than day workers (13, 39-42). In addition to the shortened duration of sleep, the sleep of night workers is disrupted and less consolidated (43). Approximately a third of night workers report long-term insomnia and excessive sleepiness (44). The impaired ability to remain asleep that occurs with healthy aging is even further impaired when the sleep occurs during the biological daytime, as it must for older night workers.

Can shift workers adapt to working at night? A mismatch between the timing of a night worker's biological clock and their desired work and sleep times can result in short, poor quality daytime sleep and difficulty staying awake at work during the night. One might expect that after working several consecutive night shifts the circadian system of the worker would adapt to the new work-rest schedule. This is what occurs with jet-lag: after a few days of misalignment between local time in the new time zone and 'body' time (set to the home time zone), the body will gradually adapt to the new local time by exposure to the light-dark cycle in the new time zone. In general, such circadian adaptation does not occur in night workers, even after days or weeks of night work, resulting in continued sleep difficulties and compounded alertness problems. Unlike the jet lag situation where the light

exposure pattern in the new time zone eventually resets the body clock to match local time, with night work there is a conflict between the light exposure pattern and the night-wake, day-sleep schedule that prevents adaptation (48, 50, 165). In particular, exposure to outdoor light during the morning commute home and adopting a night-sleep, day-active schedule on weekends are thought to be the primary factors that contribute to lack of adaptation. Findings from laboratory studies support this. Two studies of young adults conducted in our laboratory found that even after 4-6 consecutive night shifts, the circadian rhythms of participants were not completely adapted to the night work schedule (166, 167), and other research groups studying actual and simulated shift workers have reported similar findings (48, 168-170). In some specialized environments, though, night workers may adapt to their schedule. A field study of oil workers on a North Sea platform found that workers on 12-h night shifts were able to adapt, based on their reported sleepiness at work during the night (165). However, in that environment, the workers received little natural daylight exposure to conflict with their day-sleep, night-work schedules, they worked a series of continuous shifts without days off, and they were restricted to the oil platform on their off-duty hours.

Older employees, with more shift work experience, do not cope better than workers new to shift work (45). A study in which the sleep of experienced shift workers was recorded at a 2-year interval found that EEG parameters during daytime sleep were essentially unchanged, documenting that longer-term exposure to a night work schedule did not lead to better sleep quality (46). Among 300 steel workers, those younger than 45 with longer shift work experience were better able to cope with the demands of shift work, but in workers older than 45 there was a reverse trend, with increasing age associated with more difficulty coping (45). A questionnaire study of retired shift workers found that when they were asked to reflect back on their health and fatigue during the time they had been working shifts, their health and overall fatigue had been worse than they had realized at the time (177). The authors concluded that many studies of shift workers therefore may underestimate the problems associated with shift work, because workers who have been doing shift work for a long time no longer have a normal base for comparison. In general, adaptation does not occur in night workers, even after days or weeks of night work. A meta-analysis in permanent night workers found that fewer than 3% showed complete circadian adaptation, and fewer than 25% partially adjusted sufficiently to receive some benefit (47). Because the circadian system does not adapt to the night work-day rest schedule, the worker has continued sleep difficulties and compounded alertness problems (48). The primary factors that contribute to this lack of adaptation are thought to be exposure to outdoor light during the morning commute home and adopting a night-sleep, day-active schedule on days off (48-50).

Decline in alertness, performance, and safety in shift work. In addition to experiencing difficulty sleeping during the daytime following night shifts, night workers also report high levels of sleepiness during their work hours (45, 51, 52). Studies from a variety of occupations consistently show that night workers make more mistakes (53), have more occupational accidents and injuries (13, 54, 55), and are at greater risk for a fatal occupational injury (56, 57) than day workers. This is due to a mismatch between the behavior of the worker and their underlying physiology: attempting to remain awake when their biological clock is promoting sleep, combined with chronic sleep loss.

Role of the circadian timing system and prior wake duration on alertness and performance. A proper alignment between the timing of the biological clock and the timing of sleep is critical for optimal waking performance. Human cognitive functioning is modulated by a variety of factors, including the sleep-wake homeostat (elapsed time awake) and the phase (timing) of the circadian pacemaker. The sleep-wake homeostat contributes an approximately linear decline to cognitive function, while the endogenous circadian rhythm contributes a sinusoidal variation over the course of the 24-h day (58-61). Under normal conditions in well-rested individuals, these two systems interact to produce a stable level of cognitive functioning across a ~16h wake episode: in the evening the wake-dependent deterioration of alertness is opposed by the circadian timing system promoting alertness.

Unfortunately for night workers, many studies have shown that the decline in performance and alertness resulting from prior wakefulness is actually amplified during the biological night (60, 61). Therefore, night workers must not only attempt to remain awake at an adverse biological time, but the negative impact of that wakefulness is greater. To make matters worse, after attempting to remain awake all night, the typical night worker starts sleep in the morning following work (62, 63), a biological time at which it is difficult to sustain sleep for an extended duration. Not surprisingly, night workers typically report shorter sleep than their day worker counterparts (40, 42), resulting in even greater levels of sleepiness on the following night.

Furthermore, unlike the day worker who wakes on average 2-3h before reporting to work, night workers are typically awake longer than day workers before reporting to work, resulting in the end of their work occurring after more than 12h awake, reducing even further their ability to remain alert throughout the night shift. We have shown in our laboratory study that evening sleep (before the simulated night shift) combined with enhanced lighting during the latter half of the night shift can improve performance and alertness back to day shift levels (4), while morning sleep still produced significantly impaired performance, likely due to the greater duration of time awake (5).

Effects of chronic insufficient sleep on alertness and performance**.** Prolonged experience living with restricted sleep does not make someone more resistant to the performance deficits of sleep deprivation (47, 64). In all such studies, chronic insufficient sleep increases subjective sleepiness and impairs performance on the psychomotor vigilance test (PVT) (64-68), and the impairment of vigilance appears to be cumulative. In most individuals, subjective sleepiness is increased only for the first few days, while objective sleepiness and performance continue to worsen the longer the insufficient sleep continues. This disconnect between subjective and objective sleepiness means that individuals are unaware of their level of impairment due to insufficient sleep.

Effects of chronic insufficient sleep on physiological stress. A recent study demonstrated that chronic insufficient sleep, even with "catch up" sleep on days off, also has negative physiological effects. Both immune and stress markers (including cortisol), as well as subjective sleepiness and stress were evaluated over 3 weeks of 5h weekday sleep and 8h weekend sleep. The investigators found disruption of the normal interaction between the immune system and the HPA axis, but no changes in subjective stress or sleepiness (69). This disconnect between subjective and objective stress means that individuals are unaware of the negative physiological impacts of insufficient sleep.

Strategies to improve adaptation to night shifts. Strategies based on sleep and circadian principles most often manipulate sleep timing and/or light exposure (80, 169, 170, 178-183). Due to organizational limitations, light exposure interventions are not always feasible in occupational settings. Sleep strategies have an advantage in that they are independent of the occupational setting and are under the control of the individual worker. The afternoon-evening sleep schedule we will test in our study maintains the temporal relationship between sleep and work as seen in day workers: work begins within just an hour or two after awakening, minimizing the build-up of homeostatic sleep pressure prior to the beginning of night shifts. This intervention has the added benefit of allowing greater opportunity to be exposed to natural light between the end of work and the start of sleep, thus indirectly manipulating light exposure which should reinforce alignment with the internal circadian clock.

While our laboratory studies demonstrate that this sleep strategy works to improve sleep duration and quality, alertness, performance, and cortisol levels, whether it will work in the field remains unknown. When transferring such a countermeasure from the laboratory to the operational environment, it is important to evaluate not only the efficacy, but also the feasibility and acceptability from night workers' points of view. Understanding these aspects will be crucial for dissemination and implementation of this strategy in the real world, and the proposed studies will rigorously evaluate all these aspects of the sleep strategy.

In addition to testing the sleep strategy in the field, it is important to understand the variety of demographic and other factors that affect shift workers' ability and inability to adopt the sleep strategy. Sleep duration may be shortened by insufficient time between shifts and the competing demands of other aspects of personal life. In one study, night shift nurses reported an inability to balance their need to sleep with their daily life demands and social relationships, which resulted in sacrificing their sleep (70). Because many workers in their 50's and 60's no longer have young children at home, their reduction in domestic demands may make it easier for them to adapt new sleep strategies to cope better with night work. There are individual differences related to sleep strategies and adaptability to shift work, i.e. individuals adapt differently to shift work (71). In addition to exogenous factors (such as work hours, work load, domestic duties)(72-74), recent studies have identified endogenous factors that contribute to individual differences in adaptation to shift work (75-79). These include trait vulnerability to sleep loss and circadian rhythm disruption, chronotype, genetic factors, and flexibility of sleep timing (natural ability to sleep and work at unusual times of day). Therefore, it is important to evaluate the endogenous and exogenous factors that may influence individual's ability to adapt to shift work before wide dissemination and implementation of such sleep strategy in the real world.

The scientific premise for the proposed study is strong. Night and rotating shift work leads to a mismatch between

the timing of circadian rhythms and the timing of the work/sleep schedule, resulting in sleepiness during nighttime work, with greater risk for performance errors and accidents. In addition, daytime sleep is disrupted and shortened, which exacerbates the performance problems on the subsequent night shifts. When sleep occurs in the morning after work, the extended duration of waking prior to the next night shift further exacerbates performance and alertness problems. Chronic night and rotating shift work also increase the risk for many health problems such as cardiovascular disease, metabolic disorders, and certain cancers. Problems with night shift adaption are greater in older workers, and there are an estimated 3 million such older night workers in the US. Our prior laboratory study found that afternoon-evening sleep resulted in longer and better sleep, higher simulated night shift performance and alertness, and lower cortisol levels as compared to *ad lib* sleep in older adults (see below). Whether this strategy will work for actual older night workers needs to be field tested. Conducting occupational research is a key step in translating laboratory research into real-world practices. While the sleep schedule countermeasure has the promising potential to provide safety, productivity, and quality-of-life benefits to older individuals as they work night shifts, the feasibility and acceptability of this countermeasure in real-life, as we propose to evaluate in this study, is crucial to understand as well.

I.b. Preliminary Studies

In our preliminary laboratory study we evaluated a sleep and circadian based treatment to adapt older adults to a night shift schedule (4), as we found to be successful in a previous laboratory study in young adults (80). The combined treatment of scheduled afternoon-evening sleep and enhanced lighting increased sleep duration and partially aligned circadian phase with sleep and work timing, resulting in improved night shift alertness and performance in older adults. As a follow-up study (6) to the studies described above (4, 80), we also carried out a study to examine the contribution of scheduled afternoon-evening sleep by itself, to test whether the timing of the sleep episode or the duration of time-in-bed could improve sleep duration when working nights. Compared to the control group, the fixed 8h afternoon-evening sleep group had significantly longer time-in-bed and total sleep time, and greater mean sleep efficiency following night shifts. These preliminary data indicate that older adults can comply with an 8h scheduled afternoon-evening sleep episode after night shifts, and in doing so, they are able to obtain more sleep. We also found that the plasma cortisol levels were significantly reduced in the combined treatment group and evening sleep group compared with the control group, suggesting that the sleep intervention groups were **less stressed** than the ad lib sleep group. If this is the case, it may indicate that the sleep intervention can have implications for improved health outcomes. To summarize, preliminary laboratory studies have shown that an afternoon-evening sleep intervention before night work improves sleep duration, night shift sleepiness and vigilance, and cortisol independent of circadian phase shifts**.**

I.c. Rationale & potential benefits

Our proposal seeks to test a sleep timing intervention, proven to be successful in the laboratory, in a Field Trial in older night-shift workers, to improve their sleep thereby improving their alertness and performance on the night shift. This intervention is based on a strong scientific premise and the fundamental principles of circadian physiology and homeostatic sleep-wake regulation, and how these two sleep regulatory processes interact in humans. Studies by our group (58-61, 100, 101) and others (76, 102-110) have demonstrated that the length of prior wakefulness has a significant impact on alertness and performance, and that this impact is exacerbated during the biological night. The sleep schedule of our intervention was selected to minimize the duration (and therefore impact) of prior wakefulness before beginning the night shift.

The proposed translational field study is innovative, as relatively few controlled intervention field trials for sleep problems in older shift workers have been conducted (111). Previous interventions to improve performance or safety of shift workers in general (regardless of age) mostly focused on changing the shift schedule, controlling light exposure, and/or using behavioral, lifestyle or pharmacological aides to shift circadian timing, facilitate sleep, or enhance alertness (112). In real-life, work schedule changes or light exposure interventions are not always feasible from an organizational perspective, and therefore we focus on the individual older night worker and propose to test a sleep strategy as a home-based countermeasure to enhance sleep, thereby improving alertness and performance on night shifts. Furthermore, the proposed intervention does not lead to significant shifts of the circadian timing system, and thus is preferable for workers whose shift schedule rotates frequently and for those who adopt a night-sleep/day-wake schedule on days off. An intervention strategy that improves sleep, vigilance, and subjective sleepiness without shifting the underlying timing of the circadian system is thus preferable for night shift workers.

Prior interventions that focused on sleep used timed naps as a countermeasure to the alertness and

performance decrements associated with night work (113-116). Here, the innovative intervention we will field test is a long, consolidated sleep episode, typical of what most adult humans do when working days or evenings. We have found in our laboratory studies that older participants can adopt this schedule and when they do so, they have longer and less disrupted sleep. While our laboratory data suggest this approach is promising, we recognize that it may not be practical for all older shift workers. Therefore, in addition to testing the efficacy of the scheduled sleep intervention, we will investigate the acceptability of such a sleep strategy from older night workers' point of view through Focus Group discussions. In addition, it is important to evaluate the feasibility (barriers and facilitators) for adopting such a sleep strategy from the older night workers' perspective, which we will do through a Shift Worker Survey given to a large and diverse group of older shift workers. Together, the information from the proposed rigorous studies will be useful in developing specific recommendations for older night workers in general, and will allow us to maximize our ability to disseminate information about the intervention to a targeted audience and implement this in the real world of night workers.

II. SPECIFIC AIMS

Working at night or on a rotating schedule can lead to misalignment between the timing of the biological clock and the work/sleep schedule, resulting in sleepiness, inattention, and impaired performance during the night shift and poor quality, shortened sleep during the day. These adverse effects of night work are worse in older workers compared to young workers, mainly due to their decreased ability to sleep during the day.

Most interventions focus on strategies to shift the timing of the biological clock (light therapy, light-blocking glasses during morning commutes, melatonin), and/or acutely increase alertness during work (enhanced lighting, caffeine or other stimulants, exercise). What is overlooked with these strategies is that night workers typically sleep in the morning, shortly after completing work. In doing so, they typically arise 8 or more hours prior to their next night shift, unlike most day workers who arise only an hour or two prior to beginning day work. Thus, night shift workers are not only attempting to work when their biological clock is promoting sleep, they begin work with a much greater sleep pressure due to prolonged wakefulness. Furthermore, they need to sleep when their biological clock is promoting wakefulness, causing sleep difficulties.

In simulated laboratory-based night work studies in older subjects carried out in the previously, we tested a strategy focused on sleep timing: scheduling the major sleep episode to begin in the early afternoon and extend into the evening, such that the worker awakens 1-2 h prior to their next night shift. We found that older participants were able to spend 8 h in bed in the afternoon-evening, they had significantly longer and less disrupted sleep than participants who slept *ad lib*, their on-shift alertness and performance during night shifts was increased, and they showed reduced levels of the stress hormone cortisol.

Whether this sleep timing intervention works in actual older night workers, as opposed to participants in lab studies, remains to be tested. We therefore will field test, in older night workers (age 50-65 years), the sleep timing intervention that we have developed in laboratory studies; we will examine the **efficacy** of this intervention in improving sleep duration and quality, as well as performance and alertness across 3 night shifts. We will also conduct a survey study among a large group of older shift workers to examine the factors that influence their ability to adopt such a schedule. Finally, we will have participants from both studies take part in focus groups where the **feasibility** and **acceptability** of the afternoon-evening sleep intervention will be examined. To evaluate the efficacy, feasibility, and acceptability of an 8-h afternoon-evening sleep schedule in the field/real world, our study will address the following Aims:

1. Test the hypothesis that older night shift workers scheduled to an 8-h afternoon-evening sleep episode will sleep longer and have fewer sleep interruptions than those randomized to an *ad lib* sleep/control condition.
2. Test the hypothesis that older night shift workers scheduled to an 8-h afternoon-evening sleep episode will show greater subjective and objective alertness on night shifts compared to those randomized to an *ad lib* sleep/control condition.

2a. Conduct exploratory analyses to examine whether older night workers scheduled to an 8-h afternoon-evening sleep episode show reduced physiological stress (cortisol), reduced subjective stress and fatigue, and improved mood and quality of life compared to those randomized to an ad lib sleep/control condition.

2b. Conduct exploratory analyses to compare an 8-h afternoon-evening sleep schedule to an 8-h free sleep

schedule in older night shift workers for impacts on sleep duration and quality, alertness and performance, stress, subjective fatigue, mood, and quality of life, to evaluate the effect of the timing of sleep regardless of duration.
3. Test how individual factors influence the ability to adopt an 8-h sleep episode while working night shifts. In a shift worker survey, we will determine the percentage of night shift workers who report their ability to adopt an 8-h sleep schedule (regardless of timing), those who report being able to adopt an 8-h afternoon-evening sleep episode, and we will then examine how demographic (e.g., sex) and other factors (e.g., occupation) impact this adoptability in order to evaluate the *feasibility* of an 8-h afternoon-evening sleep schedule for older night workers. In debriefing focus groups, we will examine participants' perceptions of their ability to adhere to an 8-h afternoon-evening sleep schedule (*acceptability*), barriers to following such a schedule, and their willingness to adopt such a schedule outside the study for future prolonged implementation.

III. SUBJECT SELECTION

III.a. Field Trial inclusion/exclusion criteria*:* Potential participants will be employed older health care workers (aged 50-65 years) who work a minimum of 4 night shifts (8-h) per month. The participants must have the willingness and ability to comply with the work and sleep intervention schedule, including: a) must report an ability to work three successive 8-h night shifts during two weeks; and b) must report an ability to spend 8 consecutive hours in bed attempting to sleep prior to the final two successive night shifts in the second study week. This means that individuals with a second job, child or elder care responsibilities, classes, or other non-optional activities that would interfere with their ability to remain in bed attempting to sleep if randomized to an 8-h sleep group will be excluded. In addition, potential participants regularly taking prescription or over-the-counter medication(s) known to affect sleep [e.g., hypnotics] or alertness [e.g., antihistamines] will be excluded. In order that the participants are able to comply with the timing and duration of the 8-h afternoon-evening sleep intervention, they must have a typical commute time between their home and place of work of less than one hour.

III.b. Field Trial Source of subjects and recruitment methods: We will recruit up to 200 health care workers who regularly work 8-h night shifts to take part in the Field Trial in order to have up to 100 health care workers complete the entire Field Trial. We will recruit health care workers from hospitals as well as through the Massachusetts Nursing Association. We will use flyers, advertisements on websites and in newsletters, emails, internet posts, and postings on the MNA Facebook page. We will also use snowball sampling where participants may notify their coworkers.

We have selected health care workers as the occupational group in which to field test the sleep timing intervention because: (1) a large proportion of the health care workers population works night shifts; (2) night shift work has a negative impact on the safety and health of both health care workers and their patients; (3) more than half of US nurses are over age 50; (4) our prior experience has shown that health care workers are willing and valuable participants in research related to sleep and shift work; and (5) there is a large health care workers population in the surrounding community.

III.a.b. Shift Worker Survey inclusion/exclusion criteria and recruitment methods: We aim to enroll up to 1,000 participants in the Shift Worker Survey. We will use internet and newspaper advertisements and flyers to recruit employed individuals (20 or more hours per week) whose work includes overnight shifts [six or more consecutive hours between 10 pm and 7 am], with a minimum criterion of at least 4 night shifts a month. Both women and men aged 18 and older will be studied. We will recruit among all occupations, and include participants from throughout New England to take part in this web-based survey. Additionally, we will post notices in local hospitals and advertise on the Massachusetts Nursing Association Facebook page.

III.a.b. Focus Group inclusion/exclusion criteria and recruitment methods: We aim to enroll up to 60 individuals in virtual Focus Groups.

All health care workers in the Field Trial who are randomized to the 8-h afternoon/evening or the 8-h free sleep intervention groups will be invited to attend a virtual Focus Group discussion by secure videoconferencing

(via HIPAA-compliant & MGB-approved Zoom) so that we can gain in-depth information on the acceptability of the fixed 8-h sleep schedule from participants' perspective. We plan to enroll up to 30 individuals who take part in the Field Trial in Focus Groups. Virtual Focus groups will include health care workers who comply with the 8-h sleep intervention as well as those who do not comply or who withdraw from the intervention so that we may learn about facilitators and barriers for compliance with the fixed 8-h sleep schedule.

In addition to the health care workers who took part in the Field Trial, we will invite night shift workers who complete the Shift Worker Survey but indicate their inability to comply with a fixed 8-h sleep schedule to attend a remote Focus Group discussion. We expect that approximately half of the Shift Work Survey participants will indicate that they cannot comply with a fixed 8-h sleep schedule. We will email randomly chosen individuals from this cohort, inviting them to participate, until we achieve an enrollment of 30 individuals to gain in-depth information on challenges and barriers to adhering to an 8-h sleep schedule, as well as their opinions on what resources and facilitators at individual, interpersonal, and organizational levels could be used to promote use of such sleep strategies.

IV. SUBJECT ENROLLMENT

IV.a. Methods of enrollment, procedures randomization. After completing the Shift Worker Survey, participants will be asked if they are a health care worker. If they are, they will be informed that they can complete an additional Health Care Worker Questionnaire and following that they may be eligible for the Field Study. They will have the option of completing the Health Care Worker Questionnaire at the same time or logging on later to complete it. Individuals who complete both surveys and who meet the inclusion/exclusion criteria will be informed within the survey that they are eligible for the Field Study. If they indicate that they want more information, they will be provided with a description of the Field Study and the Consent Form, as well as contact information for our study recruiter. We will also ask them to provide us their contact information if they wish to be contacted about the study. The potential Field Study participant will be scheduled for a consent visit during which a member of the study team will review the study, equipment, and requirements. At the end of that visit the dates for the study will be decided, based on the participant's schedule of night shifts. As described below, randomization into one of three groups will be done during the study Intervention Week.

IV.b. Procedures for obtaining informed consent Participants in the Field Trial will provide written informed consent in person or remotely by secured video conference or phone. When remotely, subjects will sign the informed consent form using RedCAP informed consent module prior to enrolling in the study. One of the co-investigators or the Post-Doctoral Research Fellow will explain details of the study procedures including the randomization process, study duration, baseline and intervention block data collection process, and then obtain consent from each participant before the study begins.

Informed consent for the Shift Worker Survey was waived by the Partners Human Research Committee in their initial review. Participants will be given a statement about the research based on the Partners Human Research Committee "Informed Consent in Online Research" guidelines in the beginning of the REDCap survey.

Procedures related to the virtual Focus Group will be included in the Consent Form for the Field Study for participants who completed the Field Trial. Night shift workers who only completed the Shift Worker Survey and indicated their inability to comply with a fixed 8-h sleep schedule will receive a consent form only for the Focus Group.

IV.c. treatment assignment and randomization.

The field trial will use a randomized control trial design, where each participant will be randomized individually. Due to the anticipated small number of male participants, we will randomize by gender to ensure equal representation in each of the three intervention groups. The participants will be randomized to one of the 3 groups (at least 25 participants/group): A) control group (ad lib sleep); B) 8-h afternoon-evening sleep timing group; C) 8-h free sleep group.

V. STUDY PROCEDURES

Protocol overview. We will investigate the effectiveness, feasibility, and acceptability of an 8-h sleep intervention in older night workers in an operational environment. The overall goal of the **Field Trial** is to minimize sleep deficiency and negative outcomes resulting from that, including sleepiness and performance impairments during night shift work. The **Shift Worker Survey** is designed to understand some of the demographic and operational factors that enable or inhibit the ability of individual shift workers to adopt this intervention. The **Focus Groups** are designed to glean in-depth information from older shift workers who indicate that they are unable or unwilling to adopt an 8-h sleep timing intervention. Understanding these factors will assist in refining and targeting the intervention to those individuals who will be most likely to benefit from the intervention sleep timing strategy.

Field Trial. The experimental protocol of the field trail is divided into two blocks (see Protocol Schema), the Baseline block and the Intervention block, where participants will work at least 3 night shifts in a row within each block. For at least one week prior to the baseline block health care workers will work their usual shift schedule (i.e., no vacation/scheduled days off).

The Baseline Block consists of a week during which participants work at least three consecutive 8-h night shifts. The three night shifts are preceded by a day off. All participants will be instructed to continue their normal routines, maintaining their habitual self-selected sleep-wake schedule. Sleep-wake and light exposure patterns will be recorded continuously using actigraphy, and a daily sleep e-diary will be filled in within the first hour after awakening from each main sleep episode. Performance (attention), alertness and mood will be rated three times on each night shift (just prior to their shift, on a break during their shift, and immediately after their shift). The purpose of this Baseline segment is to obtain measures of sleep duration and consolidation (to address Aim 1), alertness, mood, and performance (to address Aims 2, 2a and 2b) when working night shifts following their typical sleep routine. Immediately after the third night shift, an optional saliva sample will be taken to measure stress level (cortisol) and each participant will complete a baseline questionnaire covering questions related to fatigue, recovery, stress, and quality of life (to address Aim 2a). Participants will be given a specially configured mini iPad on which the E-diary, the performance test, alertness and mood rates, and fatigue, recovery, stress and quality of life questionnaire are programmed on.

The Intervention Block is similar to the Baseline Block, consisting of at least three consecutive 8-h night shifts, with the participants wearing an activity monitor, maintaining a daily sleep e-diary, and rating alertness, mood and attention three times per night shift using a mini iPad provided by the investigators. At the end of the first night shift, the participant will be told about their randomization group. In the control group (Group A), participants will not be given any instructions about the timing or duration of their sleep, but will be instructed to follow their usual night shift sleep routine. In the 8-h afternoon-evening sleep intervention group (Group B), participants will be instructed to go to bed between 13:00 and 14:00 (depending on their individual commute time) and to remain in bed attempting to sleep for 8 hours (until 21:00-22:00) before the next two night shifts. In the 8-h free sleep group (Group C), participants will be instructed to remain in bed for 8 continuous hours before the next two night shifts, but will not be given any instruction regarding which 8 hours they should sleep. Immediately following the last night shift, the participant will has the option to take a saliva sample to measure their stress level (cortisol), and they will complete a follow-up questionnaire where their fatigue, recovery, stress, and quality of life will be reassessed to investigate any exploratory short-term changes resulting from the intervention schedule. After completion of the two blocks, the participant will send back the activity monitor and iPad in a prepaid secured return package by mail or an investigator will arrange to meet with the participant to retrieve the activity monitor, iPad, and cortisol sample. Within 3 months after completion of the study blocks the participant will be invited to take part in a virtual Focus Group by secure videoconferencing (via HIPAA-compliant & MGB-approved Zoom).

Field Trial outcome variables

Sleep measurements including Total Sleep Time, Fragmentation Index, Wake After Sleep Onset, and Subjective Sleep Quality will be measured during the Baseline block and during the Intervention block Sleep episodes in all participants will take place at home during off-shift times and will be recorded using wrist actigraphy and daily sleep e-diaries (which will be completed in the first hour after waking from the main sleep episode).

Subjective Alertness During both the Baseline and Intervention blocks, participants will complete an alertness task on the iPad three times per night shift: Once just before the night shift, once during their shift break, and once immediately following the night shift. The alertness assessment will consist of the Karolinska Sleepiness Scale (KSS) and a non-numeric bipolar (sleepy-alert) Visual Analog Scale (VAS).

Sustained Attention During both the Baseline and the Intervention Blocks, participants will complete a psychomotor vigilance task on the iPad three times per night shift: Once just before the night shift, once during their shift break, and once immediately following the night shift. The psychomotor vigilance task (PVT) is a 5-minute validated test of visual reaction time (RT) in which the participant is asked to maintain the fastest possible RTs to a simple visual stimulus.

Subjective Mood During both the Baseline and the Intervention Blocks, participants will complete a mood questionnaire on the Ipad three times per night shift: Once just before the night shift, once during their shift break, and once immediately following the night shift. Non-numeric bipolar (happy-sad) Visual Analogue Scales (VAS) will be used to assess subjective well-being and mood.

Fatigue, Inter-Shift Recovery, Subjective Stress and Quality of life will be assessed by questionnaire on the iPad immediately after the third night shift in the Baseline block and after the third night shift in the Intervention block (151, 152, 124).

Physiological Stress will be assessed by collecting a saliva sample immediately after the third night shift in the Baseline block and after the third night shift in the Intervention block to measure cortisol in subjects who live in the greater Boston area. Cortisol will be assayed in the Brigham Research Assay Core.

General Methods for Shift Worker Survey. To examine factors related to individual differences in the ability to adopt the sleep strategy, we will use a web-based survey consisting of ~70 questions developed and administered using REDCap. REDCap is a free, secure, web-based application for building and managing online surveys and databases. The complete questionnaire will take approximately 20-30 minutes to complete.

To understand the individual differences in sleep patterns adopted by shift workers, both in timing and in duration, and their ability to adjust sleep schedules, we will include demographic factors, circadian factors, questions of sleep in general and specific to night shifts, use of countermeasures, questions about non-work and work activities, and quality of life. We have selected factors which have been reported to be associated with inter-individual differences in adaptability to shift work and/or vulnerability to sleep loss, and therefore may contribute to the ability to adopt different sleep schedules in order to understand the barriers to achieving an 8-h sleep episode when working nights (72-76, 78, 117-119).

We will use questionnaires widely used in sleep research to assess morningness/circadian preference (120), flexibility of sleeping habits, vigor [i.e., the ability to overcome drowsiness (121, 122)], screening for shift work disorder (123), and qualtiy of life (124). We will also examine environmental factors (e.g. barriers/facilitators) that may be related to the feasibility of an individual being able to adopt an 8-h sleep episode, such as work hours, second jobs, work schedule (rotation and speed of rotation), type of occupation, commute time, and home sleep environment (noise, light).

For individuals who may not have access to a computer, we will provide a paper copy of the questionnaire to fill out and return.

General Methods for Focus Groups. The goal of the virtual focus groups is to gain information on the feasibility and acceptability of the fixed 8-h sleep schedule from the participants' perspective. We will seek to learn more information about the current sleep strategies they use on a regular basis, and both the facilitating and challenging aspects of the fixed-sleep countermeasure (e.g., individual, intrapersonal and organizational barriers to implementation of fixed 8-h sleep, recommended modifications to the fixed 8-h sleep schedule that would make it more user-friendly while maintaining scientific validity). Each of the virtual focus groups will consist of 4-6 individuals to stimulate thoughtful and dynamic discussion without leaving participants out. Separate focus groups for participants from the Field Trial and the Shift Worker Survey will be carried out to address the different issues of the two groups. Focus group scripts will be created and used to guide and moderate the discussions. Each focus group will last 60-90 minutes, and will be digitally-recorded and professionally transcribed. The

remote focus groups will be facilitated through secure videoconferencing (via HIPAA-compliant & MGB-approved Zoom) by Dr. Zhang (Co-Investigator), who is a nursing professor with extensive experience in facilitating focus groups of nursing staff (83-85, 158).

VI. BIOSTATISTICAL ANALYSIS

VI. a) Data variables, b) Study endpoints, c) Statistical methods

Analysis of objective sleep duration and quality, and subjective sleep quality in the Field Trial. Sleep data will be calculated in all participants from both blocks (Baseline vs. Intervention) using actigraphy. Duration of sleep (total sleep time, TST), number of awakenings, fragmentation index (FI) during the major sleep episode and subjective sleep quality from the e-diaries may be used as outcome measures to address Aim 1. After descriptive analyses, we may use linear and generalized linear mixed models to analyze main and interaction effects for factors condition (randomization group: ad lib sleep, 8-h afternoon-evening sleep, or 8-h free sleep) and shift (Baseline: B-Night 2, B-Night 3; Intervention: I-Night 2, I-Night 3). To account for inter-individual differences, we may incorporate into our statistical model a random intercept statement allowing for means to vary between participants. We will compare within subjects (shift) and between groups (condition).

Field Trial analysis of performance and subjective alertness (Aim 2). Each of the tests will be administered using an iPad app. Initial processing of tests will be calculated automatically (e.g., exact time of administration, scoring of alertness scales; mean and median reaction time; number of lapses, shortest (fastest 10%) and longest (slowest 10%) reaction times on PVT]. Following the descriptive measures, analyses of RT and lapses and subjective alertness data may be performed using linear and generalized linear mixed models to analyze main and interaction effects for factors condition (randomization group, as above) and shift (as above) with participant as a random effect.

Exploratory analysis of subjective stress and fatigue, recovery, mood, quality of life, and physiological stress in the Field Trial (Aim 2a). Scores of acute subjective fatigue, inter-shift recovery, subjective stress, and quality of life will be calculated from the questionnaire administered at the end of Baseline and the end of Intervention. Mood will be assessed from visual analog scales administered three times per shift on nights 2 and 3 in the Baseline and Intervention blocks. Physiological stress will be assessed by analyzing cortisol levels in the optional saliva samples collected immediately after the third night shift in the Baseline and Intervention blocks. We will compare data from the Baseline to data from the Intervention for the three groups using linear and generalized linear mixed model analysis with factors condition (randomization group) and block (Baseline or Intervention) and incorporating a random intercept statement allowing for means to vary between participants.

Field Trial exploratory analysis of scheduled 8-h afternoon-evening sleep vs. 8-h free sleep (Aim 2b). We may compare results described above (sleep, performance and alertness, subjective stress, fatigue, recovery, mood, quality of life, and physiological stress) between the two scheduled sleep groups to determine whether the timing of an 8-h sleep episode has a significant impact on any of the outcomes. For this analysis, data from the 8-h free sleep group will first be examined for the time of day at which it occurred. Those participants who self-selected an afternoon-evening sleep episode will be classified with the 8-h afternoon-evening sleep group. We will carry out the analyses described above using linear mixed model analysis with factors condition (randomization group) and block (Baseline or Intervention) or night, incorporating a random intercept statement allowing for means to vary between participants.

Analysis of the Shift Worker Survey. (Specific Aim 3). The initial scoring of standard questionnaires and processing of data will be calculated automatically in REDCap. Descriptive analyses for all factors of interest will be calculated, as well as the reported ability to adhere to an 8-h free sleep/ 8-h afternoon-evening sleep schedule. To understand what individual differences contribute to shift workers' sleep patterns and ability to comply with an 8-h sleep schedule, we may conduct inferential statistics including bivariate and multivariate analyses on factors related to their ability to adopt the 8-h free sleep/8-h afternoon-evening sleep. Bivariate analyses (ANOVA and cross-tabulation) will be used to interpret the correlation between each factor and the outcome (ability to adhere to 8-h afternoon-evening sleep; ability to adhere to 8-h free sleep; inability to adhere to 8-h sleep).

Multivariable analysis (logistic regression analysis) and multivariate analysis (for example, structure equation modeling) may be used to test potential predictors of the outcome.

Focus Group analysis (Specific Aim 3). Data from this aim will be qualitative in nature. Focus group transcripts will be imported into NVivo11 or similar software for analysis. We will reorganize, reduce, and categorize the qualitative data based on common themes, and use content analysis to identify recurrent themes (157, 159). The code and quotes will be discussed by the research team to resolve discrepancies through interpretive discussions, consensus building, and refinement of code definitions as needed. The data will be independently coded by the investigators and compared to achieve consistency and conformability. The research team may send the focus group analysis results to participants to verify the codes and confirm the interpretive validity (159).

VI.d. Power analysis

For the Field Trial we plan to enroll up to 100 participants, with at least 25 participants per group for three groups including A) control group (ad lib sleep); B) 8-h afternoon-evening sleep timing group; C) 8-h free sleep group. For the Shift Worker Survey, we aim to enroll up to 1,000 participants. In the Focus Groups we plan to enroll up to 60 participants, ~30 participants who complete the Field Trial and ~30 participants who complete the Shift Worker Survey.

Our sample size calculations for the Field Trial are based on the preliminary data from our laboratory study (6) comparing the ad lib sleep group with the 8-h scheduled afternoon-evening sleep group, and using total sleep time (TST) and Fragmentation Index (FI) after 2 nights as the outcome measures of interest. For TST, 25 participants per group will give us the power to detect a difference of as few as 78 minutes between groups (α=0.05, β=0.9, assumed σ=84.4 min), a difference much smaller than that observed in our preliminary study (221.4 ± 84.4 vs. 403 ± 58.5 min). For FI, 25 participants per group will give us the power to detect a difference of 37 in the fragmentation index (assumed α=0.05, β=0.9, assumed σ=39.9), a smaller difference than that observed in our preliminary study (73.3 ± 39.6 vs. 35.2 ± 20.03).

Our sample size calculations for the Shift Worker Survey are based on multivariable analysis. With at least 500 participants, we will have 90% power to detect an odds ratio of 1.51 for any continuous factor with one standard deviation difference, or 2.10 for any binary factor (yes vs. no) with a two-sized z-test at alpha=0.05 level, assuming the variance explained by other factors in the same model is 0.2.

Our sample size of 30 participants for the Focus Groups were selected to solicit qualitative information from approximately half of the Field Trial participants who were randomized to a sleep intervention, and from approximately 10% of the Shift Worker Survey participants who report being unable to adopt an 8-h sleep schedule when working night shifts.

VII. RISKS AND DISCOMFORTS

VII.a. complication of procedures none

VII. b. Drug side effects and toxicities none

VII. c. Device complications/malfunctions. The battery-operated activity monitoring device and the mini iPad are electrically safe and present minimal risk.

COMMON

VII. d. Psychosocial (non-medical) risks. Participants randomized into the 8-h scheduled sleep groups will be required to remain in bed attempting to sleep for 8 h following two successive night shifts. While they may feel frustrated with this if they cannot sleep, there is no long-term risk associated with this, and we anticipate that most participants will actually receive more sleep than they would typically get with ad lib sleep.

-It is possible that the participants randomized to the 8-h afternoon-evening sleep group will feel sleepy from the time they get off the night shift until the early afternoon scheduled bed time, which they may find frustrating. Due to the likelihood that participants randomized to the 8-h afternoon-evening sleep group will be awake for 24 or more hours after the first night shift in the Intervention week, they will be advised to use extra caution if they take part in any safety-sensitive activities that would put them at risk for an accident. All participants will be informed that they should use whatever countermeasures they routinely use to keep them safe (e.g., caffeine) and that they may withdraw from the study at any point that they feel the study conditions are too difficult

-There are minimal risks to participating in the Shift Worker Survey. Participants may experience some psychological discomfort responding to personal questions such as those about stress. Participants may choose not to answer any questions that they are not comfortable with. REDCap allows us to segregate identifiable information from the survey responses, and only the PI and one other study team member will have access to the identifiable information. There will be a code to link between the identifiable information and the survey data.

-There are minimal risks to participating in the virtual Focus Groups by secure videoconference. There is a small risk of feeling loss of confidentiality during focus group discussions. Participants will be asked to use an “alias” instead of their real name during focus group discussions. Audio recordings of focus group discussions will be destroyed upon completion of the study. No identifying information will be on the focus group transcript.

VII. e. Radiation risks none

VIII. POTENTIAL BENEFITS

VIII. a. Potential Benefits to participating individuals
Taking part in any of the proposed study activities are unlikely to benefit any individual participant.

Participants who take part in the Field Trial will be compensated as follows: $10.00 per day for wearing the wrist activity-light recorder and maintaining the daily sleep e-Diary for the Baseline week and the Intervention week (total up to $140.00); $15.00 per day for completing the thrice-daily (before start of shift, during mid-shift break, at end of shift) subjective alertness and mood assessments and the performance assessment on the three successive night shifts in the Baseline week and the Intervention week (total $90.00); $10.00 per day for collecting the optional saliva sample after the third night shift in the Baseline week and the Intervention week (total
$20); $50.00 per day for maintaining the assigned scheduled sleep episode following the two night shifts during the Intervention week (total $100.00); and a $150.00 study completion bonus for completing all the study procedures (not including the optional saliva samples). If all procedures are completed, a participant will receive up to $480 ($500 if both optional saliva samples are collected) by check.

Participants who complete the Shift Worker Survey and Health Care Worker screening survey for the Field Trial will receive a $15 gift card. These will be provided through an online vendor such as Tangocard.com. Upon completion of the questionnaire, the participant will be asked to choose the gift card they would like, and an electronic gift card will be sent to their email address, a method we have used successfully for other studies.

Participants who take part in a virtual Focus Group will receive $75.00 by check for taking part in the focus group.

VIII. b. Potential Benefits to society
Night and rotating shift work can result in shortened and disrupted sleeping during the daytime, leading to sleepiness on the following night shift and an increased risk of accidents both at work and while commuting home. While the sleep intervention we will test may appear so simplistic as to not merit testing, the facts are that most shift workers do not devote sufficient time for sleep. A rigorous field study testing whether remaining in bed attempting to sleep will result in longer and higher quality sleep could serve as important evidence that a

behavioural strategy could improve sleep quality for many shift workers. Evidence supportive of this strategy will also provide guidance for individual shift workers, employee health and wellness programs, and fatigue management plans. A practical nonpharmacologic treatment for improving the sleep of older night workers holds great potential in providing a specific and sustainable countermeasure that would enhance alertness, mood, safety, and general well-being and may result in longer-term health impacts.

IX. MONITORING AND QUALITY ASSURANCE

IX. a. independent monitoring of source data.

Data quality will be monitored by the PI and the study personnel. All data from the Field Trial (questionnaires, activity recordings, sleep diaries, performance, mood and alertness assessments and saliva samples) will be collected and recorded using a study code rather than individually-identifying information. The Shift Work Survey will be collected using REDCap. Personal identifying information will be deleted from the Focus Group transcripts before analyses.

IX. b. Safety monitoring.

The PI, with assistance from the study personnel, will be responsible for safety monitoring for participants in the Field Trial and the Focus Groups.

IX. c. Outcomes monitoring.

Ongoing study progress, including enrollment in each aspect (Field Trial, Shift Work Survey, Focus Groups), data quality/integrity, completeness, and safety issues, will be reviewed weekly by the study team. During these meetings the Principal Investigator and other members of the research team are present.

In the Field Trial, a study team member will be available to the participants at all times via telephone or text/email to answer questions, and to take reports of any accidents or injuries. The eDiary entries and performance tests will be monitored checked daily by a study team member to ensure the participant is completing them and to follow-up in cases where there are missing or potentially incorrect entries.

IX. d. Procedures for identifying, reviewing, and reporting adverse events and unanticipated problems to the IRB and NIH. The PI will be ultimately responsible for reviewing and reporting all adverse events and unanticipated problems to the IRB and the NIH as required. She will review the data and meet with the study team weekly to discuss any problems (anticipated or unanticipated) with the research study, as well as any adverse events. In addition to adverse events, the PI and study staff will regularly review study progress to identify unanticipated problems, and report these to the IRB and NIH as required.

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