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MELATONIN INTERVENTION FOR NEUROCOGNITIVE DEFICITS IN THE ST. JUDE LIFETIME COHORT

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Protocol Summary

Protocol MNEMONIC and Title: MIND - Melatonin Intervention for Neurocognitive Deficits in the St. Jude Lifetime Cohort
Principal Investigator: Tara Brinkman, Ph.D.
IND Holder: N/A
Brief Overview: This study is a randomized double-blind placebo controlled trial of time release melatonin for adult survivors of childhood cancer who demonstrate impaired neurocognitive functioning and/or delayed sleep onset latency. The sample will be stratified to generate three mutually exclusive cohorts. Cohort 1: neurocognitive impairment without delayed sleep onset latency; Cohort 2: neurocognitive impairment with delayed sleep onset latency; Cohort 3: delayed sleep onset without neurocognitive impairment. Within each group, participants will be randomly allocated to either melatonin or placebo for a 6-month trial. Participants will take 3mg of time release melatonin or placebo orally each night prior to initiating sleep onset. Baseline and follow-up evaluations will be completed to determine the effects of melatonin on specific neurocognitive processes and sleep parameters.
Intervention: Survivors who previously underwent neurocognitive evaluation as part of the SJLIFE study, as well as survivors who are eligible for future neurocognitive evaluation through SJLIFE will be recruited. Initial eligibility will be determined via review of previous neurocognitive assessment data and telephone screening. Interested survivors meeting the pre-screen criteria will complete standardized sleep measures at their baseline visit. Baseline neurocognitive assessments will occur as part of the SJLIFE study. Neurocognitive assessments will be administered again at 6 months. Subjective and objective sleep measures including actigraphy will be assessed at baseline, 3 months, and 6 months. Correlative psychosocial measures of health-related quality of life and psychological distress will be completed at baseline as part of the SJLIFE study and following 6 months on treatment. Serum melatonin will be collected at baseline and 6 month follow-up.
Brief Outline of Treatment Plan: Participants will take a fixed 3 mg oral dose of time release melatonin or placebo once per day 1-2 hours before initiating sleep onset for a 6 month period. Participants will be called biweekly throughout the intervention to monitor treatment adherence, side effects, and adverse events.

Protocol MNEMONIC and Title: MIND - Melatonin Intervention for Neurocognitive Deficits in the St. Jude Lifetime Cohort

Primary Objective:

To examine the efficacy of melatonin treatment on neurocognitive functioning in adult survivors of childhood cancer.

Responsible Investigator: Tara Brinkman and Kevin Krull

Secondary Objectives:

To evaluate the efficacy of melatonin treatment on delayed sleep onset latency in long-term childhood cancer survivors.

To investigate whether improvement in sleep onset latency due to melatonin treatment is associated with neurocognitive improvement in long-term childhood cancer survivors.

Responsible Investigators: Belinda Mandrell and Tara Brinkman

Exploratory Objective:

To explore the association between endogenous melatonin levels and improvement in sleep onset latency.

To explore the association between sleep quality and health-related quality of life and distress.

Responsible Investigators: Kevin Krull and Tara Brinkman

Estimated date for completion of data collection: [redacted]

Protocol MNEMONIC and Title: MIND - Melatonin Intervention for Neurocognitive Deficits in the St. Jude Lifetime Cohort

Hypotheses/Estimates:

- **Hypothesis 1:** Long-term survivors of childhood cancer with documented baseline neurocognitive deficits (Cohorts 1 and 2) in attention, memory, and/or executive functioning, randomized to the melatonin treatment arm, will demonstrate improved neurocognitive performance following six months of treatment compared to those randomized to placebo.

- **Hypothesis 2:** Long-term survivors of childhood cancer with delayed sleep onset latency at baseline (Cohorts 2 and 3), randomized to the melatonin treatment arm, will demonstrate improved sleep onset latency following 6 months of treatment compared to the placebo groups.

- **Hypothesis 3:** Improvement in sleep onset latency with melatonin treatment will result in improved neurocognitive performance in long-term childhood cancer survivors who have both comorbid sleep onset latency and neurocognitive deficits at baseline (Cohort 2).

- **Exploratory Hypothesis 1:** Improvement in sleep onset latency following melatonin treatment will be independent of baseline endogenous melatonin levels.

- **Exploratory Hypothesis 2:** Improved sleep quality will be associated with decreased psychological distress and enhanced quality of life.

Criteria for Evaluation:

Three domains of neurocognition will be examined as primary study outcomes 1) attention, 2) memory, and 3) executive functioning. Sleep parameters to be assessed include objective and subjective measures. Correlative psychosocial measures of health-related quality of life and psychological distress will be evaluated. Treatment adherence and side effects will be monitored.

Study Design: Prospective randomized, double-blind, placebo-controlled study

Protocol MNEMONIC and Title: MIND - Melatonin Intervention for Neurocognitive Deficits in the St. Jude Lifetime Cohort

Study Population:
Inclusion Criteria:

1) Previously treated at SJCRH and a participant in St Jude Life.
2) Is 10 or more years from diagnosis
3) FSIQ score > 79
4) ≥ 18 years of age
5) Able to speak and understand the English language
6) **Cohort 1 participant:**
   a. Has neurocognitive impairment defined as performance on at least one measure of attention, memory, and/or executive functioning ≤ 10th percentile.
   b. Is absent of delayed sleep onset latency defined as an inability to fall asleep within 30 minutes < once a week during the past month.
   Cohort 2 participant:
   a. Has neurocognitive impairment defined as performance on at least one measure of attention, memory, and/or executive functioning ≤ 10th percentile.
   b. Has delayed sleep onset latency defined as self-report of an inability to fall asleep within 30 minutes ≥ once a week during the past month.
   Cohort 3 participant:
   a. Is absent of neurocognitive impairment defined as performance >10th percentile on all six measures of attention, memory, and executive functioning.
   b. Has delayed sleep onset latency defined as self-report of an inability to fall asleep within 30 minutes ≥ once a week during the past month.

Study Population:
Exclusion Criteria:

1) Known allergy to melatonin or any ingredients of the study product or placebo
2) Currently taking Melatonin
3) Known sleep apnea
4) Known medically treated sleep disorder (e.g. restless leg syndrome)
5) Known diabetes mellitus – insulin treated
6) Uncontrolled seizure disorder in the past 12 months
7) Reported current illicit drug or alcohol abuse or dependence
8) Reported current major psychiatric illness (i.e. schizophrenia, bipolar disorder)
9) Current treatment with:
   a. Benzodiazepines or other CNS depressants
   b. Fluvoxamine
   c. Anticoagulants (e.g. Coumadin)
   d. Immunosuppressant or corticosteroids
   e. Nifedipine
10) Employed in a position that requires night work (i.e. 10pm to 6am)
11) Females who are pregnant or lactating/nursing
12) History of neurologic event unrelated to cancer or its treatment
13) Sensory impairment (vision, hearing) that prohibits completion of neurocognitive examination

Protocol MNEMONIC and Title: MIND - Melatonin Intervention for Neurocognitive Deficits in the St. Jude Lifetime Cohort

Sample Size: Targeted enrollment 987 and expected evaluable 395 research participants

- Cohort 1 = 131
- Cohort 2 = 131
- Cohort 3 = 133

Randomization:

Participants in each cohort will be randomized 1:1 to receive time release melatonin 3 mg or placebo daily for 6 months.

Data Analyses:

Primary Aim: The primary aim of this study is to determine the difference between changes in neurocognitive functioning from baseline to the 6 month follow-up in adult survivors of childhood cancer who are randomized to receive melatonin compared to those randomized to receive placebo. We hypothesize that survivors randomized to the melatonin group will have a greater improvement in neurocognitive functioning than those randomized to the placebo group. We have identified six neurocognitive domains in which the marginal impairment rate is >15% in the SJLIFE cohort. Normalized Z-scores (M=0, SD=1) are available for each domain and survivors who score at or below the 10th percentile will be classified as impaired on that specific domain. The lowest test-retest correlation coefficient for the neurocognitive measures has been observed to be 0.60. Then, assuming the difference in the Z-scores to be normally distributed but assuming (conservatively) the variance to be 1, we need outcome data for 131 survivors between the melatonin and placebo arms in Cohorts 1 and Group 2 to detect an improvement of .66 units (in standardized scale, considered to be clinically meaningful) with 80% power with type I error control α=0.05/6=0.0083 to adjust for multiplicity of 6 tests for each subscale. The analysis for Aim 1 will be completed using a two-sample t-test. Assuming an attrition and loss to follow up of 25%, we plan to enroll 987 survivors (Cohort 1=328; Cohort 2=328; Cohort 3=331).

Protocol MNEMONIC and Title: MIND - Melatonin Intervention for Neurocognitive Deficits in the St. Jude Lifetime Cohort
Secondary Aim 1: The primary interest of secondary aim one is to assess the efficacy of melatonin on delayed sleep onset latency in adult survivors of childhood cancer, which will be evaluated in Cohorts 2 and 3. We hypothesize that survivors randomized to the melatonin treatment arm will evidence a greater reduction in sleep onset latency compared to survivors randomized to placebo. The CCSS cohort mean and SD for sleep onset latency among participants with delayed sleep onset latency (i.e. SOL $\geq$ 30 minutes) is 46.2 and 27.7 minutes, respectively. The test-retest correlation for sleep onset latency from the PSQI has been observed to be in the range of 0.70. Following the justification set forth in the Primary Aim, and assuming the SD to be 27.7, we will need outcome data for 131 survivors in Cohort 2 and 133 in Cohort 3 between the melatonin and placebo arms for these Cohorts to see an improvement of 15 minutes in sleep onset latency with 80% power with type I error control α=0.05. The analysis for Aim 2 will be completed using a two-sample t-test. **Secondary Aim 2:** The aim of this objective is to investigate the association between sleep onset latency and specific neurocognitive processes [Cohort 2]. We hypothesize that decreased sleep onset latency following 6 months of melatonin treatment will be associated with improved neurocognitive performance. We will need outcome data for 131 survivors in Cohort 2 [66 randomized to melatonin, 65 randomized to placebo] so that we will have 80% power to detect a correlation of at least 0.25 between reduced sleep onset latency and improved neurocognitive performance with type 1 error control α=0.05. **Exploratory Aims:** To explore the association between endogenous melatonin levels and improvement in sleep onset latency. To explore the association between sleep quality and psychological distress and health related quality of life.
Primary Anticipated Completion Date: [redacted]
Anticipated Study Completion Date: [redacted]
Timeframe for Primary Outcome Measure: Approximately 6 months
Data Management: Data will be managed by the Neuropsychology Research Team and the Clinical and Survey Research Center in the Department of Epidemiology and Cancer Control and the Department of Nursing Research. Statistical analysis will be provided by the Biostatistics Department at St. Jude Children's Research Hospital.
Human Subjects: The risks to the subjects will be related to the side effects of melatonin which may include drowsiness, headache, additional sedation if taken with other sedating drugs, an allergic reaction, confusion, and rarely seizures, and tachycardia. Adverse events are rare, occurring at similar frequency to those with placebo in published research in adults with primary insomnia. Participants will be informed of these side effects during the informed consent discussion. Adverse events will be monitored and reported and treated accordingly.

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1.0 OBJECTIVES

Over 80% of children diagnosed with a pediatric malignancy become long-term survivors. Many of these survivors received neurotoxic cancer treatments that may interfere with the development of specific neurocognitive abilities, deficits that are lasting and appear to be progressive over time. Furthermore, survivors are at increased risk for sleep problems and fatigue that may exacerbate neurocognitive impairment. Few interventions have been offered to remediate neurocognitive deficits in adult survivors of childhood cancer and even less attention has been directed at improving sleep difficulties. Melatonin is an endogenously produced hormone with known sleep-promoting effects and recent evidence demonstrates that melatonin can improve neurocognitive functioning in adults at-risk for cognitive decline. As such, treatment with exogenous melatonin may provide an ideal method by which to intervene on these two distinct, yet interrelated late effects of childhood cancer, neurocognitive and sleep dysfunction.

This application proposes a randomized double-blind placebo controlled trial of time release melatonin for long-term adult survivors of childhood cancer who demonstrate impaired neurocognitive functioning and/or delayed sleep onset latency. The sample will be stratified to generate three mutually exclusive groups [Cohort 1: neurocognitive impairment without delayed sleep onset latency; Cohort 2: neurocognitive impairment with delayed sleep onset latency; Cohort 3: delayed sleep onset without neurocognitive impairment]. Within each cohort, participants will be randomly allocated to either melatonin or placebo treatment for a 6 month trial. Baseline and follow-up evaluations will be completed to determine the efficacy of melatonin treatment on specific neurocognitive processes and sleep parameters.

1.1 Primary Objective

1.1.1 To examine the efficacy of melatonin treatment on neurocognitive functioning in adult survivors of childhood cancer.

Hypothesis 1

Long-term survivors of childhood cancer with documented baseline neurocognitive deficits (Cohorts 1 and 2) in attention, memory, and/or executive functioning, randomized to the melatonin treatment arm, will demonstrate improved neurocognitive performance following six months of treatment compared to those randomized to placebo.

1.2 Secondary Objectives

1.2.1 To evaluate the efficacy of melatonin treatment on delayed sleep onset latency in long-term childhood cancer survivors.

Hypothesis 2

Long-term survivors of childhood cancer with delayed sleep onset latency at baseline (Cohorts 2 and 3), randomized to the melatonin treatment arm, will demonstrate improved sleep onset latency following six (6) months of treatment compared to the placebo groups.

1.2.2 To investigate whether improvement in sleep onset latency due to melatonin treatment is associated with neurocognitive improvement in long-term childhood cancer survivors.

Hypothesis 3

Improvement in sleep onset latency with melatonin treatment will result in improved neurocognitive performance in long-term childhood cancer survivors who have both comorbid delayed sleep onset latency and neurocognitive deficits at baseline (Cohort 2).

1.3 Exploratory Objectives

1.3.1 To explore the association between endogenous melatonin levels and improvement in sleep onset latency.

Exploratory Hypothesis 1

Improvement in sleep onset latency following melatonin treatment will be independent of baseline endogenous melatonin levels.

1.3.2 To explore the association between sleep quality and health-related quality of life and psychological distress.

Exploratory Hypothesis 2

Improved sleep quality will be associated with decreased psychological distress and enhanced quality of life.

2.0 BACKGROUND AND RATIONALE

2.1 Background

Neurocognitive impairment is one of the most common late effects experienced by long-term survivors of childhood cancer. Prevalence estimates indicate that 20% to 80% of long-term survivors experience neurocognitive dysfunction, varying due to sample characteristics, cognitive processes studied, measures employed, and definition of impairment utilized.[1-4] Treatment with cranial radiation therapy is a well-established risk factor for neurocognitive late effects,[1,5] although

antimetabolite chemotherapy (i.e. methotrexate) and corticosteroids also have been implicated.[6-8] Neurocognitive impairment demonstrated by survivors includes deficits in attention,[9,10] memory,[5,10] processing speed,[11] and executive function.[12] These deficits often increase with time after treatment exposure[5] and have the potential to impact multiple areas of adult functioning including educational attainment,[2] employment,[2] health behaviors,[13] quality of life[14] and social functioning.[2,15] Given the potential pervasive impact of neurocognitive impairment on daily life, interventions directed at mitigating neurocognitive dysfunction are imperative.

Survivors of childhood cancer are also frequently reported to experience fatigue and sleep disturbance. For example, survivors of childhood leukemia report significant fatigue many years after completion of treatment,[16,17] and survivors of Hodgkin lymphoma (HL) report more fatigue than their siblings and population-based controls.[18-20] Sleep disturbance and fatigue are also found to disrupt neurocognitive function, specifically in the domains of processing speed, attention and memory.[21,22] Among adults diagnosed with chronic fatigue, slowed processing speed, impaired working memory, and poor memory and learning of new information has been reported.[23,24] The presence of significant fatigue has been associated with poor neuropsychological functioning in adults with acute medical conditions.[25-28] Importantly, differential sensitivity of poor sleep quality and fatigue on neurocognitive functions within cohorts at risk for neurologic impairment may exist. Sleep is essential for neural recovery following brain injury[29] and sleep deprivation among individuals with traumatic brain injury exacerbates the degree of neurocognitive impairment.[30] Thus, the impact of fatigue and sleep loss on neurocognitive performance may be more salient in survivors who are at risk for brain injury following neurotoxic cancer therapy (i.e. cranial radiation, antimetabolite chemotherapy).

Little is known of the association between sleep problems and neurocognitive outcomes among survivors of childhood cancer. A recent report from the Childhood Cancer Survivor Study indicated that 49.5% of all survivors demonstrated significant problems with fatigue, vitality, daytime sleepiness, or sleep quality.[31] Poor sleep quality and fatigue were independently associated with a 3 to 4 fold increased prevalence of impaired attention and processing speed, as well as problems with working memory and memory retrieval. These findings suggest that neurocognitive functions in adult survivors of childhood cancer are particularly vulnerable to the effects of fatigue and sleep problems.

While significant effort has been directed at characterizing neurocognitive impairment in long-term survivors of childhood cancer, limited research has focused on interventions to ameliorate these well-established late effects. In fact, few systematic efforts have targeted remediation of neurocognitive deficits following cancer treatment, and such endeavors have been restricted to children and adolescents fewer than 10 years from

their initial diagnosis. Nonpharmacological interventions, such as cognitive training/remediation programs have yielded small, short-term improvements on select neurocognitive processes; however, such programs are extremely time-intensive, costly, and suffer from high dropout rates. Additionally, there are no published reports of interventions for sleep or fatigue problems in adult survivors of childhood cancer, despite the documented adverse effects of such problems on neurocognitive processes and other functional outcomes. There is a clear need to test interventions with the potential to impact the interrelated processes of neurocognitive functioning and sleep, and for approaches that are feasible, of low burden to the participant and have a strong potential for efficacy.

This study proposes a highly disseminable intervention for improving neurocognitive function and sleep difficulties in adult survivors of childhood cancer. Melatonin (N-acetyl-5-methoxytryptamine) is the primary hormone released nocturnally by the pineal gland with demonstrated safety and efficacy in animal models and clinical trials. Its powerful anti-oxidant and anti-inflammatory properties have been implicated in enhanced neurocognitive functions and melatonin has well known effects on sleep. Melatonin has not yet been studied in adult survivors of childhood cancer. Investigating the effectiveness of melatonin is important as it will provide a safe, non-intensive intervention approach with the strong potential to improve neurocognitive and sleep dysfunction in an at-risk population.

2.2 Rationale

Research on childhood cancer survivors has reached a critical juncture where a shift from characterization of late effects to remediation of these deficits is necessary. Toward this aim, this study proposes the novel use of melatonin to intervene on two distinct, yet highly interrelated late effects of childhood cancer. This extends the traditional conceptualization of melatonin as a hormone that promotes sleep onset to one with the additive benefit of enhancing neurocognition.

2.2.1 Melatonin and neurocognition: Cognitive dysfunction is one of the most common late effects following treatment with CNS directed therapies for childhood cancer. While the pathogenesis of radiation-induced cognitive decline is not well understood, recent evidence suggests that disruption of hippocampal neurogenesis may be involved.[32] Additionally, oxidative stress has been identified as a potential biological mechanism for CNS injury and predictor of neurocognitive dysfunction in survivors of childhood leukemia.[33,34] Importantly, Manda et al[35] reported that treatment with melatonin protected against cranial irradiation induced inhibition of hippocampal neurogenesis by reducing oxidative stress in mice. Specifically, melatonin was found to reduce neuronal damage by scavenging free radicals and activating antioxidative enzymes[36] and

mounting evidence from animal models indicates that melatonin enhances neurocognitive function through its strong anti-inflammatory and anti-oxidant properties. Taken together, these lines of research provide a framework for understanding the potential mechanisms by which melatonin may address the delayed neurocognitive effects of cranial radiation therapy in childhood cancer survivors.

Patterns of neurocognitive impairment in adult survivors of childhood cancer may reflect premature aging,[37] thus normal aging may provide a model for understanding the potential effects of melatonin on cognition. As endogenous melatonin production decreases with age, it is suggested that antioxidant defenses are reduced, leading to neuronal death and the behavioral correlates of aging (i.e., memory decline).[38] Although clinical trials in humans have begun to explore this hypothesis, much of the supporting evidence is founded in animal research. For example, Esteban and colleagues[38] determined that aged rats chronically treated with melatonin performed better on working memory and motor coordination tasks compared to untreated aged rats. This functional improvement was attributed to the direct impact of melatonin on the synthesis and uptake of serotonin, dopamine and norepinephrine, neurotransmitters implicated in a myriad of cognitive functions.

Given the association of decreasing melatonin secretion with aging, increasing melatonin levels through exogenous administration has been identified as a possible preventative treatment for the cognitive decline seen in advanced aging, as well as Alzheimer's disease (AD) and other disorders associated with progressive cognitive impairment.[39] Importantly, children who experience traumatic brain injury are at increased risk for early onset of dementia.[40,41] One possible mechanism is the over-expression of amyloid precursor protein which may result in the formation of neuritic plaques, a pathognomonic finding of AD.[40] Similar to traumatic brain injury, children who received neurotoxic cancer treatments have sustained diffuse CNS injury, and therefore may be vulnerable to similar cognitive decline and dementia.

Animal models of several diseases lend further support to the neuroprotective characteristic of melatonin, especially in age related neurodegenerative disorders where oxidative burden is a major culprit. Familial AD is a specific animal model that has been used to elucidate the antioxidant properties of melatonin and its impact on functional outcomes. The AD animal model is particularly important as melatonin levels measured in cerebrospinal fluid have been found to be reduced in pre-clinical AD human cohorts. This implicates low melatonin levels as a potential risk factor for AD and supports the relationship between melatonin and cognition. Olcese and colleagues[42] reported that chronic melatonin treatment protected AD mice from expected cognitive decline. In fact, AD mice treated with melatonin were cognitively indistinguishable from normal mice. The protection against cognitive decline was attributed

to three mechanisms including: 1) reduced presence of human protein B-amyloid in the brain, 2) decreased inflammatory cytokines within the brain, and 3) reduced oxidative stress within the brain.

Beneficial effects of exogenous melatonin on neurocognition have also been reported in open-label studies of human adults with and without neurodegenerative disease. Specifically, melatonin has been proposed as a potential therapeutic agent for mild cognitive impairment (MCI).[43] In patients with MCI, treatment with 3-9mg of melatonin for 9-24 months was associated with improved performance on measures of attention, verbal learning, executive functioning, and mental status.[43,44] Similarly, 6mg of melatonin treatment over 10 days was associated with improved verbal memory in elderly patients with MCI.[39] Melatonin treatment also has been reported to attenuate progression of cognitive decline in AD.[45] Cognitive enhancement has been reported in healthy older adults as melatonin treatment has been associated with improved verbal recall following interference.[46] While these studies provide important preliminary data on the potential benefit of melatonin on specific neurocognitive processes, there is a need for larger, randomized controlled trials. Furthermore, while growing evidence indicates that melatonin may enhance aspects of cognitive function in elderly and early dementia patients, additional studies are needed to examine the potential impact of melatonin on cognition in other populations who may be at risk for cognitive impairment. Childhood cancer survivors who received neurotoxic treatments are at heightened risk for long-term cognitive dysfunction and thus comprise a population for whom interventions targeted toward ameliorating cognitive deficits is warranted.

2.2.2 Melatonin and sleep: Melatonin also has demonstrated efficacy in stimulating sleep onset in animals and humans. Nonhuman primates are considered an ideal model, as the suprachiasmatic nucleus (SCN) exerts similar regulatory properties on the circadian system in humans and monkeys.[47] Zhdanova et al[48] evaluated the effects of melatonin on several sleep properties in three macaque species using actigraphy. Across species, melatonin significantly reduced sleep onset latency, resulting in extended total sleep time.[48] Sleep offset time was not altered, suggesting that although melatonin promoted sleep, it did not cause a circadian phase shift.[47] Such findings provide additional evidence of the sleep promoting effect of melatonin and support the use of sleep onset latency as an outcome variable.

Exogenous melatonin also has been demonstrated to promote sleep onset latency in healthy adult humans,[49] as well as adults with insomnia combined with dementia,[50] and mild cognitive impairment.[43] A meta-analysis on the efficacy of exogenous melatonin for primary insomnia reported reduced sleep onset latency of -7.2 minutes (95% CI -12.0 to -2.4).[51] Efficacy has further been demonstrated in individuals with intellectual disabilities and autism spectrum disorder.[52] Recent meta-

analyses of the effects of exogenous melatonin on sleep parameters reported decreased sleep latency of 23 and 34 minutes in individuals with delayed sleep phase disorder[53] and intellectual disabilities,[54] respectively. In a large randomized double blind placebo controlled trial, Wade and colleagues demonstrated significantly reduced sleep onset latency in adults 18-80 years of age over a six month trial, with a treatment effect of -6.8 minutes (95% CI -10.9 to -2.6).[55] Furthermore, their data demonstrated that treatment efficacy was independent of endogenous melatonin levels with no signs of tolerance or reduction in benefit during the 6-month treatment period.

2.2.3 A safe intervention: Importantly, animal and human studies have shown melatonin toxicity to be remarkably low with no serious negative side effects even at high doses. In a randomized, double-blind placebo controlled trial, Seabra et al[56] investigated the toxicology of 10mg of melatonin administered to healthy adults for 28 days. The most common side effects included somnolence and headache, with intensity of symptoms most often reported as light or moderate. No difference in frequency or intensity of side effects was observed between melatonin and placebo. Similarly, in the largest double-blind randomized placebo controlled trial of sustained release melatonin, Wade et al[55] reported no difference in the type or frequency of adverse events between melatonin and placebo treatment groups during a 6 month trial with sample size of 722. Twelve percent of patients treated with 2mg of sustained release melatonin reported a drug related adverse event compared to 17% of patients treated with placebo.[55] Two recent meta-analyses of melatonin treatment reported the most common adverse events were headache, dizziness, nausea, and drowsiness, with no significant difference between melatonin and placebo.[51,57] The safety and efficacy of 4 to 6mg of sustained release melatonin over a treatment period of 6 to 72 months was demonstrated in children with neurodevelopmental disorders.[58]

Most recently, Lemoine et al[59] reported results from a 6-12 month open-label study of the efficacy, safety, and withdrawal of 2mg prolonged release melatonin in 244 adults, ages 20-80, who previously participated in a double-blind placebo-controlled trial (i.e. Wade et al[55]). The efficacy of prolonged release melatonin was maintained during the open-label period and no differences were reported in safety parameters between patients who were treated for 6 compared to 12 months. Additionally, few rebound and withdrawal symptoms were reported following discontinuation of melatonin treatment.

2.2.4 Novel contributions of the current proposal: There are nearly 300,000 survivors of childhood cancer in the United States, many of whom received neurotoxic treatment that interfered with the development of neurocognitive abilities. Moreover, these treatment effects appear to be progressive over time, thus increasing risk for early cognitive decline among adult survivors of childhood cancer. Neurocognitive difficulties

appear to be exacerbated in the context of poor sleep and fatigue, with increased vulnerability observed in childhood cancer survivors. There are few interventions for neurocognitive deficits and those available are limited by problems of feasibility (i.e. high dropout rates, limited disseminability), resource requirements (i.e. time intensive, supervision, cost), and questionable efficacy. This protocol is innovative as it proposes an intervention that is cost-effective, safe, and of low burden to the cancer survivor. The intervention is portable and uses a single treatment modality to target two distinct, highly prevalent late effects in childhood cancer survivors, neurocognitive and sleep dysfunction.

2.3 PRELIMINARY STUDIES

Data from ongoing and completed studies by SJCRH researchers further elucidate the association between sleep, fatigue and neurocognitive impairment in adult survivors of childhood cancer. These data underscore the need for interventions that have the potential to ameliorate both neurocognitive and sleep dysfunction in adult survivors of childhood cancer.

2.3.1 Sleep, Fatigue and Neurocognition: Research efforts led by Dr. Krull using the Childhood Cancer Survivor Study (CCSS) cohort provide strong evidence for the associations between sleep quality, fatigue and neurocognitive impairment. Participants included 1,426 adult survivors of childhood cancer who were treated before 18 years of age and survived >5 years from their original diagnosis. Among those with fatigue, 53% reported impaired attention and processing speed compared to 15% of those without fatigue. Similarly, 40% of survivors with poor sleep quality had impaired attention and processing speed compared to 16% of those without poor sleep. Multivariable logistic regression models controlling for sex, age, cranial radiation therapy, psychological distress, and household income revealed increased risk for impaired attention and processing speed for survivors with reduced vitality (RR=1.75, 95% CI, 1.33-2.30), fatigue (RR=1.34, 95% CI, 1.13-1.59), daytime sleepiness (RR=1.68, 95% CI, 1.55-1.83), and poor sleep quality (RR=1.23; 95% CI, 1.01-1.49). Reduced vitality (RR=2.01, 95% CI, 1.42-2.86), daytime sleepiness (RR=2.05, 95% CI, 1.63-2.58), and poor sleep quality (RR=1.45, 95% CI, 1.19-1.76) significantly predicted impaired memory. Importantly, the risk for neurocognitive impairment associated with fatigue and sleep disturbance was roughly equivalent to that seen with high-dose cranial radiation.

2.3.2 Actigraphy and Neurocognition: Drs. Mandrell and Krull recently completed a pilot study examining sleep parameters in relation to specific neurocognitive processes in 35 adult survivors of Hodgkin's disease using the St. Jude Lifetime Cohort (SJLIFE) at SJCRH. Participants were on average 15 years old at the time of their cancer diagnosis (range, 5 to 18 years) and 42 years of age at the time of study completion (range, 34 to 55 years). Survivors completed the Epworth

Sleepiness Scale, Pittsburgh Sleep Quality Index and five days of actigraphy. Seventeen (49%) participants reported impaired daytime sleepiness while 21 (60%) reported poor sleep quality. Actigraphy data are presented in Table A.

Table A: Sleep parameters in childhood cancer survivors

	Mean	Range
Sleep onset latency (mins)	44	0-133
Wake after sleep onset (mins)	66	0-168
Sleep efficiency (%)	82	10-100
Wake episodes (number)	10	n/a

Increased daytime sleepiness was associated with reduced short-term memory (p=0.017), learning (p=0.017), and aspects of executive functioning including shifting attention (p=0.026) and emotional control (p=0.021). Poorer sleep quality was associated with reduced working memory (p=0.024) and fatigue (p=0.005). Longer sleep onset latency was associated with reduced long-term memory (p=0.02) and organizational difficulties (p=0.01). Greater number of minutes awake after sleep onset was associated with decreased learning (p=0.02) and reduced working memory (p=0.02). Lastly, total number of minutes slept and greater sleep efficiency were positively associated with better rates of learning new information (p=0.005; p=0.017, respectively). These data demonstrate the associations between performance-based neurocognitive measures and objectively measured sleep parameters.

3.0 RESEARCH PARTICIPANT ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

According to institutional and NIH policy, the study will accession research participants regardless of gender and ethnic background. Institutional experience confirms broad representation in this regard.

3.1 Inclusion Criteria

3.1.1 A St Jude Life participant who was previously treated at SJCRH.

3.1.2 Participant is 10 or more years from diagnosis.

3.1.3. Participant is $\geq$ 18 years of age.

3.1.4 Participant is able to speak and understand the English language.

3.1.5 Participant has a FSIQ score >79.

3.1.6 **Cohort 1 participant:**

a. Has neurocognitive impairment defined as performance on at least one measure of attention, memory, and/or executive functioning ≤10th percentile.

b. Is absent of delayed sleep onset latency defined as an inability to fall asleep within 30 minutes < once a week during the past month.

Cohort 2 participant:

a. Has neurocognitive impairment defined as performance on at least one measure of attention, memory, and/ or executive functioning ≤10th percentile.

b. Has delayed sleep onset latency defined as self-report of an inability to fall asleep within 30 minutes ≥ once a week during the past month.

Cohort 3 participant:

a. Is absent of neurocognitive impairment defined as performance >10th percentile on all six measures of attention, memory, and executive functioning.

b. Has delayed sleep onset latency defined as self-report of an inability to fall asleep within 30 minutes ≥ once a week during the past month.

3.1.7 Female participant of childbearing age must not be pregnant (confirmed by serum or urine pregnancy test within 1 week of eligibility) or lactating.

3.1.8 Female research participant of childbearing age and male research participant of child fathering potential must agree to use safe contraceptive methods.

3.2 Exclusion Criteria

3.2.1 Participant has a known allergy to melatonin or any ingredients of the study product or placebo

3.2.2 Participant currently is taking Melatonin

3.2.2 Participant has known sleep apnea or medically treated sleep disorder (e.g. restless leg syndrome)

3.2.3 Participant has known diabetes mellitus – insulin treated

3.2.3 Participant has uncontrolled seizure disorder in past 12 months

3.2.4 Participant has current reported illicit drug or alcohol abuse or dependence

3.2.5 Participant has current major psychiatric illness (i.e. schizophrenia, bipolar disorder)

3.2.6 Participant is currently receiving treatment with benzodiazepines or other CNS depressants

3.2.7 Participant is currently receiving treatment with fluvoxamine

3.2.8 Participant is currently receiving treatment with anticoagulants (e.g. Coumadin)

3.2.9 Participant is currently receiving treatment with immunosuppressants or corticosteroids

3.2.10 Participant is currently receiving treatment with Nifedipine (Procardia XL®)

3.2.11 Participant is employed in a position that requires night work (i.e. 10pm to 6am)

3.2.12 Female participants who are pregnant or lactating/nursing

3.2.13 Participant has a history of neurologic event (i.e. traumatic brain injury) unrelated to cancer or its treatment

3.2.14 Participant has a sensory impairment (vision, hearing) that prohibits completion of neurocognitive examination

3.3 Research Participant Recruitment

Recruitment: The study sample will be recruited from participants in the St. Jude Lifetime Cohort (SJLIFE) at SJCRH. This established survivor cohort includes all individuals diagnosed and treated at SJCRH during childhood who are now 10 or more years from diagnosis and are 18 years of age or older. Cohort participants receive risk-based medical follow-up care during their SJLIFE evaluation. Complete medical and treatment records for all survivors are available for review. Survivors undergo a neurocognitive evaluation as a part of the established SJLIFE parent

protocol. We will recruit survivors who previously underwent neurocognitive evaluation as a part of the parent protocol, as well as survivors who are eligible for future neurocognitive evaluation through SJLIFE.

As of June 6, 2012, 4,287 patients treated at SJCRH are eligible for participation in SJLIFE and 2,809 have agreed to return to the SJCRH campus for a SJLIFE evaluation. We propose to recruit 342 patients from the available sample, 232 with documented neurocognitive impairment and 110 without neurocognitive impairment. Between December 2007 and June 2011 we completed neurocognitive evaluations for 1,183 SJLIFE participants. Of these, 986 have a measured IQ >79 (83%). Sixty percent of patients with IQ >79 had observed impairment in ≥1 of the six neurocognitive domains required for inclusion in the current study. Based on sleep data obtained from the Childhood Cancer Survivor Study Cohort, we estimate that approximately 30% of survivors will have delayed sleep onset latency (SOL) ≥30 minutes once per week or more frequently. Figure 1 provides a schematic representation of expected study participants eligible for recruitment.

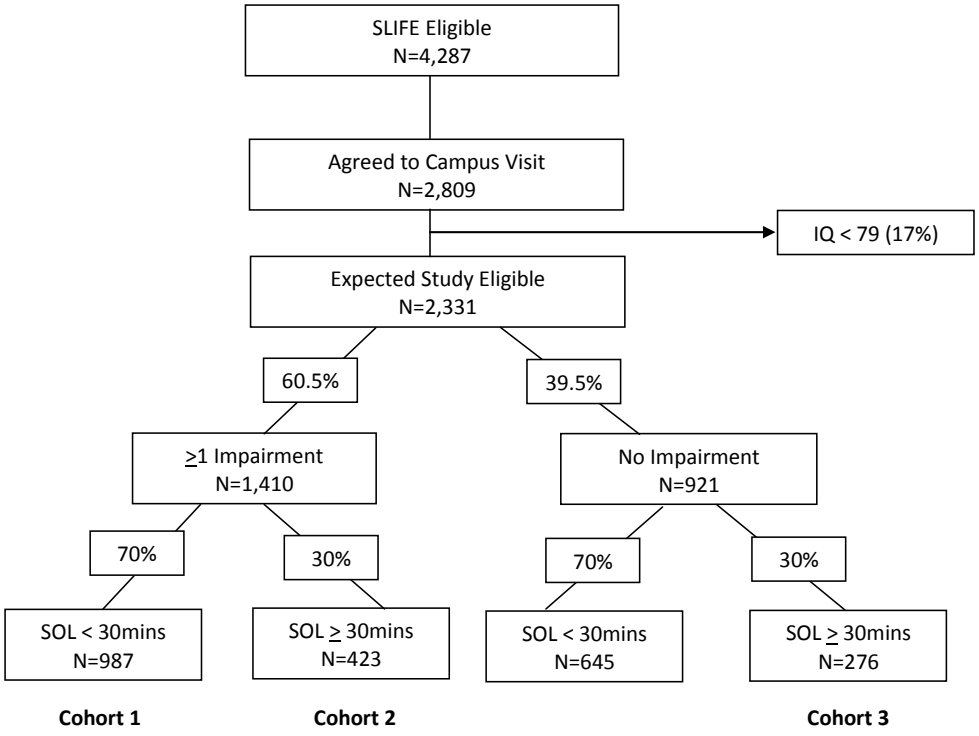

Figure 1. Flow diagram of expected study participants eligible for recruitment

3.4 Procedures for Identifying Research Participants

Potentially eligible study participants will be mailed a letter to introduce the study and inform him or her of their potential eligibility. The letter will state that a study team member will be contacting them in approximately two weeks to discuss the study, answer questions they may have, and ask if they are interested in participating. A toll-free number is in place to receive calls from participants if they wish to call sooner to discuss the study or if they would like to decline participation. A study-specific pre-screening form will be included with the mailing for their review. This form will ask two questions about his or her sleep habits and questions relevant to the exclusion criteria in Section 3.2.

Approximately two weeks after the letter has been mailed a study team member will contact each potentially eligible participant to discuss the study, answer questions, and see if they are interested in participating. If interested, preliminary eligibility will be reviewed by use of the pre-screening form. If the potential participant meets the prescreening criteria, he or she will be scheduled to complete a SJLIFE campus visit. Prior to arriving on campus, all SJLIFE participants are mailed a packet of health status questionnaires, including measures of health-related quality of life and psychological distress, to complete and return prior to their campus visit. Participants who do not return the measures by mail will have the opportunity to complete the measures during their SJLIFE campus visit.

3.5 Enrollment on Study

A member of the study team will confirm potential participant eligibility as defined in Section 3.1-3.2, complete and sign the 'Participant Eligibility Checklist'. The study team will enter the Eligibility Checklist information into the Patient Protocol Manager (PPM) system. Initial eligibility will be reviewed, and a research participant-specific consent form will be generated. The complete signed Eligibility Checklist and consent/assent form(s) must be faxed or sent electronically to the CPDMO to complete the enrollment process.

The CPDMO is staffed 7:30 am-5:00 pm CST, Monday through Friday. A staff member is available at [redacted] for enrollment during the weekend.

3.6 Procedures for Randomizing Research Participants

Once participants have completed baseline neurocognitive and sleep evaluations, they will be stratified into three cohorts. For stratification purposes the following definitions will apply:

1) **Neurocognitive impairment** will be defined as performance on at least one measure of attention, memory, and/or executive functioning $\leq$10th

percentile. Performance will be measured using the following tests: Trail Making Test Part B, Digit Span Forward and Backward, Controlled Oral Word Association Test, California Verbal Learning Test-II (long delay free recall), and Conners' Continuous Performance Test-II (variability index).

2) **Absence of neurocognitive impairment** will be defined as performance >10th percentile on all six measures of attention, memory, and executive functioning.

3) **Delayed sleep onset latency** will be defined as self-report of inability to fall asleep within 30 minutes ≥ once a week during the past month.

4) **Absence of delayed sleep onset latency** will be defined as inability to fall asleep within 30 minutes < once a week during the past month.

Each of the cohorts is described below:

Cohort 1:

a. Has neurocognitive impairment defined as performance on at least one measure of attention, memory, and/or executive functioning ≤10th percentile.
b. Is absent of delayed sleep onset latency defined as an inability to fall asleep within 30 minutes < once a week during the past month.

Cohort 2:

a. Has neurocognitive impairment defined as performance on at least one measure of attention, memory, and/ or executive functioning ≤10th percentile.
b. Has delayed sleep onset latency defined as self-report of an inability to fall asleep within 30 minutes ≥ once a week during the past month.

Cohort 3:

a. Is absent of neurocognitive impairment defined as performance >10th percentile on all six measures of attention, memory, and executive functioning.

b. Has delayed sleep onset latency defined as self-report of an inability to fall asleep within 30 minutes ≥ once a week during the past month.

Upon completion of baseline neurocognitive and sleep evaluations, if it is determined that the participant does not have neurocognitive impairment and no delayed sleep onset latency, he or she will not be randomized and will be taken off study.

Randomization & Blinding: This is a double-blind study in which neither the participant nor investigator will know the treatment assignment. Upon determination of cohort assignment, the participants in each cohort assignment will be randomized 1:1 to receive time release melatonin 3 mg or placebo daily for 6 months. The randomization to melatonin/placebo arms will be done using a program written in C++. This program resides in the Department of Biostatistics and has been routinely used for randomization since 1992. Access to the program will be provided to a member of the Pharmaceutical Services department for randomization. The system stores all required data for randomization into a secure Access database. Once a participant is randomized all related data are frozen in the database and cannot be changed. Blinding of group assignment will be maintained until the study is complete or in the case of an adverse event for which removal of the blind is necessary to allow for appropriate patient care.

4.0 Study Procedures

4.1 Neurocognitive Functioning Measures

During their visit to SJCRH all participants in the St. Jude Lifetime Cohort undergo a general neurocognitive evaluation focused on assessment of intelligence, academic skills, attention, processing speed, memory and executive functions (Table B). This battery, which requires 120 minutes for completion, will be administered at baseline and following 6 months of melatonin/placebo treatment. For this study, three domains of neurocognition will be examined as primary study outcomes 1) attention, 2) memory, and 3) executive functioning. Observed rates of impairment in each of these domains is >15% for current SJLIFE participants. Importantly, these neurocognitive processes constitute common areas of impairment in long-term childhood cancer survivors, are known to be vulnerable to the effects of poor sleep and fatigue, and have been shown to be amenable to treatment with exogenous melatonin. To control for practice effects, alternate tests forms will be used, as available, at the 6-month follow-up evaluation. All test scores will be converted to Z-score distributions (M=0, SD=1). All neurocognitive tests will be administered by trained psychological examiners under the direct supervision of Dr. Brinkman, Dr. Krull, or Dr. Kimberg.

Table B. Neurocognitive Measures		
Variable	**Test Descriptor**	**Neurocognitive Process**
Intelligence		
	Wechsler Abbreviated Intelligence Scale – Full Scale IQ	Global cognitive functioning
Academics		
	Woodcock – Johnson – Letter/Word Identification Test	Basic reading skills
	Woodcock – Johnson – Calculation Test	Basic math skills
Attention		
	Trail Making Test: Part A	Focused attention
	Conners' Continuous Performance Test	Sustained attention, consistency of attention
	Digit Span Test – Forward Span	Attention span
Memory		
	California Verbal Learning Test	Short and long term memory for new information
	Visual Selective Reminding Test	Short and long term visual memory
Processing Speed		
	Grooved Pegboard Dominant Hand Score	Speed of visual-motor processing using the dominant hand
	Coding Test from the Wechsler Scale	Speed of copying number-symbol associations
	Symbol Search Test from the Wechsler Scale	Speed of visually scanning symbol patterns
Executive Function		
	Trail Making Test: Part B	Cognitive Flexibility
	Verbal Fluency test	Cognitive Fluency
	Digit Span Test – Backward Span	Working Memory
	Behavior Rating Inventory of Executive Function	Self-report of executive functioning problems

4.1.1 Attention

Digit Span Forward: Digit Span Forward (DSF), from the Digit Span subtest on the WAIS-IV, is a measure of focused attention and short-term memory span. The examiner reads aloud numbers and the participant is required to repeat the numbers in the same order. The number of digits recalled in the longest span is converted to a standard score using age-based norms. Considered a process score on the WAIS-IV DSF is found to have acceptable reliability and validity parameters.

Conners' Continuous Performance Test- II, Version 5- Variability: The Conners' Continuous Performance Test- II, Version 5 (CPT-II), is a computerized attention task that assesses several components of attention. The Variability index is a measure of sustained attention, specifically the extent to which hit reaction time changes over the course of the task. The CPT-II is widely accepted as a measure of attention and demonstrates good psychometric properties.

4.1.2 Memory

Digit Span Backward: Digit Span Backward (DSB), from the Digit Span subtest on the WAIS-IV, is a measure of working memory. The examiner reads aloud numbers and the participant is required to repeat the numbers backwards. The number of digits recalled in the longest span is converted

to a standard score using age-based norms. Considered a process score on the WAIS-IV DSB is found to have acceptable reliability and validity parameters.

California Verbal Learning Test-Second Edition- Long Delay Free Recall: The California Verbal Learning Test- Second Edition (CVLT-II) is a measure of verbal memory during which examinees are read a list of words and asked to recall them across five trials. Long Delay Free Recall is administered after a 20 minute delay and participants are asked to recall the list of words. An alternate form of the CVLT-II has been developed to reduce practice effects and will be utilized in the second study visit. The CVLT-II is found to have acceptable psychometric properties.

4.1.3 Executive Function

Trails B: This is a timed task that requires a participant to shift his/her attention adaptively and flexibly. Specifically, participants are asked to draw a line from a number to a letter in ascending order as quickly as possible. Considered a measure of cognitive flexibility, Trails B is found to have adequate psychometric properties.

Controlled Oral Word Association (COWA): This is a task of verbal fluency. Participants are given a letter and must say as many words that start with that letter within 60 seconds. There are two versions of the test, one using the letters FAS and the other using CFL, to control for practice effects.

4.2 Sleep Measures

Sleep parameters will be assessed at three time points during the study: Baseline, 3-months, and 6-months. The Baseline assessment will occur prior to initiation of the melatonin intervention. The two follow-up assessments will occur while participants are actively enrolled on the intervention trial. Each assessment will include the objective and subjective measures as outlined below.

4.2.1 Actigraphy

Sleep-pattern measures of each participant will be measured with Actigraphy to be worn over 5 consecutive days at three specified intervals [Baseline, 3 months, 6 months]. Actigraphy provides objective assessment of wrist movement that infers wakefulness and sleep. Functionally, the actigraph provides sleep-pattern measures including: sleep onset latency (SOL), wake after sleep onset (WASO), and total sleep time (TST). Movement triggering the actigraph is relatively high during wakefulness and decreases to near-zero values during sleep. The actigraphy will collect data in the zero crossing mode, where the transducer signal is compared with a fixed sensitivity threshold. The number of times the signal voltage

crosses the reference voltage is accumulated in temporary memory storage until the user-defined epoch length has transpired.

[Acceleration Index—the acceleration index (AI) is calculated by the formula: $AI=2p-1$]

Where p is the proportion of the interval required for 50% of the total activity in the interval to be completed. For example, for a 1-hour interval, if the activity total for the interval was 1000 and 800 counts occurred in the first 20 minutes of the interval, p would be 20/60 or .33. Doubling p and subtracting 1 scales the index form -1 to +1. Thus, negative values represent slowing during the interval, 0 represents uniform distribution of activity during the interval, and positive values represent acceleration during the interval.

Analysis of actigraphic records reveals sleep-wake patterns that correlate closely with patterns obtained via polysomnographic recordings and behavioral observations.[60-67] Furthermore, actigraphy is a reliable method for assessing sleep-wake patterns and monitoring of treatment response among insomnia patients.[67] The American Academy of Sleep Medicine practice parameters state that actigraphy is an accurate estimate of sleep patterns in normal healthy adults and there is evidence to support the use of actigraphy to describe sleep patterns among those with insomnia and as a study outcome measure.[68] Actigraphy is able to sensitively capture change in sleep-wake patterns before and after behavioral or medical interventions, and actigraphic data from either wrist is highly similar.

4.2.2 Daily Sleep Diary

The daily sleep diary is a 15 item self-report measure that assesses participant sleep patterns during the previous night. The items measure sleep parameters such as onset latency, efficiency, duration, and quality.[69] The sleep diary will be completed for five consecutive days to correspond with 5 days of actigraphy data collection. Sleep logs are widely employed in research and are more accurate than a single, global, and retrospective estimate of sleep parameters.[70]

4.2.3 Pittsburgh Sleep Quality Index (PSQI)

The PSQI assesses sleep quality over the previous month and is comprised of 19 items that are scored on a 4-point Likert scale (0 = not at all during the past month to 3 = three or more times a week). Seven equally weighted components are measured by the PSQI, including subjective sleep quality, sleep onset latency, sleep duration, habitual efficiency, sleep disturbance, and daytime dysfunction. Component scores can be evaluated individually or summed to provide an overall score from 0 to 21. Higher scores indicate poorer quality of sleep. The overall reliability coefficient (Cronbach alpha) is 0.83 and test-retest reliability has a Pearson correlation of 0.85.

4.2.4 Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

The FACIT-Fatigue is a measure of physical and functional consequences associated with fatigue. The 13 items comprising this measure are scored on a reverse 4-point Likert scale (4 = not at all to 0 = very much). Scores range from 0 to 52 with lower scores indicating more fatigue. The FACIT-Fatigue has been validated in cancer patients and has good test-retest reliability (r=0.90) and internal consistency (alpha's=0.93-0.95).

4.2.5 Epworth Sleepiness Scale (ESS)

The ESS measures daytime sleepiness and likelihood of falling asleep during routine daily situations. The ESS is comprised of 8 items which are scored on a 4-point Likert scale (0=would never doze to 3=high chance of dozing). Scores range from 0 to 24, with higher scores indicating increased daytime sleepiness. Cronbach alpha is 0.88 and test-retest correlation is $r = 0.82$.

4.3 Correlative Psychosocial Measures

Psychosocial measures of health-related quality of life and psychological distress will be completed at baseline as part of the SJLIFE protocol and following 6 months of melatonin/placebo treatment. Previous studies have demonstrated an association between melatonin treatment and depressive symptoms and quality of life has been identified as an important functional outcome of clinical trials.

4.3.1 Medical Outcomes Survey 36-Item Short Form Health Survey (SF-36)

Health-related quality of life (HRQOL) will be measured with the SF-36, a widely used generic health profile which provides subscale scores for 8 domains of HRQOL: general health, role physical, physical function, bodily pain, vitality, mental health, social function, and role emotional. The SF-36 provides age and sex-specific norms to generate T scores with a mean of 50 and standard deviation of 10. The internal consistency, validity, and test-retest reliability are excellent.[71]

4.3.2 Brief Symptom Inventory-18 (BSI-18).

Psychological distress will measured by the BSI-18.[72] Sex-specific scores from the BSI-18 will calculated based on standardized normative values (M=50, SD=10) and scores falling $\geq 90^{th}$ percentile will classified as demonstrating a clinical level of acute emotional distress. Subscales are provided for anxiety, depression, and somatization as well as an overall global severity index. This measure has previously been validated in adult survivors of childhood cancer.

4.4 Serum Melatonin

Biological samples will be collected at baseline and at the 6 month follow-up evaluation. A total of 12mL of blood will be drawn from every participant at each time point according to standard procedures. These samples will be collected in combination with labs collected for routine clinical reasons when possible. Blood will be collected into three, 4mL red top tubes. Samples will be taken to the TTU Shared Resources Laboratory where within 30 minutes of collection, the samples will be processed according to Standard Operating Procedures. The serum will be removed and aliquoted to 1.2 mL cryovials which hold 0.5mL of serum. The vials will be labeled with the participant's assigned study number. Of note, it is necessary to collect 12mL of blood per participant since melatonin levels have not been previously established in this unique participant population. Therefore, it is possible that samples will need to be processed multiple times to accurately characterize the levels The cryovials will be stored at -70 to -80 degrees Celsius in a freezer located in the TTU Shared Resources Laboratory. Samples will be stored until they are ready for testing, at which point samples will be sent to an outside testing service via standardized shipping procedures.

Serum melatonin will be analyzed via quantitative radioimmunoassay. Recent data indicate strong correlations between serum and plasma levels as well as urine and serum levels, suggesting that serum is a useful specimen for the quantification of melatonin levels. Daytime adult levels range from 3.4 to 53.9pg/mL while nighttime levels range from 7.1 to 89.5pg/mL. Importantly, a five-fold difference in melatonin levels has been reported with serum collected in the morning hours compared to that collected in the afternoon. Therefore, all blood samples will be drawn in the morning.[73]Participants may choose to participate in the Melatonin blood sample at the baseline and 6 month visits as part of the consent process.

4.5 Intervention

Melatonin

To our knowledge, there are no studies reporting on the use of exogenous melatonin in adult survivors of childhood cancer. Studies have reported low nocturnal salivary[74] and 24-hour plasma[75] levels of endogenous melatonin in childhood survivors of craniopharyngioma. Increased daytime sleepiness was associated with decreased nocturnal melatonin levels in these survivors and supplementation with 6mg of exogenous melatonin resulted in improved daytime sleepiness.[74]

Data are lacking on the pharmacokinetics and pharmacodynamics of melatonin in cancer survivors, although among adults individual variation is apparent. The ability to synthesize melatonin varies among individuals with low secretors (18 to 40pg/mL) and high secretors (54 to 75pg/mL) distinguished.[76] Immediate release exogenous melatonin has rapid absorption, with peak levels occurring 20-30 minutes after administration,

though estimates of its half-life in serum range from 30 to 60 minutes.[76] Approximately 90% of the supplement is cleared by hepatic first-pass metabolism and involves oxidation by CYP1A2 and CYP2C19.[77] When formulated with absorption retarding binders, melatonin availability mimics that of normal nocturnal secretion.[78,79] Sustained release melatonin circumvents the fast clearance of the hormone and essentially mimics physiological patterns of endogenous secretion of the hormone. Sustained release products are have been demonstrated to maintain, high, near physiological, plasmas levels for 5 to 7 hours.[80]

The optimal dosing of melatonin is unclear. Clinically, melatonin has two primary uses including soporific (3mg) which is sleep inducing and phase shifting which may be achieved with a lower dose (0.5mg)[81] That is, lower doses are commonly used for shift phasing purposes while higher doses are found most effective in promoting sleep onset. The most common dose used in studies for free running sleep disorder was 3 mg and the duration of treatment ranged from 1 month to 6 years.[82] Pharmacological doses of melatonin range from 0.1-10mg and doses greater than 0.5mg produce endogenous levels greater than those observed physiologically. At the high end of the dosage range melatonin levels can be thousands of times higher than normal. 3mg of melatonin may produce peak levels that are 10 times physiological concentrations.[83] Attenburrow et al[84] demonstrated that 1mg but not 0.3mg improved sleep in middle-aged adults, suggesting a supraphysiological threshold is necessary for sleep-promoting effects.

The active melatonin product will be purchased in its marketed form from Natrol®, a reputable manufacturer in the United States. For the current study Natrol® 3mg time release melatonin will be utilized. Additional ingredients included in the Natrol® 3 mg time release melatonin tablets includes Vitamin B6 (from pyridoxine hydrochloride), cellulose, dibasic calcium phosphate, hypromellose, silica, stearic acid, magnesium stearate, methylcellulose and glycerin. Melatonin is considered a nutraceutical and is not FDA approved for prevention, diagnosis or treatment of disease.

UPM Pharmaceuticals, Inc. will develop and manufacture placebo tablets matching the melatonin product to achieve similar shape, weight and color of the Natrol® brand melatonin tablet. UPM Pharmaceuticals will test the potency, content uniformity, and timed release dissolution of the melatonin in its marketed form. Both active melatonin and placebo will be shipped to St. Jude Pharmaceutical Services, and these bulk shipments will be repackaged into appropriate containers for dispensing to patients, with appropriate labeling. All study drugs will be stored and processed by Pharmaceutical Services at SJCRH. Both melatonin and placebo will be labeled in a manner that will assure blinding of the study. Melatonin/placebo will be dispensed in 1 bottle, containing 60 tablets. Medication will be sent via FedEx (2 day delivery) or other commercial courier at 2-month intervals. Dr. Greene (co-Investigator) has extensive

experience with randomized clinical drug trials and will manage the processing and blinded distribution of melatonin/placebo to participants.

Participants will be instructed to take one 3mg tablet of time release melatonin or placebo each night during the 6-month trial. Consistent with procedures described by Wade et al[55] participants will be instructed to take one tablet of melatonin/placebo orally, 1-2 hours before initiating sleep onset, preferably at the same time each night.

4.5.1 Adherence

Medication Event Monitoring Systems
Electronic monitors are often considered the "gold standard", with respect to adherence measurement.[85] Medication event monitoring systems (MEMS), a type of electronic monitor, registers the date and time when a medication vial cap is opened,[86] thus, providing real-time monitoring and documentation of medication adherence. Despite this, MEMS caps are a proxy for adherence measurement, as there is no confirmation that a participant actually takes the medication after opening the pill bottle. Therefore, it is recommended that electronic monitoring be used in conjunction with other adherence measures.

Pill Count
Pills counts have been widely used to assess adherence to medication regimens. Pill counts compare the amount of medication remaining in a container with the amount that would be left if all prescribed medication was consumed. A study staff member will contact each participant by telephone or electronic mail. He or she will be asked to self-report the number of melatonin/placebo pills remaining in their medication container. The self-reported pill counts will be obtained approximately every 30 days while on the study. Adherence for study drug will be documented through the use of a telephone log.

Problem Solving
Participants who do not demonstrate at least 80% adherence to the prescribed intervention, as measured by monthly pill counts, will be contacted via telephone to participate in a problem-solving exercise. Dr. Kimberg will monitor participant adherence throughout the interventions trial and will contact participants who demonstrate poor adherence behaviors to problem-solve potential barriers to adherence, as well as identify and discuss possible solutions (see problem solving phone script).

4.5.2 Side Effect Monitoring

Side Effect Profile

Reports of adverse events will be monitored. The research participant will be contacted at the end of the first week on study drug then biweekly for the duration of the study. Adverse event information will be collected throughout the study by participant reporting and direct questioning using the patient report of incidence of side effects (PRISE), frequency and intensity of side effect rating (FISER), and global rating of side effects burden (GRSEB). The PRISE form assesses the presence of side effects for a variety of biological systems. For each of the nine organ/function systems (gastrointestinal, nervous system, heart, eyes/ears, skin, genital/urinary, sleep, sexual functioning, and other), the participant indicates the presence of a side effect, and if present, the tolerability of the side effect (tolerable or distressing). The FISER and GRSEB assess three domains of medication side effect impact: frequency, intensity, and burden. Each domain is rated on a 7-point Likert scale (i.e. Frequency, ranging from no side effects to present all the time; Intensity, ranging from no side effects to intolerable; and Burden, ranging from no impairment to unable to function due to side effects). Reliability and validity have been reported.

4.6 Dose Modifications

There will be no dose modifications for melatonin or placebo. Treatment will be discontinued if a participant reports an adverse event that is not tolerable which the investigator deems related to the study drug. The participant will end treatment on the study and arrangements will be made for the return of unused melatonin/placebo.

4.7 Concomitant Therapy

Females may take oral contraceptives. If at any time during the six months of study treatment with melatonin/placebo, the participant must start the use of any of the medications listed in the exclusion criteria for medical conditions not present at the time of enrollment, he/she will be taken off-treatment. These medications include: 1) benzodiazepines or other CNS depressants; 2) fluvoxamine; 3) anticoagulants 4) immuno-suppressants or corticosteroids and 5) Nifedipine (Procardia XL)

5.0 DRUG INFORMATION

Melatonin

Source and Pharmacology: Melatonin (N-Acetyl-5-Methoxytryptamine) is a neurohormone produced in the pineal gland that is involved in the promotion of sleep. It is naturally released during the dark hours of the normal day-night cycle. It is also thought to play a role in regulating the secretion of growth hormones and gonadotropic hormones. Melatonin may also possess some antioxidant properties. Melatonin undergoes significant first-pass metabolism (up to 60%) with an oral dosage form, and is metabolized into two inactive metabolites: 6-hydroxymelatonin and N-acetyl serotonin. Clearance is severely reduced in patients with hepatic insufficiency. Melatonin is mostly excreted in the urine as the inactive metabolite 6-hydroxymelatonin. Adults experience approximately a 37% decline in melatonin production between the ages of 20 and 70 years.

In vitro data suggests that melatonin may inhibit the CYP1A2 isoenzyme and may affect the disposition of CYP2C9. Use with caution in individuals taking medications influenced by these enzyme systems. Melatonin may interact with calcium channel blockers leading to an increase in blood pressure. Possible immune-stimulating effects of melatonin may interfere with immunosuppressant therapy.

Formulation and Stability: Melatonin 3 mg time release tablets will be used. The tablets are to be stored at controlled room temperature and are stable according to manufacturer's labeling.

Supplier: Commercially available from various manufacturers. For the current study Natrol® 3mg time release melatonin will be utilized. Additional ingredients included in the Natrol® 3 mg time release melatonin tablets includes Vitamin B6 (from pyridoxine hydrochloride), cellulose, dibasic calcium phosphate, hypromellose, silica, stearic acid, magnesium stearate, methylcellulose and glycerin. Melatonin is considered a nutraceutical and is not FDA approved for prevention, diagnosis or treatment of disease.

Toxicity: Drug toxicities with melatonin are rare. Serious side effects have not been reported but long term studies have not been performed. The most common side effects of using melatonin are drowsiness and confusion, especially if used with other CNS sedating drugs. Other toxicities that have been associated with melatonin are headache, hypersensitivity, tachycardia, hypothermia, and increased seizure activity. Melatonin may reduce glucose tolerance and insulin sensitivity. Use with caution in individuals with a history of bleeding disorders, hemostatic disorders and in individuals taking anticoagulant medications (warfarin, aspirin, NSAIDs or antiplatelet agents) or antidiabetic agents or insulin. Avoid use in women who are pregnant or may become pregnant.

Dosage and Route of Administration: Participants will be instructed to take one 3mg time released tablet of melatonin or placebo by mouth approximately 1-2 hours before initiating sleep onset, preferably at the same time each night.

Placebo

Placebo tablets to match the melatonin will be comprised of inert substances. Placebo will be developed and manufactured by UPM Pharmaceuticals, Inc. Jim Knight, Director of Quality Assurance at the St. Jude GMP Facility, has reviewed the proposed placebo development methods to assure that Good Manufacturing Processes are used.

6.0 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

6.1 Pre-Screening Evaluations for Eligibility

Pre-screening will occur to determine eligibility prior to scheduling participants for their campus visit. If the participant appears eligible based upon telephone screening, a SJLIFE study visit will be scheduled. The remaining evaluations for study eligibility will occur prior to randomization on the study. All of the evaluations have been described in detail in section 4 above.

Baseline Measures: Baseline evaluation for all participants will include a medical evaluation, neurocognitive assessment, and collection of biological samples. Because evaluations performed, as detailed in the Children's Oncology Group "Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers," are standard care in the SJLIFE clinic, no additional monetary funds will be required for the baseline medical or neurocognitive evaluation in the proposed study cohort. Medical evaluations are based on primary cancer diagnosis, age at diagnosis, and therapeutic interventions and are limited to screening and diagnostic evaluations to characterize cancer-related health complications. Complete treatment records, including all information from all medical follow-up, will be available to study investigators. Dr. Hudson is the Director of the SJLIFE clinic and carefully reviews and approves each abstracted treatment summary and medical history. The existing data give us the ability to carefully evaluate whether patients in our study are similar to or differ from nonparticipants. Table D summarizes the pre-screening evaluations and baseline measures.

Table D: Pre-screen and Baseline Measures

Evaluations – must be obtained prior to randomization	**Prescreen**	**Baseline Visit**
Inclusion/Exclusion criteria questions	X[1]	
Sleep-related questions		**X**
Informed consent		X
HIPAA		X
Standardized Sleep Measures		X
Melatonin		X[3]
Correlative Psychosocial Measures		X[2]
PRISE (side effect monitoring)		X
Neurocognitive Assessment Measures		X[2]
Pregnancy Test**		X[2]
History and Physical Exam		X[2]

** The St. Jude IRB requires that a female patient of childbearing potential must have a negative pregnancy test as a condition of clinical research eligibility.

[1]Mailed with introductory letter.

[2]Completed as part of SJLIFE protocol

[3]Optional

6.2 Evaluations During Therapy

After completion of the campus visit, participants will complete a five (5) day home-based sleep assessment to include actigraphy and a daily sleep diary. Participants will be contacted after the first week $\pm$7 days of taking the study drug and biweekly $\pm$7 days thereafter to monitor for side effects and adverse events. Monthly $\pm$10 days, research participants will be asked to conduct a pill count and report the number of pills remaining in their medication vial as a measure of treatment adherence. Three (3) months $\pm$ 1 week into the intervention trial, participants will complete objective and subjective sleep measures at home, including five days of actigraphy, a daily sleep diary, and standardized sleep measures. These data will allow for the examination of short-term effects of melatonin on sleep parameters. Table E summarizes the evaluations to be completed during therapy.

Table E: Evaluations During Therapy

Evaluation	7-10 days after baseline visit	Monthly (±10 days)	3 months (±1 week)	6 months (± 4weeks)
• Actigraphy	X[1]		X[1]	X[1]
• Daily Sleep Diary	X[1]		X[1]	X[1]
• Standardized Sleep Measures			X[1]	X[1]
• Side effect monitoring	X[2]	X[2]		
• Study drug adherence (Pill Count)		X[3]		
• Correlative Psychosocial Measures				X[1]
• Interim History and Visit with a Medical Provider				X
• Neurocognitive Assessment Measures				X
• Melatonin				X[4]

[1]Completed at home.
[2]Initially after the first week ±7 days of taking study drug, then biweekly ±7 days for the duration on study.
[3]Obtained every 30 days +10 for duration on study.
[4]Optional

6.3 End of Study Evaluations

An interval of approximately six (6) months will occur between completion of baseline and follow-up measures. Participants will be scheduled for a return visit to SJCRH within 6 months ±4 weeks to complete a follow-up evaluation. One to two weeks prior to their scheduled follow-up visit, participants will complete objective and subjective sleep measures at home, including five days of actigraphy, daily sleep diary, and standardized sleep measures. Participants will also complete measures of health-related quality of life and psychological distress prior to returning to SJCRH. During their campus visit participants will have a visit with a medical provider, provide an interim history, undergo a neurocognitive evaluation, and have biological samples collected. If a participant is unable to return to St. Jude to complete their 6 month visit, a standardized neurocognitive questionnaire, which is also administered at baseline, along with the objective and subjective sleep measures will be mailed to them to complete at home and return. The follow-up assessment will be scheduled to occur while participants are actively taking melatonin/placebo. However, treatment with melatonin/placebo will not be extended by more than two weeks.**6.4 Long-Term Follow-up Evaluations**

The study is approximately six (6) months in duration. No long-term

follow-up evaluations will be performed.

7.0 EVALUATION CRITERIA

7.1 Response Criteria

Three domains of neurocognitive functioning will be evaluated as primary study outcomes 1) attention, 2) memory, and 3) executive functioning. These will be examined at the 6 month interval. The secondary outcomes will be evaluated by subjective and objective sleep parameters assessed at the 3 month and 6 month time periods.

Response in the neurocognitive functioning domains of attention, memory, and executive functioning will be documented as either 1) Improvement; 2) No change; or 3) Worsened. The same responses will be used for sleep onset latency. Correlative psychosocial measures of health-related quality of life and psychological distress will be examined at 6 months of melatonin/placebo treatment.

7.2 Toxicity Evaluation Criteria

Adverse events will be monitored and graded according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). A copy of the current version of the CTCAE version 4.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov) or from the St. Jude home page.

7.3 Acceptable Percentage of Missed Doses for Research and Standard of Care Drugs

Participant adherence to melatonin/placebo treatment will be monitored following the first week of therapy and monthly thereafter during the six month trial. Participants who reported <80% adherence will be contacted by telephone to problem-solve potential barriers to adherence and brainstorm solutions to improve adherence. A standardized problem-solving model will be utilized for this process. The participant will select one solution that he/she is willing to try over the next month and this solution will be operationalized. Participants will not be removed from the study trial due to poor adherence.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF-STUDY CRITERIA

8.1 Off-study Criteria

8.1.1 Death
8.1.2 Lost to follow-up
8.1.3 Request of the research participant
8.1.4 Development of unacceptable toxicity during treatment
8.1.5 Discretion of the Study PI, such as the following:

- The researcher decides that continuing in the study would be harmful
- A treatment/medication is needed that is not allowed on this study
- New information is learned that a better treatment is available
- The study is not in the participant's best interest

8.1.6 Participant develops a subsequent malignant neoplasm while on study
8.1.7 Participant develops a serious and/or life threatening medical condition while on study
8.1.8 Study evaluations are complete
8.1.9 Participant does not have neurocognitive impairment and no delayed sleep onset latency at baseline

9.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

9.1 Reporting Adverse Experiences and Deaths

Principal investigators are responsible for promptly reporting to the IRB any adverse events that are unanticipated, serious, and that may represent potential harm or increased risk to research participants. When an unanticipated death occurs, the PI should report it to the Director of the Office of Human Subjects' Protection immediately, by phone: ([redacted], Cell: [redacted], fax: [redacted], or e-mail: [redacted]).

A reportable event entry into TRACKS should follow within 48 hours. Serious, unanticipated, and related or possibly related events must be reported within 10 working days.

The principal investigator is responsible for reviewing the aggregate toxicity reports and reporting to the IRB if the frequency or severity of serious toxicities exceed those expected as defined in the protocol or based on clinical experience or the published literature. Any proposed changes in the consent form or research procedures resulting from the report are to be prepared by the study team and submitted with the report to the IRB for approval.

The following definitions apply:

A **serious event** refers to any event in which the outcome is fatal or life-threatening, results in permanent disability, causes inpatient hospitalization or prolongs existing inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

An **unanticipated adverse event** refers to those not identified in their nature, severity, or frequency in the current risk documents (e.g., investigator's brochure), or consistent with the investigational plan.

The following are considered reportable: Any injuries, serious event or other unanticipated adverse events involving risk to participants or others which occur at a frequency above that considered acceptable by the investigators and the IRB. (FDA) As described in 4.3 above, the OHSP Director or designee performs the initial review of unanticipated problems or serious adverse event reports. Internal reports of events that are unanticipated, serious, and related or possibly related to study interventions or procedures are then forwarded to the IRB Chair or designee and if necessary, referred to the full IRB. Based on the frequency and seriousness of adverse events, the IRB Chair or Committee may deem it necessary to suspend or terminate a research study or studies.

All anticipated Grade III or IV adverse events will be reported to the IRB in the continuing review report and/or summary. The DSMB will monitor accrual and toxicities every six months.

9.2 Recording Adverse Events and Serious Adverse Events

All serious adverse events will be recorded in the source, database and/or case report form. Adverse events unrelated to the trial will not be recorded unless they are grade III or above (CTCAEv4). Adverse events that are related to the trial will be captured in the source document, database and/or case report form. Adverse events related to the trial will be collected until the time of the participant's six month follow-up visit.

10.0 DATA COLLECTION, STUDY MONITORING, & CONFIDENTIALITY

10.1 Data Collection

Data for this study will be managed by the Neuropsychology Research Team and the Clinical and Survey Research Center in the Department of Epidemiology and Cancer Control. Data collected at baseline and follow-up assessments will be entered by optical scanning. The optical scanning program has the capacity for designer specific error checks, flagged at the time the questionnaires are scanned. After data are scanned, they are processed and converted into a SAS (Cary, NC) format where a second error check is completed. Data from neurocognitive tests are double-

entered into a separate secure Access database and compared for accuracy. Data from biological specimens will be transmitted to the survey research center with a secure file transport protocol, double-entered and compared for accuracy. All data mismatches will be reviewed by two members of the survey center staff and compared to the original documents (when applicable) for resolution. Actigraphy and MEMS cap data will be downloaded using software provided by the product manufacturers and processed with published coding algorithms.

10.2 Study Monitoring

Source document verification of eligibility for all SJCRH cases will be performed within two weeks of completion of enrollment. This will include verification of appropriate documentation of consent. Monitoring of timeliness of serious adverse event reporting will be done as events are reported in TRACKS.

Monitoring of this protocol is considered to be in the "moderate" risk category. The Monitoring Plan is outlined in a separate document from this protocol, but has been submitted for review and approval by the Clinical Trials Scientific Review Committee and the Institutional Review Board (IRB).

The study team will hold monthly meetings and review case histories or quality summaries on participants. Source document verification of eligibility and informed consent for 100% of St. Jude participants will be performed by the Eligibility Coordinators within 10 working days of completion of enrollment. The Clinical Research Monitor will perform monitoring of applicable essential regulatory documentation. Also, reviewing for the timeliness of serious adverse event reporting (type, grade, attribution, duration, timeliness and appropriateness) for selected study participants *semi-annually* and track accrual continuously. The monitor will verify those data points relating to the primary study objective for a certain number of study enrollees as specified in the Moderate Risk monitoring plan checklist for this study. Protocol compliance monitoring will include participant status, safety assessments, eligibility, the informed consent process, participant protocol status, off-study, and off-therapy criteria. The Monitor will generate a formal report which is shared with the Principal Investigator (PI), study team and the Internal Monitoring Committee (IMC).

The DSMB will monitor the study every 6 months.

Monitoring may be conducted more frequently if deemed necessary by the CPDMO or the IMC. Continuing reviews by the IRB and CT-SRC will occur at least annually. In addition, SAE reports in TRACKS (Total Research and Knowledge System) are reviewed in a timely manner by the IRB/ OHSP.

10.3 Confidentiality

All study information will be stored in locked research files and password protected databases. Any information learned from this study in which the subject might be identified will be confidential and disclosed only with the subject's permission. Publications will present the results in such a way as to make it impossible to identify individuals. Upon agreeing to participate, the consent form and Health Insurance Portability and Accountability ACT (HIPAA) compliance form will be signed by the participant and the principal investigator or designee.

11.0 STATISTICAL CONSIDERATIONS

The primary focus of this study is to evaluate the efficacy of melatonin on neurocognitive functioning in long term survivors of childhood cancer. Currently, there are 2,331 survivors potentially eligible for this study and 1,410 (61% have been identified as expected to have least one area of neurocognitive impairment. Further, it is estimated that among all the eligible survivors roughly 30% will have delayed sleep (sleep onset latency ≥ 30 minutes). Thus, the eligible survivors can be classified into three distinct cohorts (I) Those who are neurocognitively impaired but don't have delayed sleep 987 (II) Those who are neurocognitively impaired and have delayed sleep 423, i.e. 30% of 1,410, and (III) Those who don't have neurocognitive impairment but have delayed sleep problems (this would be roughly 30% (276) of those who are not neurocognitively impaired. Targeted enrollment for the study is 987 survivors and expected evaluable is 395.

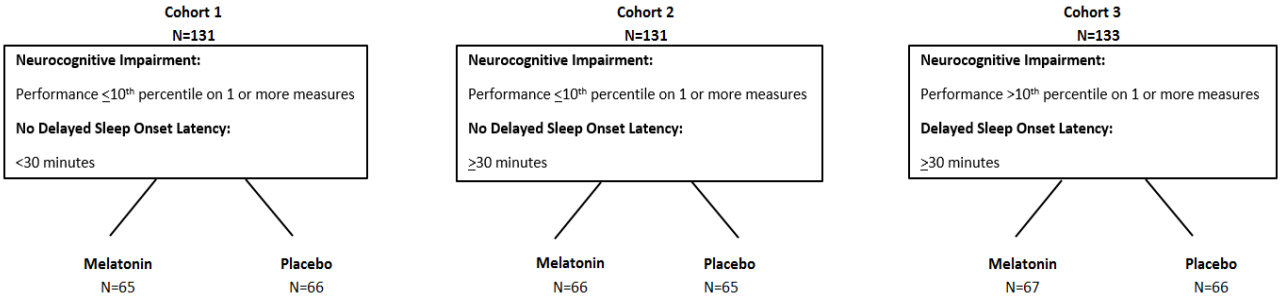

Figure 2. Three group stratification with parallel allocation to melatonin/placebo

Primary Objective: Examine the efficacy of melatonin treatment on neurocognitive functioning in adult survivors of childhood cancer.

- Hypothesis 1: Long-term survivors of childhood cancer with documented baseline neurocognitive deficits (Cohorts 1 and 2), in attention, memory,

and/or executive functioning, randomized to the melatonin treatment arm, will demonstrate improved neurocognitive performance following six months of treatment compared to those randomized to placebo.

The primary objective of this study is to demonstrate that treatment with melatonin will be associated with improvement in neurocognitive performance. This will be evaluated in Cohorts 1 and 2 independently. The study will be conducted by randomizing survivors to melatonin or placebo within each of the two Cohorts.

For those who are in Cohorts 1 and 2 baseline neurocognitive evaluation along with other evaluations will be obtained prior to randomization to melatonin or placebo arm. After randomization, sleep data will be collected using actigraphy in week one when the survivors are in their homes. The intervention will be delivered for a period of six months with regular phone calls for monitoring. Then one week before the six month visit sleep data using actigraphy will be collected. The neurocognitive data will be collected at the 6 month return visit (post-treatment).

There are 10 subscales on which a survivor could be impaired and, out of 10 such subscales, we have identified six in which the marginal impairment rates were seen to be greater than 15%. There are normalized Z-scores available for each subscale and a survivor that falls below the 10% ($\leq$ -1.3) is classified as impaired on that subscale . It is possible that a survivor could be impaired on more than one subscale but we will assess improvement in each subscale independently. Thus, we will have the Z-score corresponding to each of the subscales within at baseline and at follow-up visit. For simplicity, consider the first subscale. We don't expect to see any change in the Z-scores for the placebo arm but we do expect to see an improvement in the melatonin arm. Let Z^1_{1m} and Z^1_{2m} denote the Z-scores at baseline and follow-up time points for the first subscale on melatonin arm and let Z^1_{1p} and Z^1_{2p} denote the Z-scores at baseline and follow-up time points for the first subscale in the placebo arm. Let $Z^1_{DM} = Z^1_{2m} - Z^1_{1m}$ and $Z^1_{DP} = Z^1_{2p} - Z^1_{1p}$ denote the difference between the two time points in the two arms. Then our interest is in testing the null hypothesis $H_0: \mu_{Z^1_{DM}} = \mu_{Z^1_{DP}}$ vs $H_1: \mu_{Z^1_{DM}} \neq \mu_{Z^1_{DP}}$ i.e. the mean of the difference scores for the first subscale would be same for the two arms vs. they will be different. The lowest test-retest correlation coefficient for the neurocognitive measures has been observed to be 0.60. Then, assuming the difference in the Z-scores to be normally distributed but assuming (conservatively) the variance to be 1, we will need to randomize 131 survivors between the melatonin and placebo arm to detect an improvement of 0.66 units (in standardized scale, considered to be clinically meaningful) with 80% power with type I error control α=0.05/6=0.0083 to adjust for multiplicity of 6 tests for each subscale. However, the sample size required to evaluate the secondary objective in cohorts 2 and 3 is 131 and 133, respectively, per cohort. Thus, we plan to enroll 131 research participants from Cohorts 1 and 2 and 133 research participants from Cohort 3.

In addition to analyzing the differences for each subscale we will also analyze the data in an alternative manner as follows. For each subscale an improvement will be defined if the difference in the Z-score (follow-up time point – baseline) is greater than 0.6 units ($\geq$0.6). Let us assume that the probability of observing an improvement in a subscale in an individual in the placebo group is about 5% and then the total of 6 subscales (assuming them to be independent with the same probability of improvement) will follow a Binomial distribution B(6, 0.05) with a mean of 0.3 and SD of 0.54. If we assume that the probability of improvement to be higher say about 12% in the melatonin group then the total score in that group will follow a Binomial distribution B(6, 0.12) with a mean of 0.72 and SD of 0.80. Then, we will use two-sample Behrens-Fisher t-statistic to compare the two means. With a sample size of between 65 and 67 in each group we will have roughly 90% power to detect a difference of 0.42 units with type I error control α=0.05.

Secondary Objective: Evaluate the efficacy of melatonin treatment on delayed sleep onset latency in long-term childhood cancer survivors.

- Hypothesis 2: Long-term survivors of childhood cancer with delayed sleep onset latency at baseline (Cohorts 2 and 3), randomized to the melatonin treatment arm, will demonstrate improved sleep onset latency following six months of treatment compared to the placebo groups.

The primary interest of Objective 2 is to assess the efficacy of melatonin on delayed sleep onset latency in adult survivors of childhood cancer, which will be evaluated in Cohorts 2 and 3. We hypothesize that survivors randomized to the melatonin treatment arm will evidence a greater improvement in sleep onset latency compared to survivors randomized to placebo. The CCSS cohort mean and SD for sleep onset latency among participants with delayed sleep onset latency (i.e. SOL $\geq$ 30minutes) is 46.2 and 27.7 minutes, respectively. The test-retest correlation for sleep onset latency from the PSQI has been observed to be in the range of 0.70. Following the justification set forth in Aim 1, and assuming the SD to be 27.7, we will need to randomize 131 and 133 survivors between the melatonin and placebo arms in Cohort 2 and Cohort 3, respectively, to see an improvement of 15 minutes in sleep onset latency with 80% power with type I error control α=0.05. The analysis for Aim 2 will be completed using a two-sample t-test.

Secondary Objective: Investigate whether improvement in sleep onset latency due to melatonin treatment is associated with neurocognitive improvement in long-term childhood cancer survivors.

- Hypothesis 3: Improvement in sleep onset latency with melatonin treatment will result in improved neurocognitive performance in long-term childhood cancer survivors who have both comorbid sleep onset latency and neurocognitive deficits at baseline (Cohort 2).

The secondary interest of Objective 2 is to investigate the association between

sleep onset latency and specific neurocognitive processes in survivors with comorbid sleep and neurocognitive dysfunction [Cohort 2]. We hypothesize that decreased sleep onset latency following 6 months of melatonin treatment will be associated with improved neurocognitive performance. With a sample size of 131 in Cohort 2 [66 randomized to melatonin, 65 randomized to placebo] we will have 80% power to detect a correlation of at least 0.25 between reduced sleep onset latency and improved neurocognitive performance with type 1 error control α=0.05.

Exploratory Objective: Explore the association between endogenous melatonin levels and improvement in sleep onset latency.

- Exploratory Hypothesis 1: Improvement in sleep onset latency following melatonin treatment will be independent of baseline endogenous melatonin levels.

Linear regression model and/or logistic regression model will be used to evaluate the association between serum melatonin and improvement in sleep.

Exploratory Objective: Explore the association between sleep quality and health-related quality of life and distress.

- Exploratory Hypothesis 3: Improved sleep quality will be associated with decreased psychological distress and enhanced quality of life.

Once again regression approaches, as discussed above, will be utilized to evaluate the association between sleep quality and health-related quality of life and psychological distress.

11.1 Anticipated Completion Dates

Anticipated Primary Completion Date:	[redacted]
Anticipated Study Completion Date:	[redacted]

11.2 Summary of Primary and Secondary Objectives

Primary and Secondary Summary of Objectives

Objective #	Objective Type	Analysis #	Resp Party	Stat	Safety	Analysis Measure	Analysis Title	Data Collection Time Frame	# of Participants
1.1	P	1	TB	KS	N	Patient Neurocognition	Compare neurocognitive function by treatment group	Baseline 6 month	232
2.1	S	1	TB	KS	N	Patient Sleep onset latency	Compare sleep onset latency by treatment group	Baseline 3 month 6 month	226
2.2	S	1	TB	KS	N	Patient Neurocognition and Sleep onset latency	Evaluate impact of sleep on neurocognitive function	Baseline 6 month	131
3.1	E	1	TB	KS	N	Patient Melatonin	Evaluate endogenous melatonin levels	Baseline 6 month	395
3.2	E	1	TB	KS	N	Patient Melatonin, Neurocognition Sleep onset latency	Evaluate association between endogenous melatonin and sleep	Baseline 6 month	395

12.0 OBTAINING INFORMED CONSENT

Potentially eligible study participants will be mailed a letter to introduce the study and inform him or her of their potential eligibility. The letter will state that a study team member will be contacting them in approximately two weeks to discuss the study, answer questions they may have, and see if they are interested in participating. The letter will include a toll free number that participants can call sooner to discuss the study or if they would like to decline participation. A study-specific pre-screening form will be included with the mailing for their review. This form will ask two questions about his or her sleep habits and questions relevant to the exclusion criteria for the study. Approximately two weeks after the letter is mailed, a research team member will contact each eligible participant to discuss the study, ask if they have any questions and to see if they are interested in participating. The formal informed consent will take place at SJCRH when the participant comes in for their SJLIFE and screening measures visit. A research team member will explain the research study; the measures involved in the study, and review the potential risks and benefits. The participant will have time to read the consent and have all questions answered by the study team member. Upon agreeing to participate, the consent form and a Health Insurance Portability and Accountability ACT (HIPAA) compliance form will be signed by the research participant and the principal investigator or designee.

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APPENDICES

Appendix I: Schedule of Evaluations

	Eligibility	Baseline	On-Study			End
Evaluation	**Pre-Screen**	**Study Entry**	**Within 7–10 days of baseline visit**	**Monthly (±10 days)**	**3 months (± 1 week)**	**6 months (± 28 days)**
Inclusion/Exclusion criteria questions	X[1]					
Sleep-related questions		**X**				
Informed consent		X				
HIPAA		X				
Standardized Sleep Measures		X			X[3]	X[3]
Neurocognitive Assessment Measures		X[2]				X
Correlative Psychosocial Measures		X[2]				X[3]
Pregnancy test		X[2]				
History and Medical Provider visit		X[2]				X
Actigraphy			X[3]		X[3]	X[3]
Daily Sleep Diary			X[3]		X[3]	X[3]
Side effect monitoring		X	X[4]			
Study drug adherence (Pill Count)				X		

[1]Mailed with introductory letter
[2]Completed as part of SJLIFE protocol
[3]Actigraph and sleep measures mailed to participant's home for completion. Standardized sleep measures completed at home at 3 months and 6 months. Correlative psychosocial measures completed at home at 6 months.
[4]Initially completed after 7-10 days on study medication; then bi-weekly for remainder of study.

APPENDIX II: RESEARCH TESTS

Research Test	Time Point	
Standardized Sleep Measures	Baseline 3 month 6 month	Required
Neurocognitive Assessment Measures[1]	Baseline 6 month	Required
Correlative Psychosocial Measures[1]	Baseline 6 month	Required
Actigraphy	Baseline 90 day 6 month	Required
Daily Sleep Diary	Baseline 90 day 6 month	Required
Melatonin – blood	Baseline 6 month	Required

[1]Baseline measures completed as part of SJLIFE Study

Appendix III: Sleep Measures
[NOTE: This appendix contains copyrighted material and has been redacted.]

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Appendix IV - Neurocognitive Functioning Measures
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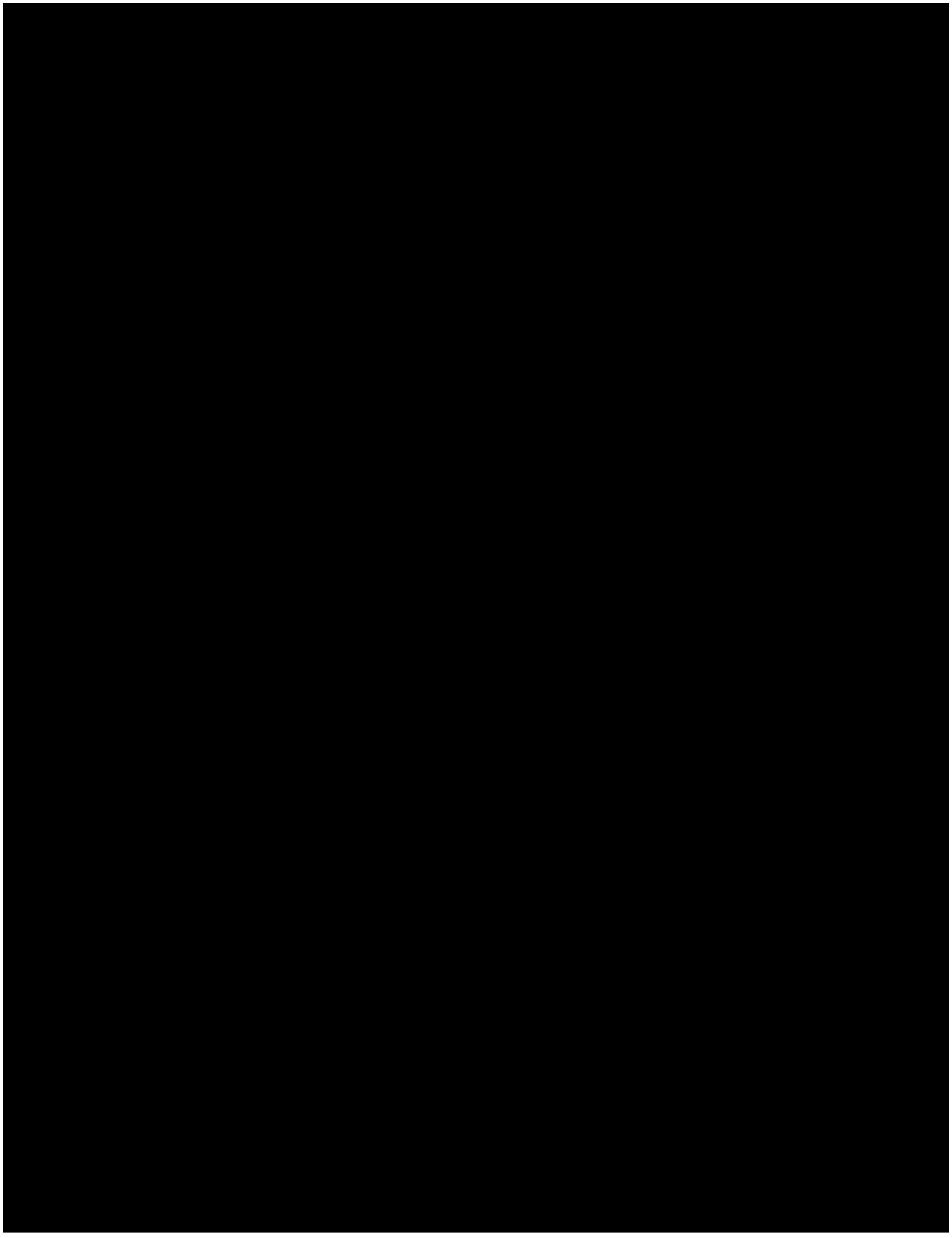

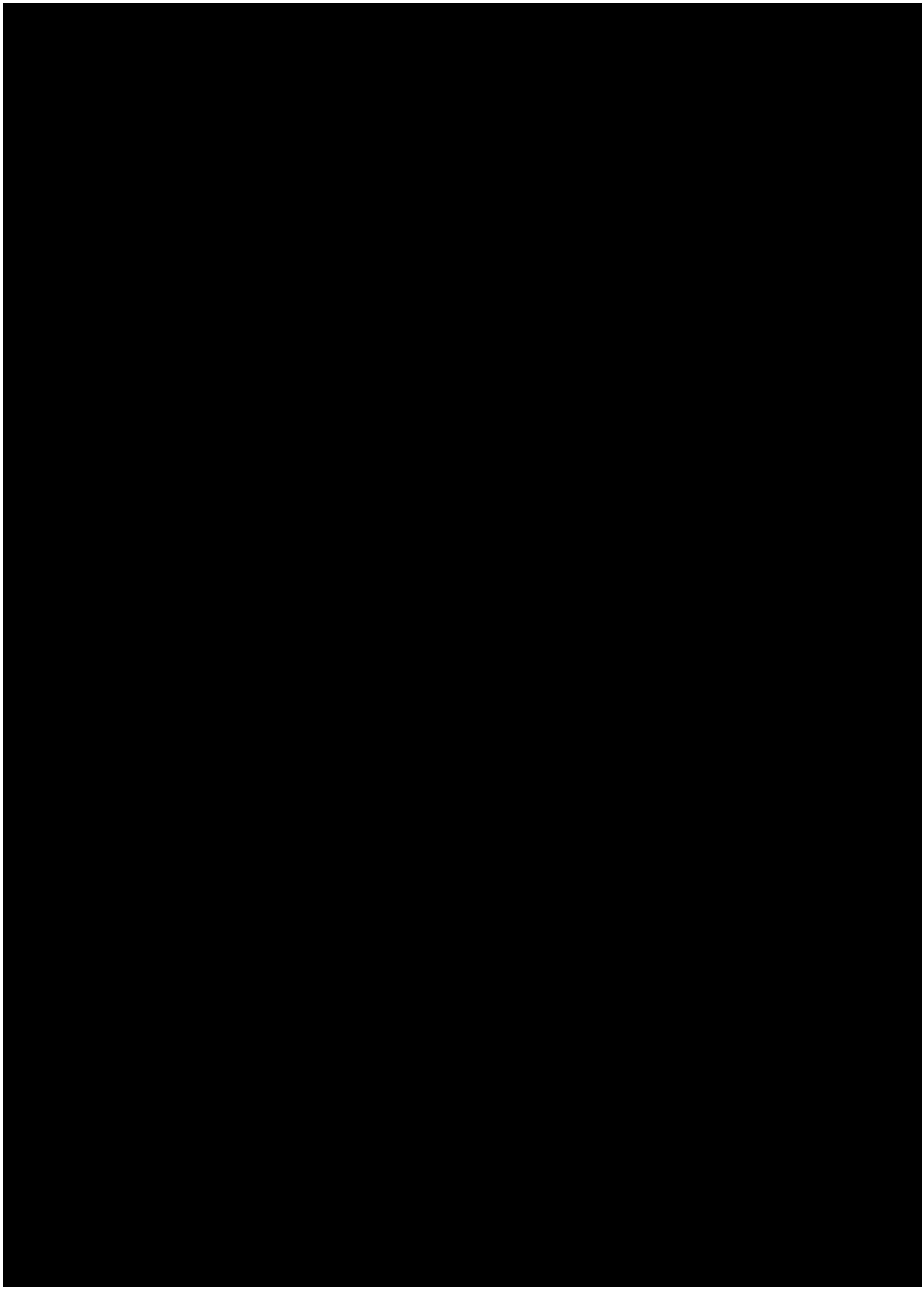

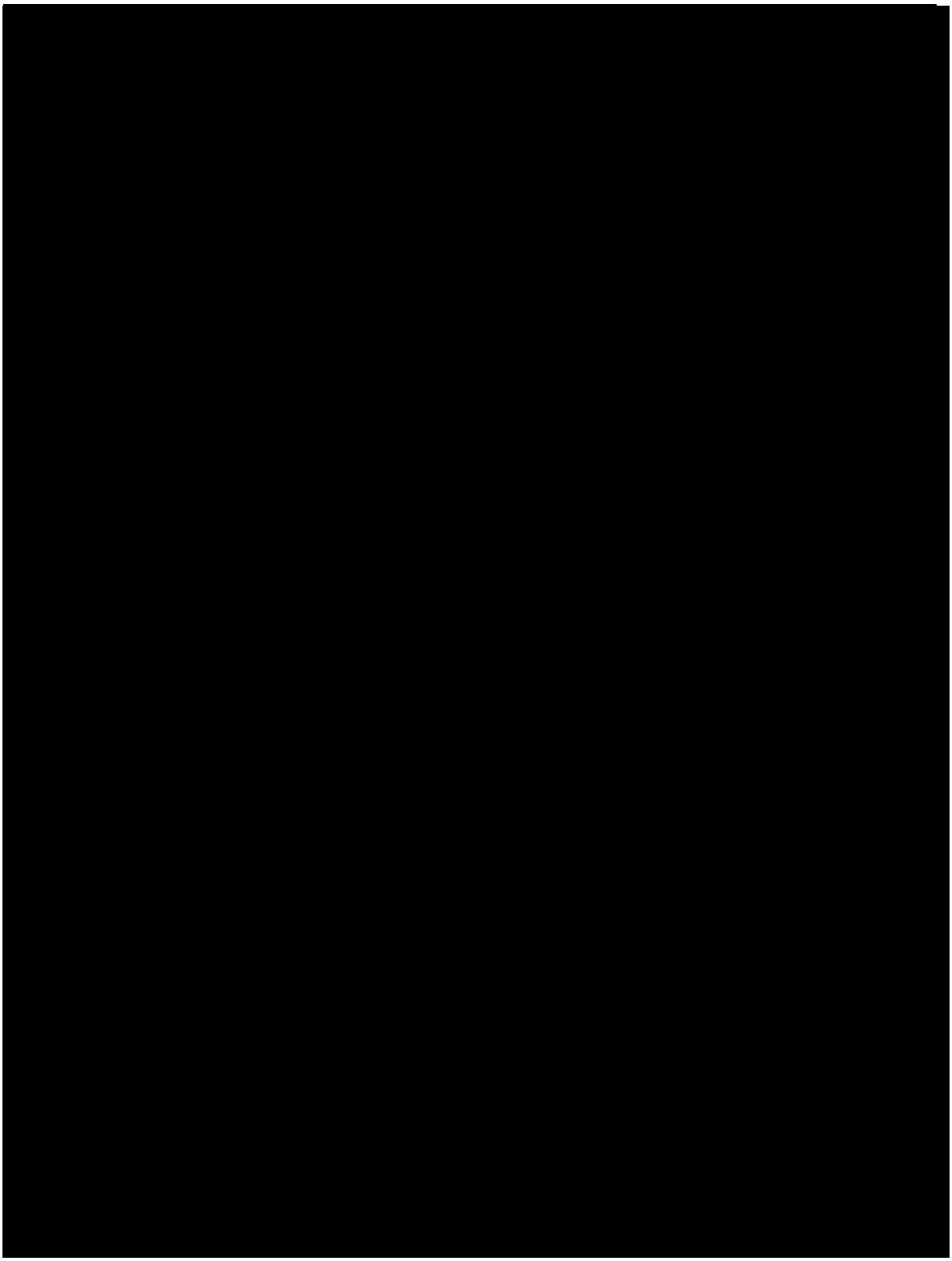

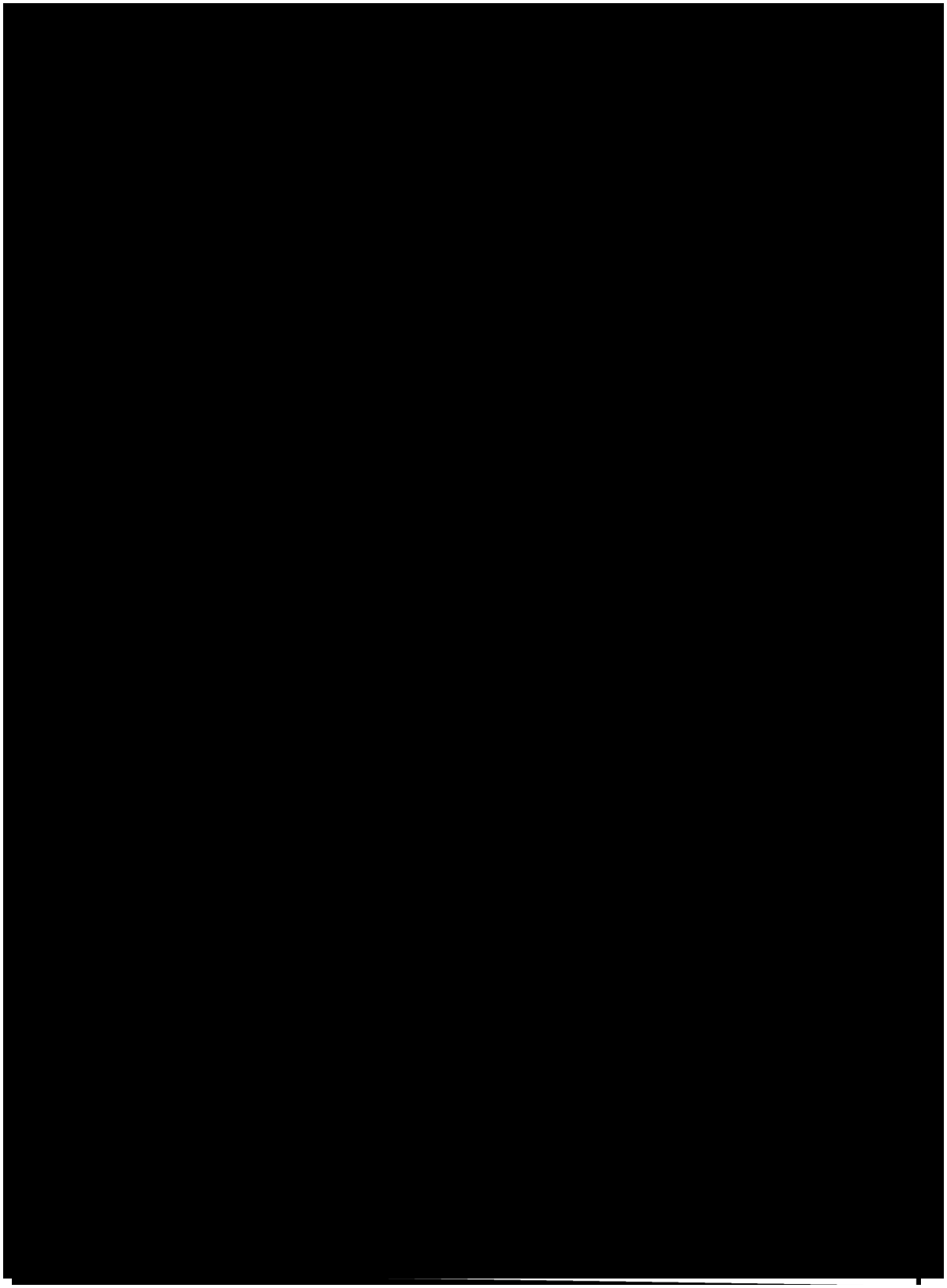

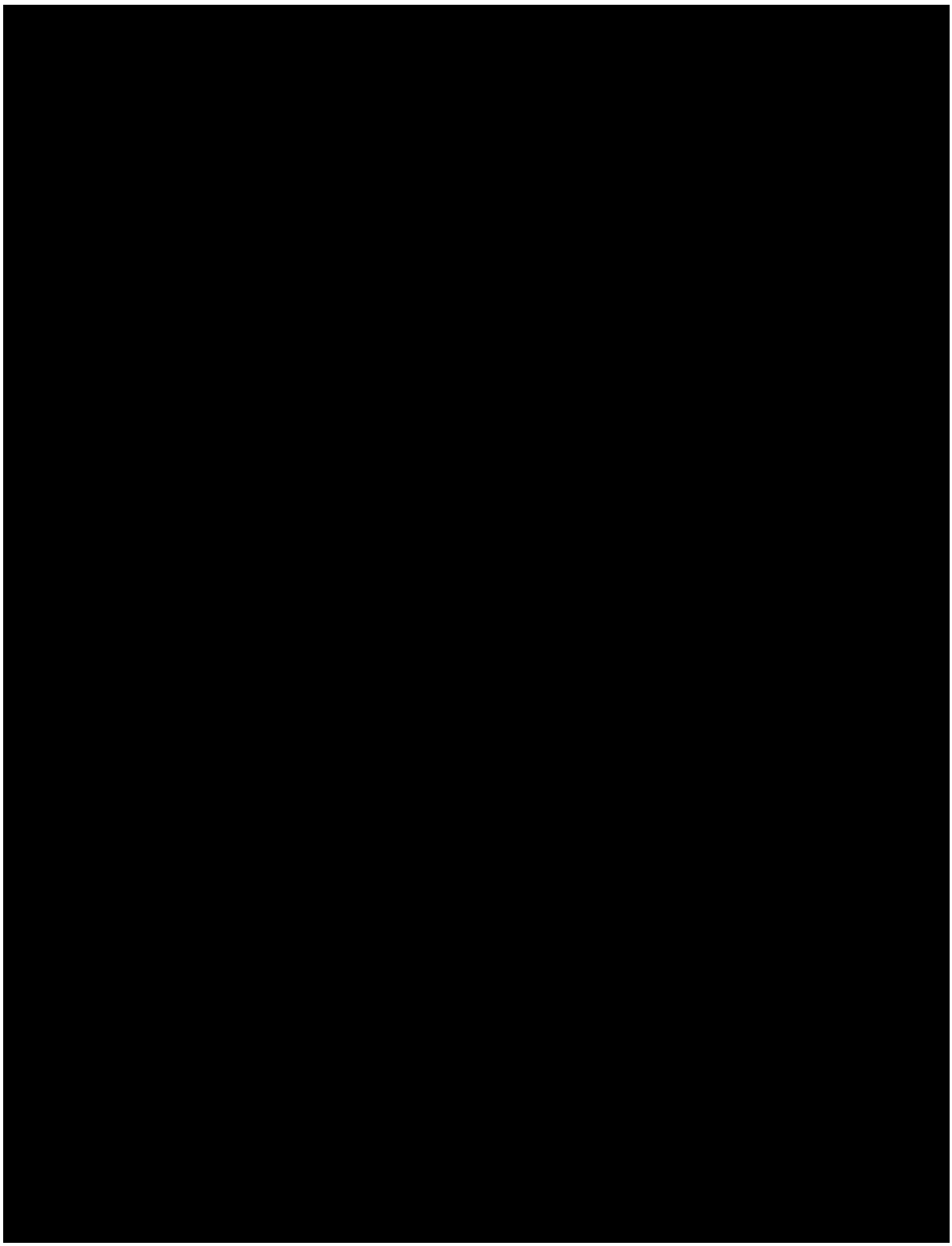

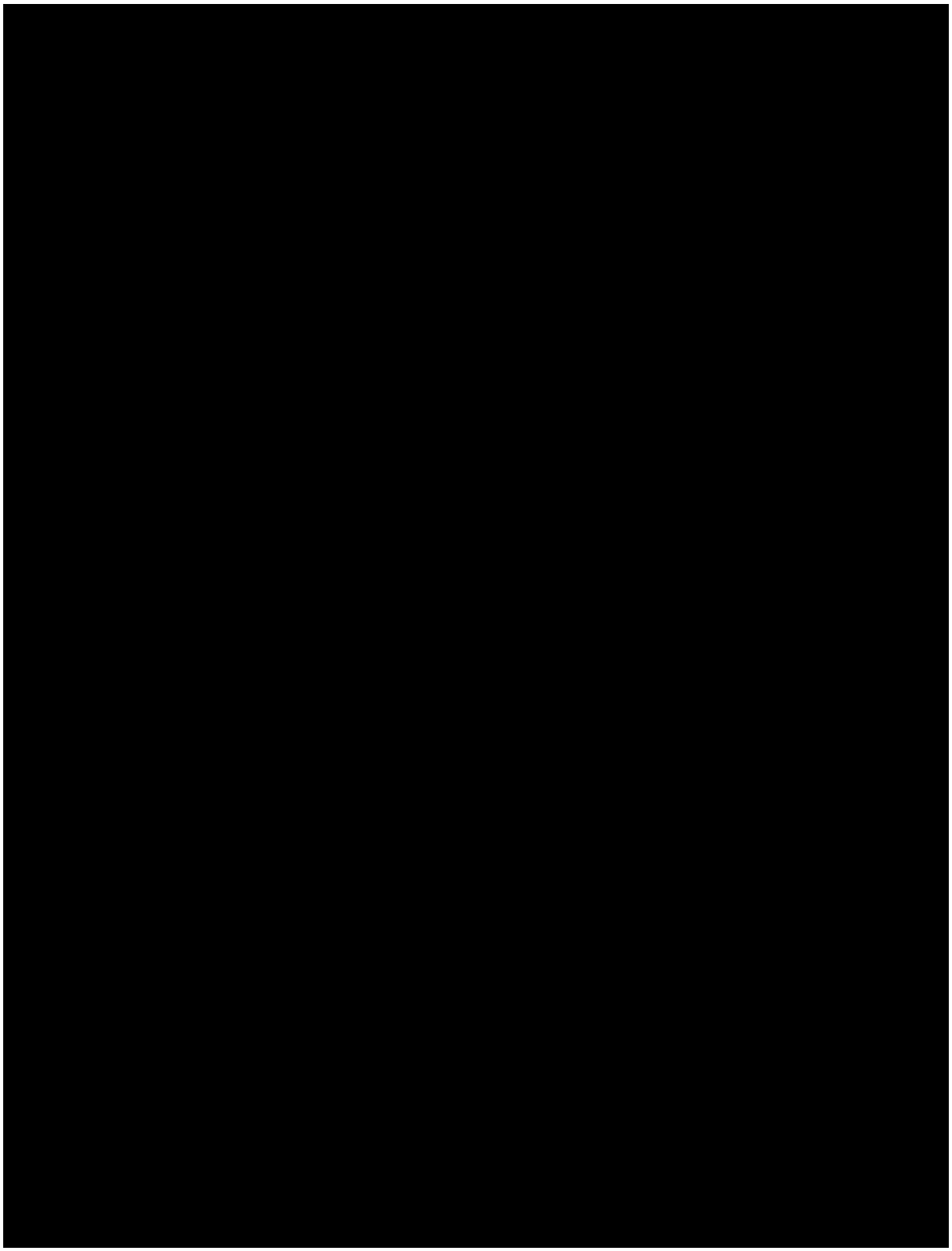

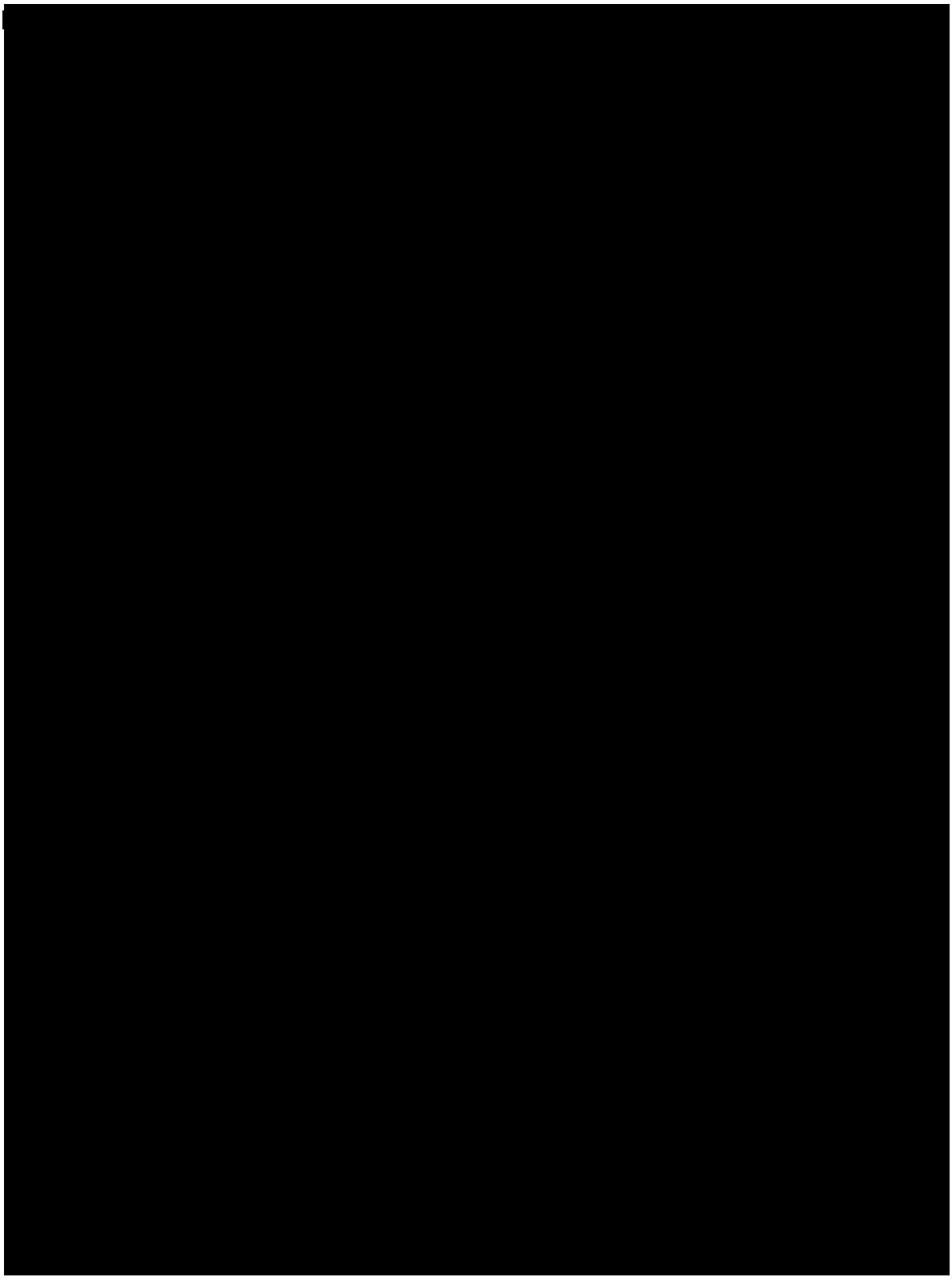

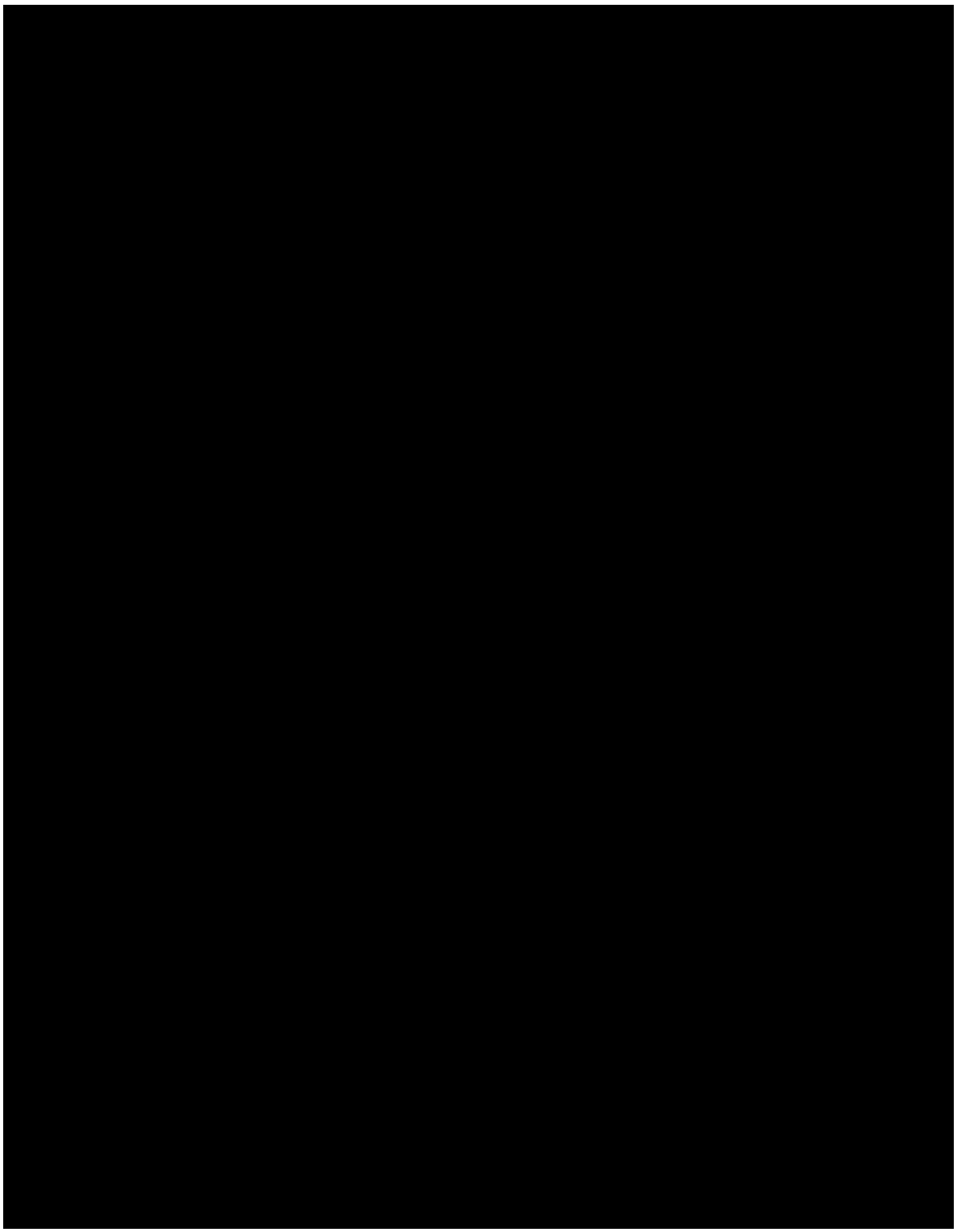

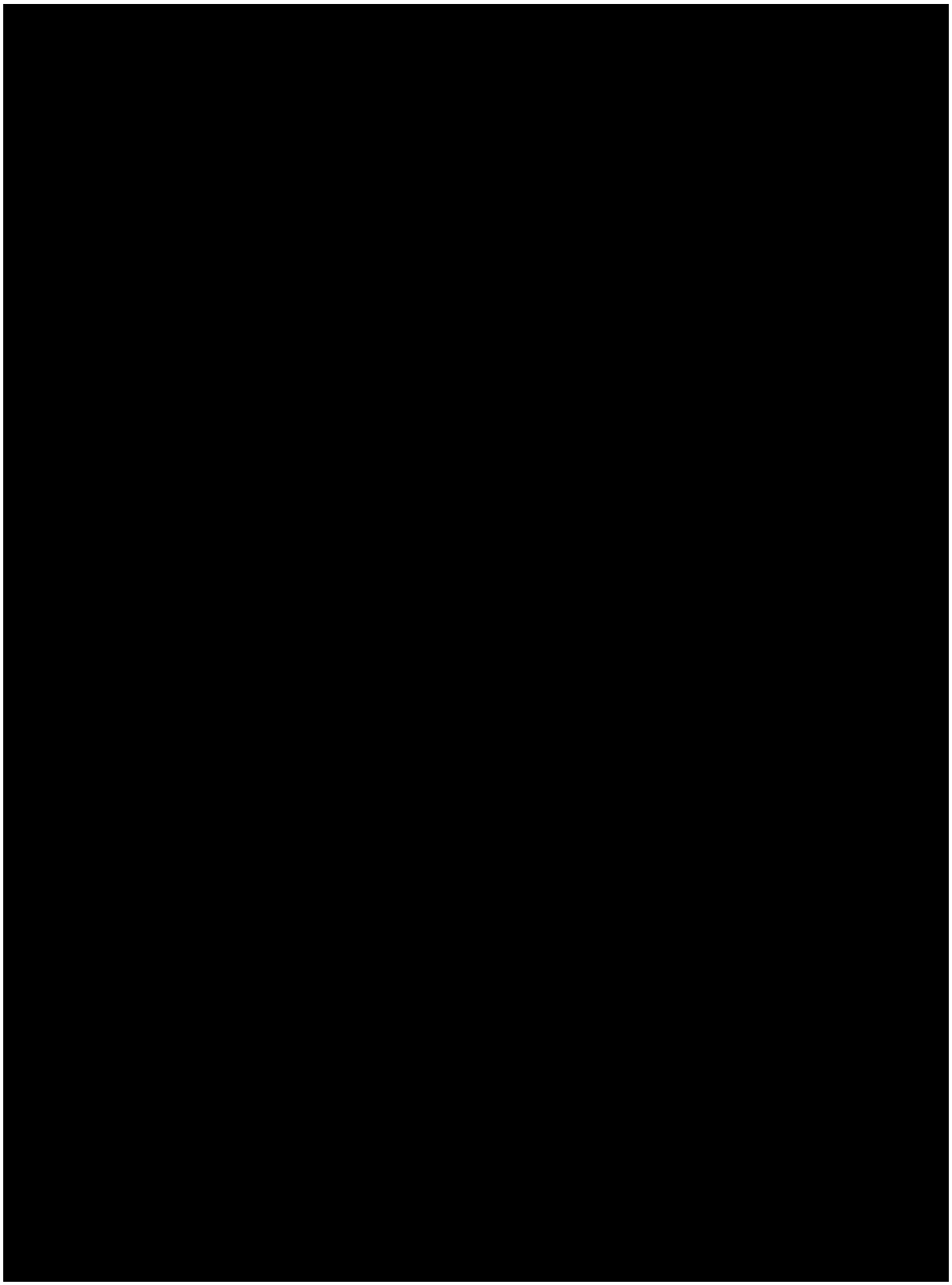

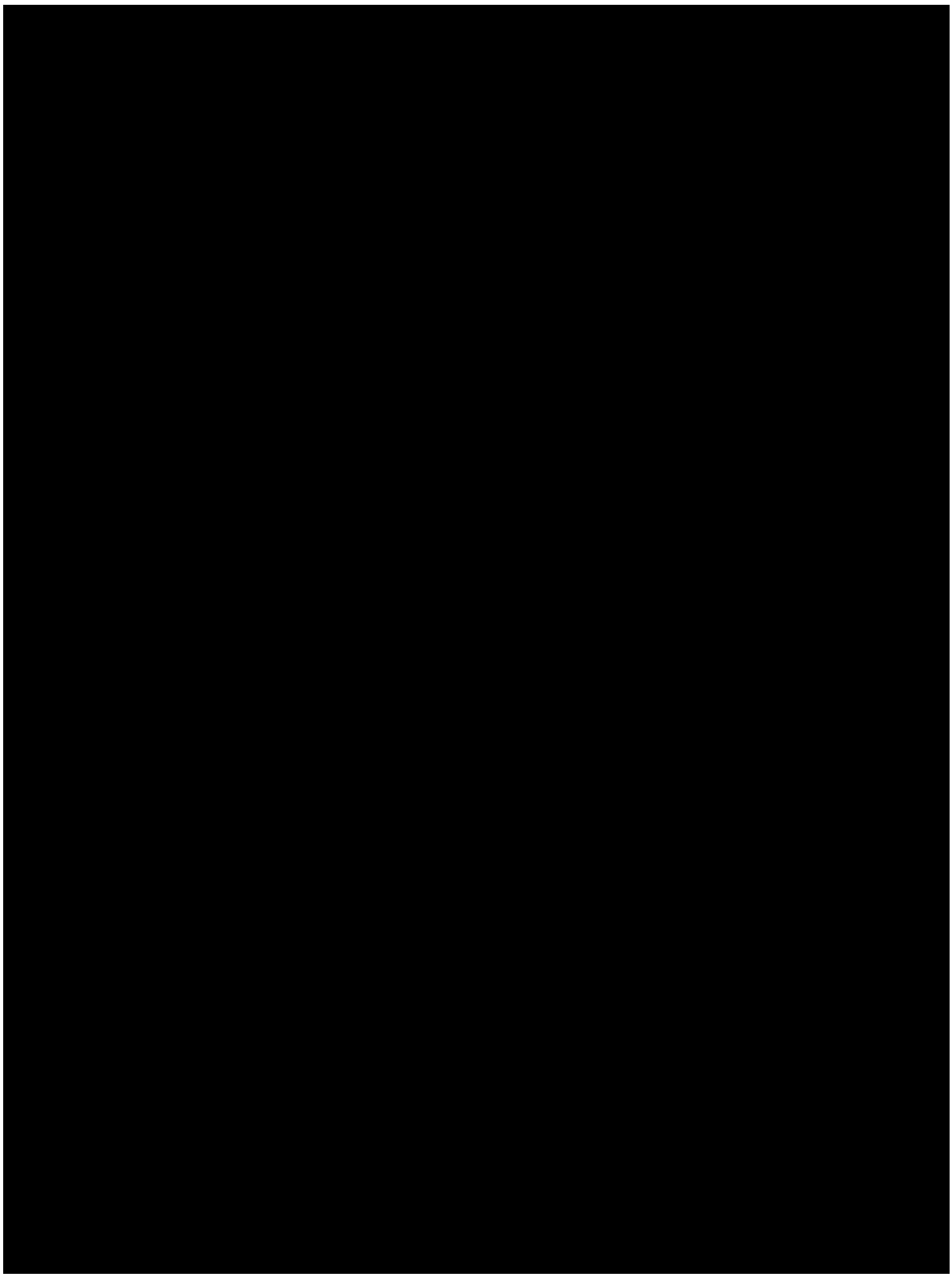

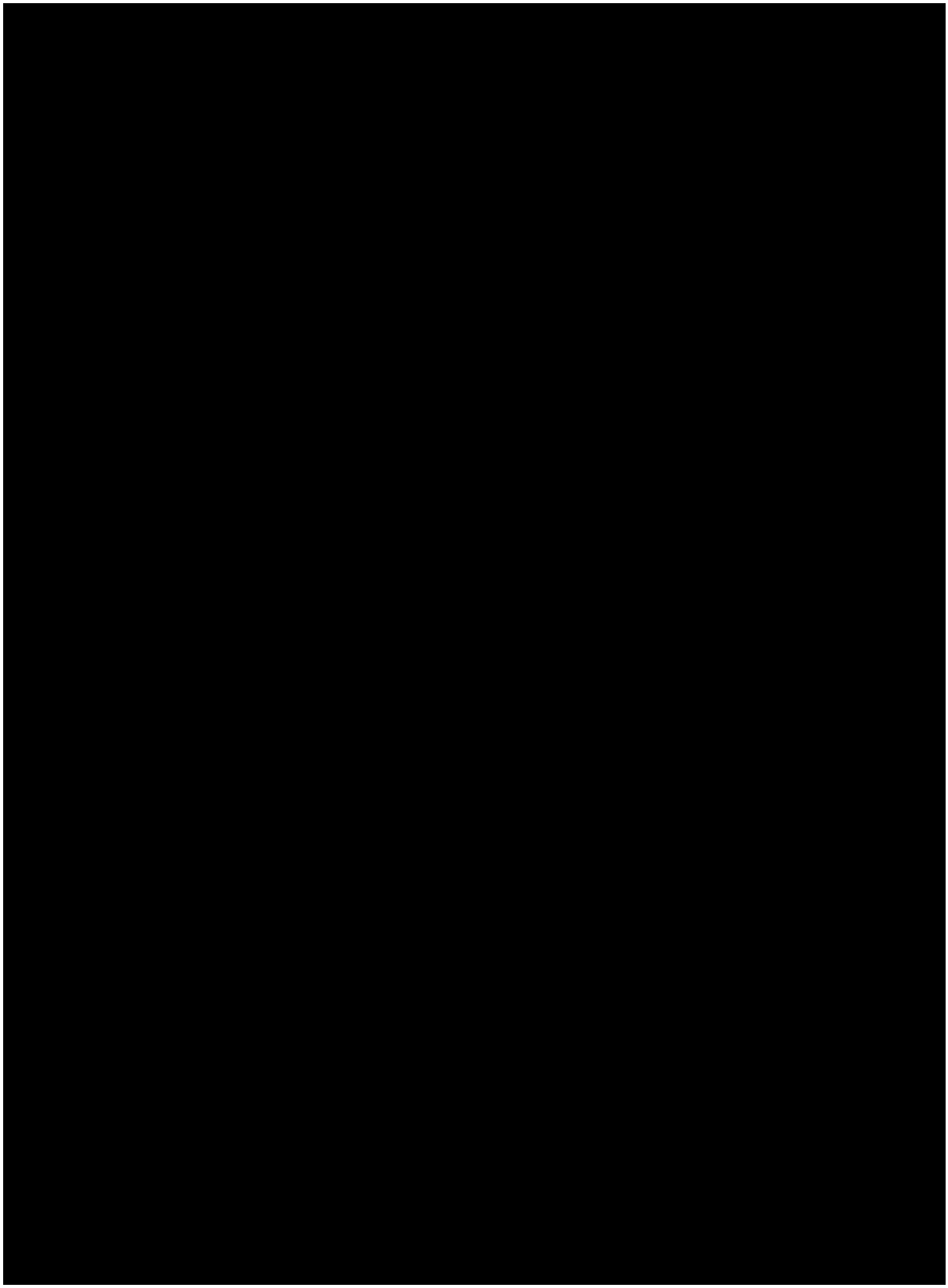

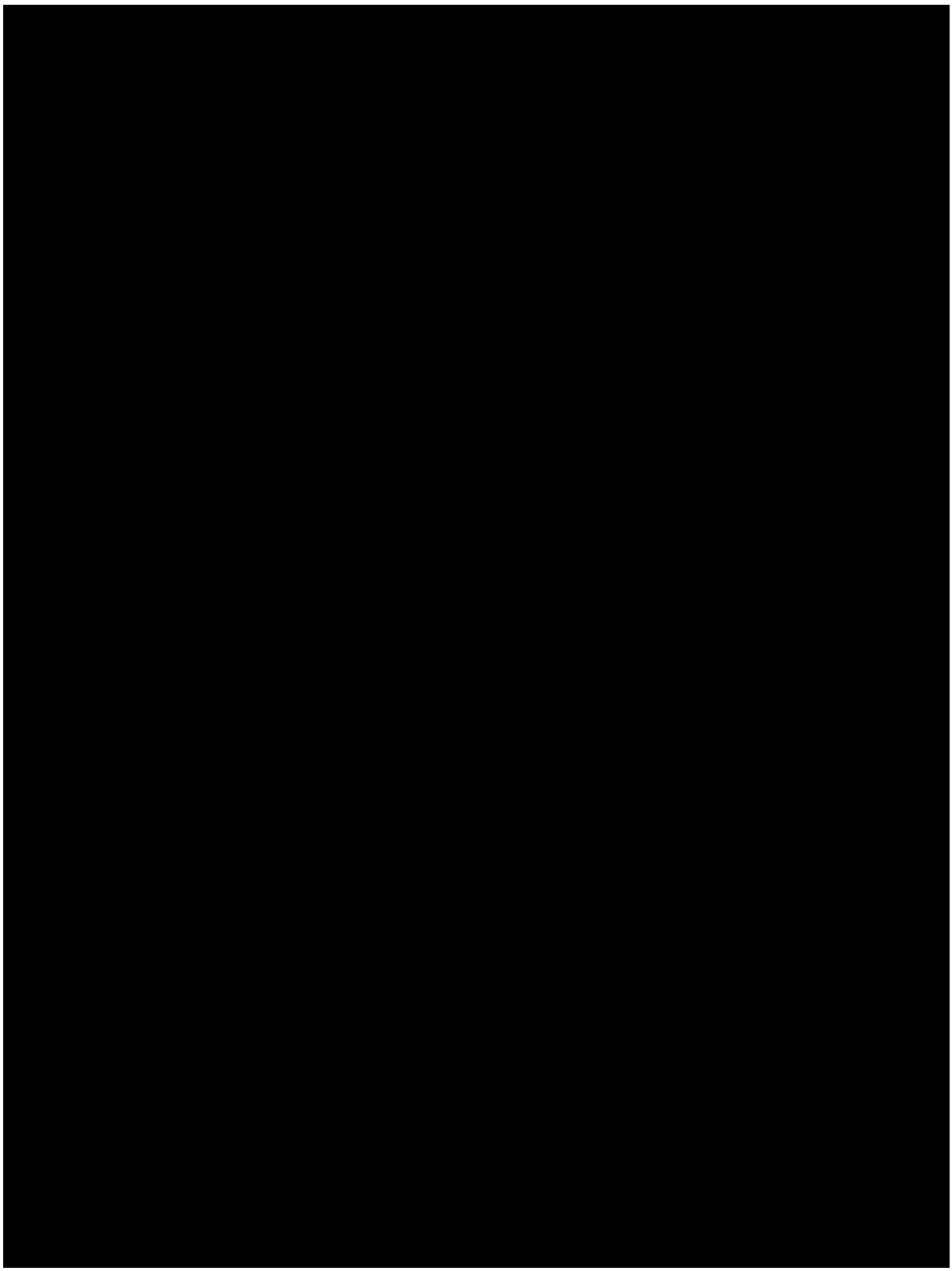

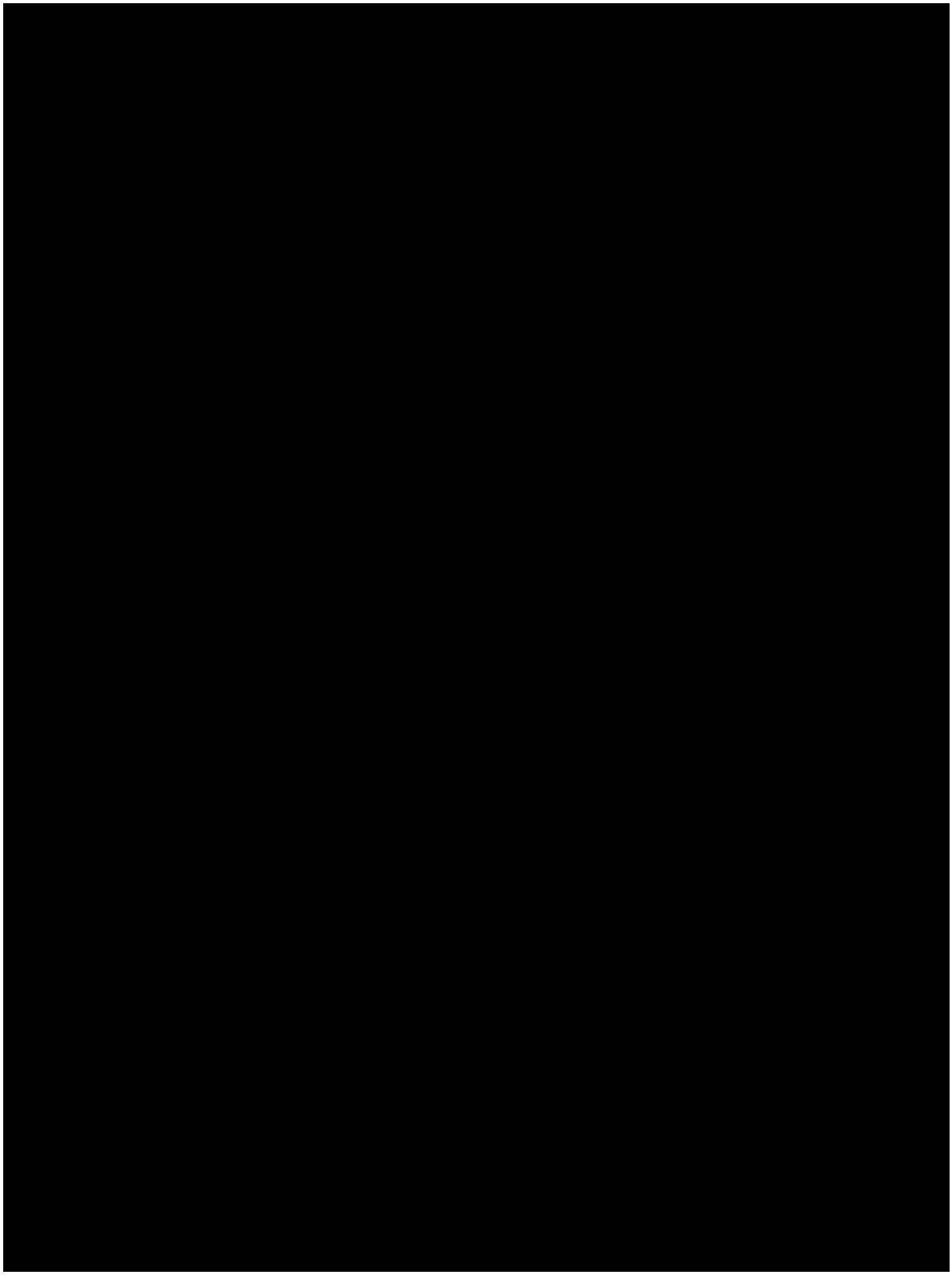

Appendix V – Correlative Psychosocial Measures
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