A PRELIMINARY INVESTIGATION OF THE

BIOLOGICAL EFFECTS OF SECONDHAND SMOKE

EXPOSURE IN YOUTH DIAGNOSED WITH SICKLE CELL

DISEASE

By

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A PRELIMINARY INVESTIGATION OF THE BIOLOGICAL EFFECTS OF SECONDHAND SMOKE EXPOSURE IN YOUTH DIAGNOSED WITH SICKLE CELL DISEASE

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Title of Study: A PRELIMINARY INVESTIGATION OF THE BIOLOGICAL EFFECTS OF SECONDHAND SMOKE EXPOSURE IN YOUTH DIAGNOSED WITH SICKLE CELL DISESAE

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Abstract: Children's exposure to secondhand smoke (SHSe) can lead to significant health consequences, including respiratory illness, asthma, and impaired pulmonary function. For children diagnosed with a chronic illness, such as Sickle Cell Disease, SHSe can compound an already difficult problem. Among children with SCD, SHSe causes displacement of oxygen from hemoglobin, injury to vascular endothelium, and abnormal activation of platelets, each of which increases the prevalence of sickle cell crises. Sickle cell crises are painful episodes that occur when sickle-shaped red blood cells block blood vessels from providing oxygen to the bodies organs and tissues, resulting in severe pain. To date, no prevalence data or objective measurement of SHSe exists to document rates of SHSe in children diagnosed with SCD. Therefore, the overall aim of the current study is to determine to what extent children diagnosed with SCD are exposed to SHSe. We recruited two groups of families, those who smoke and have children exposed to SHSe versus nonexposed children. Each child from both the exposed and nonexposed group provided a sample of saliva to examine cotinine levels (i.e., object measurement of SHSe). In addition, a medical chart review will provide a preliminary examination of any differences in health care utilization for each group. Thirty-one youth and their primary caregiver were recruited to participate in the present study. Due to equipment failure, four cotinine samples were unable to be processed. The remaining 27 cotinine samples indicated that regardless of parent-reported SHSe, 24 of the 27 children were exposed to SHS. Because 24 of the 27 children were exposed to some level of SHSe, no inferential statistics were utilized. Descriptive statistics regarding tobacco use, perceived harm, and frequency of sickle cell crises, emergency department utilizations, and acute chest syndromes are reported. The findings in this dissertation, particularly those identifying the frequency of individuals exposed to SHSe, indicate a need to assess for SHSe in this population in the future. Future research should aim to better understand and, ultimately, reduce the factors that might increase exposure to SHSe in youth with SCD, and therefore decrease potential harm associated with SHSe.

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# RESEARCH STRATIGY

## Specific Aims

Children's exposure to secondhand smoke (SHSe) can lead to significant health consequences, including respiratory illness, asthma, and impaired pulmonary function (Chen, Burton, Baker, Mastey, & Mannino, 2010; Health & Services, 2006; Jinot & Bayard, 1992; Marano, Schober, Brody, & Zhang, 2009; Needs, 2009; Pickett, Schober, Brody, Curtin, & Giovino, 2006; Schwab, McDermott, & Spengler, 1992). For children diagnosed with a chronic illness, such as Sickle Cell Disease, SHSe can compound an already difficult problem.

Children with SCD are an underserved and understudied population with high risk for morbidity and mortality (CDC, 2012). Literature has shown that children with SCD incurred medical expenditures that were $9369 and $13,469 higher than those of children without SCD enrolled in Medicaid and private insurance, respectively (Amendah, Mvundura, Kavanagh, Sprinz, & Grosse, 2010), with expenditures of children with SCD being 6 and 11 times higher than children without SCD (Amendah et al, 2010). In 2005, SCD-attributable medical expenditures in children were conservatively and approximately estimated at $335 million (Amendah et al., 2010). Among children with SCD, SHSe causes displacement of oxygen from hemoglobin (Davis, Shelton, & Watanabe, 1989; West et al., 2003), injury to vascular endothelium, and abnormal

activation of platelets (Celermajer et al., 1996; Davis et al., 1989), each of which increases the prevalence of sickle cell crises. Sickle cell crises are painful episodes that occurs when sickle-shaped red blood cells block blood vessels from providing oxygen to the bodies organs and tissues, resulting in severe pain (West et al., 2003).

To date, ***no prevalence data or objective measurement of SHSe exists to document rates of SHSe in children diagnosed with SCD***. Establishing prevalence rates as well as utilization of health care services and corresponding negative health events is an important first step to estimate the scale of the problem. In addition, such research will help identify the potential positive individual and public health impact SHSe intervention efforts may have. Therefore, the overall aim of the current study was to determine to what extent children diagnosed with SCD are exposed to SHSe. We recruited two groups of families, those who smoke and have children exposed to SHSe versus nonexposed children. Each child from both the exposed and nonexposed group provided a sample of saliva to examine cotinine levels (i.e., object measurement of SHSe). In addition, a medical chart review will provide a preliminary examination of any differences in health care utilization for each group. To our knowledge, this was the first attempt to determine the prevalence rates for SHSe in children with SCD as well as use objective measurement of SHSe (Cohen et al., 2013; Glassberg, Wang, Cohen, Richardson, & DeBaun, 2012; West et al., 2003).

**Aim 1:** To determine the prevalence of secondhand smoke exposure in children diagnosed with SCD via self-report, parental report, and objective measurement (i.e., salivary cotinine).

Hypothesis 1.1: Based on previous non-representative studies, it is expected that approximately 30 – 40% of sample will be exposed to SHSe, which would be consistent with the three studies in the literature to date.

**Aim 2:** To examine the relationship between levels of salivary cotinine and utilization of health care services (i.e., Emergency Department Visits) and negative health events (e.g., acute chest syndrome, sickle cell crises, pulmonary morbidity).

Hypothesis 2.1: Youth who have cotinine values > .15 ng/mL, an indication of significant SHSe (Salimetrics, 2014; Benowitz, et al., 2009), will demonstrate higher levels of utilization of health care services (i.e., Emergency Department Visits) and negative health events (e.g., acute chest syndrome, sickle cell crises, pulmonary morbidity) compared to those with no exposure.

## Significance

**The Risks of Secondhand Smoke Exposure (SHSe) to Children**: Secondhand tobacco smoke contains at least 250 chemicals that are known to be toxic or carcinogenic. It has been identified as a known human (Class A) carcinogen that presents a serious public health risk (Chen, Burton, Baker, Mastey, & Mannino, 2010; Jinot & Bayard, 1992). Children experience the highest amount of SHSe of any age group, with more than 50% of children in the U.S. exposed to secondhand smoke (Control & Prevention, 2010; Health & Services, 2006). Children between the ages of 3 and 11-years-old have the highest levels of SHSe, likely because they spend a majority of their time in close proximity to a caregiver who smokes (Gergen, Fowler, Maurer, Davis, & Overpeck, 1998; Health & Services, 2006; Pirkle, Bernert, Caudill, Sosnoff, & Pechacek, 2006; Schwab, McDermott, & Spengler, 1992). Nationally, more than 18% of youth ages 0 to 17-year-olds live with a smoker (approximately 12,480 children) and surprisingly, 20% (approximately 3,463) of children ages 0 – 17 who have a special health care need live with a smoker (Needs, 2009). In Oklahoma, it is estimated that 35% of healthy children live with a smoker, and 42% of children who have been identified as having a special

health care need live with a smoker (Needs, 2009). Furthermore, despite smoking bans in public spaces, children living with smokers have not experienced any reduction in their exposure as evidenced by mean serum cotinine levels (Asplund, 2003; Marano, Schober, Brody, & Zhang, 2009; Pickett, Schober, Brody, Curtin, & Giovino, 2006; Pirkle et al., 2006). Although SHSe in the home is often problematic, SHSe in the car is also a substantial concern (Park et al., 1997). Despite the use of forced ventilation or open car windows, children are still exposed to dangerous levels of SHSe (Semple et al., 2012).

SHSe decreases lung growth and increases the incidence of sudden infant death, respiratory illness, middle-ear disease, wheezing, and asthma (Health & Services, 2006; Mannino, Moorman, Kingsley, Rose, & Repace, 2001). For young children, it is estimated that 150,000 to 300,000 new cases of pneumonia and bronchitis and 7,500 to 15,000 hospitalizations occur each year due directly to SHSe (Jinot & Bayard, 1992). SHSe is also associated with lower cognitive test scores and increased school absence (Mannino et al., 2001; Yolton, Dietrich, Auinger, Lanphear, & Hornung, 2005). ***Identifying and assessing the extent to which children with SCD are exposed to SHSe is critical to decreasing negative health and functional impairment consequences.***

**The Risks of Secondhand Smoke Exposure (SHSe) to Medically At-Risk Children:**

Although all children, whether medically at-risk or not, should be protected from SHSe, there are a number of issues that distinguish clinical and research efforts with at-risk populations from those children who are not at risk because of their medical status. The life threatening nature of some childhood diseases, such as Sickle Cell Disease (SCD), and their often invasive and intensive treatment regimens present a demanding challenge for parents of medically compromised children. However, limited data are available regarding exposure rates among medically at-risk children (Needs, 2009*)*. More disturbing, children with chronic medical conditions may be physically unable to remove

themselves from the smoke to avoid exposure, and thus more likely to spend a significant proportion of their time indoors with their parents or caregiver due to disease restrictions, and thereby increase their risk for SHSe.

***To date, only three studies have examined SHSe exposure in SCD*** (Cohen et al., 2013; Glassberg, Wang, Cohen, Richardson, & DeBaun, 2012; West et al., 2003). West et al. (2003) found that 42% of children with SCD were exposed to SHS and estimated that SHSe increased the risk of a sickle cell crisis by as much as 90%. Patients were considered exposed if either their parent or primary caretaker identified anyone living in the home that smoked any tobacco products in the preceding two years (West et al., 2003). The second study examined potential risk factors associated with increased emergency department (ED) use in children with SCD (Glassberg et al., 2012). Of the 985 children recruited from the United States, Canada, England, and France, study results found that SHSe in the home was associated with 73% more ED visits for acute chest syndrome (Glassberg et al., 2012). Lastly, the third study examined pulmonary morbidity due to SHSe in children ages 4 to 20-years-old with sickle cell anemia (SCA) from three sites, including Missouri, Ohio, and London, England (Cohen et al., 2013). They found that roughly 108 of the 245 children (44%) self-reported a history of exposure to SHSe and 71 of the 245 (29%) reported current exposure to SHS (Cohen et al., 2013). Children who reported current and infant SHSe exposure had poorer forced expiratory flow (i.e., the speed of air coming out of the lungs during the middle portion of a forced expiration), midexpiratory phase/FVC ratio (i.e., the ratio of speed of air and force of air coming from the lungs), increased airway obstruction and increased bronchodilator responsiveness (i.e., phenotypic characteristic of chronic obstructive pulmonary disease;(Cohen et al., 2013). *Importantly, none of these studies involved an objective, physiological measurement of smoke exposure, which significantly limits our knowledge of the true extent of exposure to smoke.* While each of these studies makes a significant contribution to the extant

literature examining the impact current and previous SHSe has on children with SCD and SCA, ***our study is the first to objectively measure SHSe in the clinic setting at point of care.***

**Many Smokers are Uninterested, Unwilling, or Unable to Quit:**

Nearly 50% of smokers make a quit attempt each year, but less than 5% remain abstinent for 3-12 months after quitting (18 – 23). Although smokers double their chances of long-term abstinence with psychological (Lancaster & Stead, 2005; Stead & Lancaster, 2002) and pharmacological (Hughes, Stead, & Lancaster, 2005; Stead, Perera, Bullen, Mant, & Lancaster, 2008) interventions, few smokers utilize these methods (Fiore, 2000). As a result, the prevalence of cigarette smoking among adults in the U.S. has only slightly decreased between 2005 to 2010 (20.9% vs. 19.3%, respectively) and remains disturbingly high (Control & Prevention, 2011). Even among caregivers of children with asthma, a medically at-risk population that are generally more motivated to quit smoking, the percent who were interested in quitting in the next month was only 27% (Farber et al., 2008), representing a minority of caregivers. Moreover, approximately 39% of caregivers were not interested in quitting smoking at all (Farber et al., 2008). ***This is a critical concern due to the impact SHSe has on children with SCD and the difficulty caregivers face when attempting to quit smoking. Understanding the needs of these families to reduce SHSe is key to providing appropriate resources to families in need***.

**Innovation.**

Currently, there is limited research examining biomarkers of SHSe in children who are medically at-risk (Tyc et al., 2013). To our knowledge, with regard to SHSe biomarkers in SCD, no research has examined the prevalence rates of SHSe in a SCD population or the potential dose-response relationship that SHSe may have on health

outcomes such as increased ED utilization and other medical complications (e.g., acute chest syndrome, sickle cell pain crises) in children diagnosed with SCD.

***Impact on science and clinical practice***: Our study is the first to: 1) objectively examine the prevalence of SHSe in children with SCD and 2) identify a preliminary dose-response relationship between SHSe and health outcomes (e.g., ED visits, sickle pain crises, acute chest syndrome). Our study is the foundation in identifying the potential need to provide interventions to children exposed to SHSe with SCD.

**Approach.**

**Overview of Project**: We conducted a prevalence survey of all eligible parents of children ages 1 month-17-years-old diagnosed with SCD at the University of Oklahoma Health Sciences Center, a tertiary care center which provides care to many underserved urban and rural populations. Using a battery of questionnaires given to both caregivers and children, we assessed health care behaviors and status, health care utilization, and smoking history. We collected cotinine measurements from each child to examine smoking status and SHSe exposure. Samples were processed using the Salimetrics (College Station, PA) cotinine enzymatic immunoassay kits, per each standard kit protocol. Briefly, samples and standards are loaded onto a 96-well plate then incubated with cotinine-horseradish peroxidase conjugate and rabbit anti-cotinine antibodies at 37C for 1.5 hours with shaking. After incubation, plates are washed then treated with tetramethylbenzidine substrate before mixing for 5 minutes then incubating in darkness at RT for 25 minutes. The reaction is then stopped with 2M sulfuric acid for 3 minutes before reading absorbance at 450nm. Data are corrected at 630nm. Results are fit using a 4-parameter logistic regression.

Samples taken at the Oklahoma University Health Sciences Center (OUHSC) were processed immediately or stored in sterile cryovials for no longer than 48 hours

before being frozen at -20C for short term storage (<30 days) or at -80C for long-term (>30 days) storage. A chart review ranging from 2 years prior- to 1 year after the baseline collection date was conducted to document previous and future health events.

*Previous research experience*

Alayna Tackett, MS (PI) has been a primary research coordinator for five NIH funded clinical research trials (1R01DK092977-01; *1R01CA157460-01A; NCI 1R21CA164521-01A1; 1R01NR01424801A1; 5R01HD07457902)* examining adherence, psychosocial interventions, and health disparities in children with solid organ and hematopoietic stem cell transplantation, disorders of sexual development, and pediatric cancer. Ms. Tackett also assisted with Dr. Wagener's (CO-I) R21 (5R21CA16452102) examining the efficacy of using a smoke-free, nicotine-containing product (medicinal nicotine lozenge vs. dissolvable tobacco lozenge) as a means of reducing the SHSe of healthy children among a sample of parents who smoked and were uninterested in quitting. Her background and training in research design along with the support of the proposed research team provides the knowledge and skill needed to succeed in the implementation of this project.

**Study Procedures: Recruitment**

We recruited all eligible participants who have children diagnosed with SCD through the Jimmy Everest Cancer (JEC) Center Sickle Cell Clinic at the Oklahoma University Health Sciences Center as part of a regularly scheduled clinic visit. This recruitment strategy was consistent with previous studies conducted by Drs. Wagener (CO-I) and Mullins (CO-I).

**Inclusion/Exclusion Criteria**

In order to be included in the study, participants must: 1) be the primary

caregiver (defined as a person who spends the most time with the child and spends a minimum of 4 hours per day in the presence of the child); 2) be the parent of a child between the ages of 1 month-17-years-old, and diagnosed with a form of SCD. If a caregiver had more one or more children between 1 month-17-years-old, we included the youngest as these children are typically exposed to more SHSe (e.g., Priest et al., 2008); 3) be fluent in English, 4) the child may not be on palliative care, and 5) have no major psychiatric impairment, including psychosis, and/or any current alcohol/drug abuse or dependence. Participants' eligibility was determined in person during Sickle Cell Clinic. As part of a regularly scheduled clinic visit, a research assistant approached eligible families to ask if they were interested in participating in a research study. If interested, the research assistant then completed the informed consent and child assent, administered questionnaires, and collected salivary samples.

**Participant Compensation**

Each dyad received $30 for participating in the one-time study visit and salivary collection.

**Measurements**

A trained research assistant administered all assessments and collections. Participants were compensated for completing these assessments.

**Variables Measured**

Caregivers (N =31; Mothers = 87.1%, Age M = 35.82, SD = 8.21) and their children (Male = 52.4%; Age M = 8.55, SD = 5.03) with sickle cell disease were asked to provide demographic information, smoking status, and complete biochemical verification of smoking

status via exhaled carbon monoxide (CO), using a piCO+ Smokerlyzer (Bedfont Scientific, 2007), with CO≤10 parts per millions (p.p.m.) indicating confirmed smoking cessation. No participants refused CO verification. All children (n= 31), regardless of self-reported tobacco exposure, were also asked to provide salivary samples to assess levels of secondhand smoke exposure via salivary cotinine analyses and were asked to complete a pulmonary function test using forced spirometry. All medical information and history of negative health events were obtained via medical chart review. Additional caregiver and child demographics are reported in Tables 1 and 2 in Appendix C.

The institutional review board at the hospital where the study was conducted approved this study and it was carried out in compliance with the American Psychological Association ethical guidelines. Participants were recruited from as part of a regularly scheduled sickle cell comprehensive clinic appointment in the pediatric hematology and oncology clinic in a large teaching hospital in the Midwest region of the United States. Eligible caregiver/child dyads were first identified through the hematology/oncology clinic patient database and medical eligibility was assessed through consultation with the attending physician. Participants' eligibility was determined in person during Sickle Cell Clinic.

As part of a regularly scheduled clinic visit, a research assistant approached eligible families to ask if they are interested in participating in a research study. If interested, the research assistant completed the informed consent and when appropriate, child assent, administered questionnaires, and collected salivary samples. Eligible caregivers (n = 35) were approached and 31 were consented (88%) to participate in a private location within the clinic. Reasons for declining to participate included too busy (n=2) and not interested (n=2). All caregivers self-identified as the legal guardian and this was confirmed by the medical team. Participants were given modest monetary compensation for study participation ($30).

**Child Variables**

To obtain an estimate of pulmonary functioning, children were asked to complete 5 trials of forced spirometry. Each child was given age-appropriate instruction and two practice attempts with the spirometry device, after which, each child performed three forced expiratory trials, according to the methods recommended by the American Thoracic Society (Medical Section of the American Lung Association, 2012). Tests were performed in the standing position. Nose clips were not utilized. Spirometric indices were automatically recorded for the "best" test as defined by the American Thoracic Society (Medical Section of the American Lung Association, 2012; Barreiro, & Perillo, 2004).

Children also completed exhaled carbon monoxide (eCO) to preliminarily assess for SHSe via a commonly used and relative technique. eCO has a half-life range between 2–8 hours. Factors such as an individual's level of physical activity, frequency of tobacco product use, and proximity to a wood burning fireplace or stove may impact eCO. eCO has the ability to detect smoking between a 6–24 hour period (SRNT Subcommittee on Biochemical Verification, 2002). Measurement of eCO is a brief noninvasive procedure that provides immediate results. Following the initial purchase of a carbon monoxide (CO) monitor (current models cost around $800-900) testing eCO is relatively inexpensive.

Lastly, children provided salivary cotinine as an additional and more objective measure of SHSe. During the inhalation of traditional tobacco cigarettes and use of other nicotine products (e.g., electronic cigarettes, nicotine replacement therapy, smokeless tobacco), nicotine is absorbed and distributed in the body within seconds (Benowitz, 1996). The detection of exposure to tobacco smoke by measurement of cotinine is the preferred method (e.g., Benowitz, 1996; Benoqitz, Hukkanen, & Jacob, 2009; Alterman, Fariti, & Niedbala, 2002; Foulds, Bryant, Stapleton, Jarvis, & Russell, 1994; Granger, et al., 2007). Salivary and serum cotinine samples are highly correlated (Van Vunakis, Tashkin, Rigas, Simmons, Gjika, & Clark, 1989; Bernet, McGuffey, Morrison, & Pirkle, 2000) and have an estimated measurement half-life around 17 hours (Benowitz, 1996). Cotinine levels in biologic fluids can be processed and examined using

chromatographic or enzyme immunoassay (EIA) techniques. Despite the ability of chromatographic methods achieving higher specificity and sensitivity (Benowitz, 1996), EIA cotinine results have been documented to have near precise agreement with chromatographic methodology (Alterman, Gariti, & Niedbala, 2002). EIA methodology is also advantageous because this technique requires smaller sample volumes than chromatographic methodology (Watts, Longone, Knight, & Lewtas, 1990) and can detect cotinine concentrations as low as 0-1 ng/mL (Salimetrics, 2014). Therefore, because of the age of the individuals providing cotinine samples (e.g., children and youth) and the brief nature of the present study (e.g., data collection as part of a regular clinic visit), the EIA technique was utilized.

Regardless of age, all participants were asked to collect salivary samples. If age appropriate and willing, whole saliva was collected by tilting the child's head forward, allowing the saliva to pool on the floor of the mouth, and then passing the saliva into a polypropylene vial as directed using the Salimetrics salivary collection protocol (Salimetrics, 2014). Samples from younger children or children who were unable to pool saliva were collected with the SalivaBio Children's Swab (SCS; Salimertics, 2014). This was conduct by having the child hold the SalivaBio Swab under the tongue for 60-90 seconds (Salimetrics, 2014). Samples were frozen in an -80 degree lab freezer within five hours of collection for later assay by EIA (Salimetrics, 2014).

**Caregiver Variables**

Smoking history was assessed by asking caregivers a series of questionnaire items ranging from number of family members that smoke, interest/confidence in quitting, and perception of harm. Additionally, caregivers completed questionnaires assessing their demographics. eCO levels were also collected.

**Rationale for Design**

Because little to no information is available regarding prevalence of SHSe in SCD, all children and caregivers who present to the SCD clinics were recruited. Because no data exists for SCD specifically, the available data for caregivers of healthy children suggests the existence of large minority of caregivers who smoke (~40%) and studies have shown that they have difficulty achieving and maintaining alterations to smoking behavior that reduce child SHSe (Priest et al., 2008). To date, only one research study has prospectively examined SHSe in medically at-risk children (i.e., pediatric cancer; (Tyc et al., 2013)), ***however no data exists examining SHSe in children of SCD using biological objective measurement.*** The three previous studies examining SHSe in SCD (Cohen et al., 2013; Glassberg et al., 2012; West et al., 2003) were retrospective (i.e., chart review) in design and included only self-report measurement regarding smoking status. Therefore, ***our approach is the first logical step to identifying the extent to which children who are diagnosed with sickle cell disease are exposed to SHSe***. We only included primary caregivers with a child between the ages of 1 month-17-years-old, since this is the age range with the highest level of SHSe (Health & Services, 2006). We chose the youngest child if the caregiver has more than one child whom he/she spends 4 or more hours with per day since previous research shows that younger children in this age range are typically exposed to higher levels of SHSe (Priest et al., 2008).

**Statistical Analyses:**

**Sample Size**

The focus of this proposal is not on statistical hypothesis testing, but rather on assessing preliminary prevalence rates of SHSe. Child salivary cotinine is the primary outcome of interest and thus we estimated power for the proposed study based on this outcome. For the current study, we enrolled 31 dyads. Four families declined to participate due to being too busy or not interested in participating in the study.

**Data Analytic Plan Aim 1**

**Aim 1:** To determine the prevalence of secondhand smoke exposure in children diagnosed with SCD via self-report, parental report, and objective measurement (i.e., salivary cotinine).

**Hypothesis 1.1**: Based on previous non-representative studies, it was expected that approximately 30 – 40% of sample would be exposed to SHSe, which would be consistent with the three studies in the literature to date.

**Aim 1 Analyses**: The prevalence of SHSe was calculated as a measure of frequency (Ressing, Blettner, & Klug, 2010).

**Data Analytic Plan Aim 2**:

**Aim 2:** To examine the relationship between levels of salivary cotinine and utilization of health care services (i.e., Emergency Department Visits) and negative health events (e.g., acute chest syndrome, sickle cell crises, pulmonary morbidity).

**Hypothesis 2.1**: Youth who have cotinine values > .15 ng/mL, an indication of significant SHSe (Salimetrics, 2014; Benowitz, et al., 2009), will demonstrate an increase in utilization of health care services (i.e., Emergency Department Visits) and negative health events (e.g., acute chest syndrome, sickle cell crises, pulmonary morbidity) compared to youth who have a cotinine values less than .15 ng/ml (Salimetrics, 2014; Benowitz, et al., 2009).

**Aim 2 Analyses**: All cotinine values were examined using the Salimetrics (Salimetrics, 2014) research guidelines (Benowitz, Bernert, Caraballo, Holiday, & Wang, 2009) to determine if caregivers are active tobacco/nicotine users and the level of SHSe for the child. A person who is actively using tobacco/nicotine product will typically have cotinine values ≥3 ng/mL (Salimetrics, 2014; Benowitz, et al., 2009). Therefore, we used

cotinine values > .15 ng/mL to indicate SHSe (Salimetrics, 2014; Benowitz, et al., 2009). We hypothesized that youth who have cotinine values greater than .15 ng/mL would demonstrate an increase in utilization of health care services (i.e., Emergency Department Visits) and increased maladaptive health events (e.g., acute chest syndrome, sickle cell crises, pulmonary morbidity) compared to youth who have a cotinine values less than .15 ng/mL (Salimetrics, 2014; Benowitz, et al., 2009).

**Descriptive Statistics**

To provide additional information about caregiver nicotine/tobacco use and caregiver perceptions of relative harm related to specific tobacco/nicotine products descriptive statistics were utilized. Bivariate correlations were employed to examine any potential correlations between child or caregiver demographic information and child cotinine, child emergency department utilization, number of sickle cell crises, and number of acute chest syndrome. Caregivers were asked about current use of tobacco/nicotine (i.e., "Do you now smoke regular cigarettes") and previous or ever-use of tobacco (i.e., "Have you smoked at least 100 regular cigarettes in your life?", "Please select which answer best describes your experience with the following products: never tried, not even once, tried it before, use occasionally, or use daily.", and "What was the first tobacco product you've ever tried?").

Caregivers were also asked about the number of the individuals in the home who use a tobacco or nicotine product to assess household SHSe or secondhand vape exposure (SHVe; "How many people in your home: smoke regularly cigarettes, use an e-cigarette, use a tank system, use both regular cigarettes and a e-cigarette/tank system."). To assess caregiver perceptions of harm, two questions were utilized: 1) "Which, if any, of these products are safer than regular cigarettes?"; 2) "On a scale from 0 – 10, where 0 = not at all harmful, and 10 = extremely harmful, how harmful to your health do you think the following are?". Please see Appendix B for entire nicotine/tobacco questionnaire.

**Missing Data:** In the event of missing data, we contacted participants immediately by phone. However, if they refused to be contacted or otherwise lose contact with the investigators, we censored data at point of loss. When possible, we used a more conservative intent to treat approach in which missing outcomes are imputed using last observation carried forward (LOCF).

*Limitations and Pitfalls.* The first anticipated problem is that children and parents may refuse to enroll in the study. Therefore, we asked these individuals to provide reasons for non-participation to allow for feasibility and acceptability assessments for the proposed study. The second anticipated problem arises from our enrollment of youth across a large developmental range (e.g., 1 month-17-years-old). A broad developmental range was chosen over a more restricted one because the previous research has shown that children experience the highest amount of SHSe of all age groups, with more than 50% of children in the U.S. exposed to secondhand smoke (Control & Prevention, 2010; Health & Services, 2006). Children who are between the ages of 3 to 11-years-old have the highest levels of SHSe, likely because they spend a majority of their time in close proximity to a caregiver who smokes (Gergen et al., 1998; Health & Services, 2006; Pirkle et al., 2006; Schwab et al., 1992).

# CHAPTER II

# FINDINGS

## Spirometry

Due to the age of the child ($M_{age}$ = 2.72; *SD* = 1.77), seven of the 31 children did not provide pulmonary functioning measurement. Overall, majority of children had spirometry results in the normal range ($FEV_1$ between 80% and 120%, n = 19, 61.3%; $FEV_1$/FCV greater than 70% predicted, n = 22, 71.0%). Of the 24 participants who completed forced spirometry, 11 were previously diagnosed with asthma, but the majority fell in the normal range of pulmonary functioning ($FEV_1$ between 80% and 120%, n = 10, 90.9%; $FEV_1$/FCV greater than 70% predicted, n = 6, 54.5%). All medical information and biochemical data are reported in Table 3 in Appendix C.

## Exhaled Carbon Monoxide

Overall, the majority of families in the present study had nonsmoking estimates (eCO ≤ 10 p.p.m.) of eCO (caregiver eCO *M* = 3.93 p.p.m.., *SD* = 4.54; child eCO *M* = 4.35, *SD* =2.58). eCO values are in Table 3, Appendix C.

## Salivary Cotinine

Due to equipment malfunction, four samples were unable to be processed. Of the remaining 27 samples, 24 children were exposed to SHS via ng/mL of .15 or greater ($M_{cotinine}$= .92,

*SD* = 1.28, Range = 0.00 ng/mL – 5.47 ng/mL). Cotinine values are reported in Table 3 in Appendix C.

**Data Analyses for Specific Aims**

**Aim 1:** To determine the prevalence of secondhand smoke exposure in children diagnosed with SCD via self-report, parental report, and objective measurement (i.e., salivary cotinine).

**Hypothesis 1**: Based on previous non-representative studies, it was expected that approximately 30 – 40% of sample will be exposed to SHSe, which would be consistent with the three studies in the literature to date.

**Aim 1 Results:** In the present study, the prevalence of SHSe was calculated as a measure of frequency (Ressing, Blettner, & Klug, 2010). According to exhaled CO and parental self-report, only six of the 31 children (19%) were exposed to secondhand smoke. However, when examining exposure related to levels of salivary cotinine, 24 of the 27 participants (88%) had cotinine levels greater than .15 ng/mL ($M_{cotinine}$ = .92, *SD* = 1.28). It should be noted that due to equipment malfunction four participants salivary samples were unable to be processed. Physician reported secondhand smoke exposure successfully identified two of the six biochemically confirmed and self-reported caregiver smokers. Of the remaining 29 participants, 21 were nonexposed/nonsmoking families via physician report, and no information regarding secondhand smoke exposure was provided for five families.

**Aim 2:** To examine the relationship between levels of salivary cotinine and utilization of health care services (i.e., Emergency Department Visits) and negative health events (e.g., acute chest syndrome, sickle cell crises, pulmonary morbidity).

**Hypothesis 2**: Youth who have cotinine values greater than .15 ng/mL, will indicate significant SHSe (Salimetrics, 2014; Benowitz, et al., 2009), will demonstrate an increase in utilization of health care services (i.e., Emergency Department Visits) and negative health events (e.g., acute chest syndrome, sickle cell crises, pulmonary morbidity) compared to youth who have a cotinine values less than .15 ng/mL (i.e., no exposure; Salimetrics, 2014; Benowitz, et al., 2009).

**Aim 2 Analyses**: All cotinine values were examined using the Salimetrics (Salimetrics, 2014) research guidelines (Benowitz, Bernert, Caraballo, Holiday, & Wang, 2009) to determine if caregivers are active tobacco/nicotine users and the level of SHSe for the child. A person who is actively using tobacco/nicotine product will typically have cotinine values ≥3 ng/mL (Salimetrics, 2014; Benowitz, et al., 2009).

**Aim 2 Results:** In the present sample, 24 of the 27 children had cotinine values ≥.15 ng/mL, of those children that were exposed. The majority of children had cotinine values less than 1 but greater than .15 ng/mL (n = 22; range = .21 ng/mL - .96 ng/mL). Two children had cotinine values between 1 ng/mL and 2.9 ng/mL (1.07 ng/mL; 2.75 ng/mL). Two children had cotinine levels similar to that of a light smoker (e.g., ≥3 ng/mL; 4.41 ng/mL and 5.47). Nine caregivers endorsed nicotine/tobacco exposure in the home via self-report (n = 2 electronic cigarette, $M_{cotinine}$ = .48 ng/mL, *SD* = .01 ng/mL); n = 7 cigarette tobacco, $M_{cotinine}$ =1.64 ng/mL, *SD* = 2.11 ng/mL). The mean difference in cotinine values for caregiver reported household exposure ($M_{cotinine}$ = .1.36 ng/mL, *SD* = .1.87 ng/mL) versus no report of household exposure ($M_{cotinine}$ = .63 ng/mL, *SD* = .38 ng/mL) was .73 ng/mL. Because 24 of the 27 individuals were exposed to SHSe, no inferential statistical analyses could be conducted.

## Descriptive Statistics

No significant correlations were observed between child or caregiver demographic information and child cotinine, child emergency department utilization, number of sickle cell crises, and number of acute chest syndrome. However, caregiver endorsement of using 100 or more cigarettes in their lifetime and child cotinine was significantly correlated at the $p \leq .05$ level ($r = .482$). Number of sickle cell crises was significantly correlated with number of emergency department utilizations ($r = .863$) and number of acute chest syndrome ($r = .730$), both at the $p \leq .001$ level. Lastly, acute chest syndrome and the number of emergency department utilizations were significantly correlated at the $p \leq .001$ level ($r = .686$). All other correlations are reported in Table 4 in Appendix C.

Eight of the 31 caregivers reported smoking 100 cigarettes or more in their lifetime. Twenty-seven caregivers denied smoking cigarettes on a regular basis, two caregivers indicated using cigarettes daily, and two caregivers endorsed using cigarettes occasionally. No caregivers endorsed ever using dissolvable tobacco or snus, one caregiver had previously used roll your own cigarettes, and two caregivers endorsed previous hookah use. The majority of caregivers had never tried electronic cigarettes (n = 24), five caregivers had previously tried electronic cigarettes, one caregiver endorsed occasional electronic cigarette use, and one caregiver endorsed daily use. The majority of caregivers had never tried nicotine replacement therapy (NRT; n = 30) with one caregiver endorsing previous use.

Perceptions of products safer than traditional tobacco cigarettes, four caregivers endorsed skoal, one caregiver endorsed snus, and one caregiver endorsed hookah as safer than traditional tobacco cigarettes. Interestingly, 11 caregivers perceived electronic cigarettes, and 9 caregivers perceived NRT as safer than traditional tobacco cigarettes. No caregivers thought dissolvable tobacco or roll your own cigarettes were safer than traditional tobacco cigarettes. All caregivers reported all nicotine and tobacco products, as well as NRT and smoking cessation medications (i.e., Wellbutrin, Chantix), as potentially harmful (Range $M = 5.97$ to $M = 9.26$). Additional

descriptive statistics related to nicotine/tobacco use and perceptions of harm/safety are reported in Table 5 in Appendix C.

Caregivers were also asked to report their tobacco history starting with the first tobacco product ever tried. Ten caregivers reported traditional tobacco cigarettes as their first tobacco product tried, two caregivers reported beginning use with smokeless (e.g., skoal) tobacco, and one caregiver reported first use began with NRT. Two caregivers endorsed an electronic cigarettes as the first product used, and two endorsed marijuana as the first product ever used. Lastly, caregivers were asked to report "how many people in your home use the following products: Regular Cigarettes, Electronic Cigarettes, Tank Electronic Cigarette, and/or Both Regular Cigarettes and an Electronic Cigarette." Seven caregivers reported someone in their household used traditional cigarettes, one caregiver reported household use of an electronic cigarette, one caregiver indicated household use of a tank system, and no caregivers endorsed household use of both regular cigarettes and a tank or electronic cigarette system. Please see Table 5 in Appendix C for additional information related to caregiver nicotine/tobacco use.

# CHAPTER V

## CONCLUSIONS

The present study sought to achieve two aims, first to estimate the number of children diagnosed with sickle cell disease who are exposed to secondhand smoke (SHSe), and second, to assess if SHSe among children with sickle cell disease is associated with increased utilization of health care (i.e., emergency department utilization) services and increased disease severity (i.e., higher frequency of sickle cell crises and/or acute chest syndrome, increased pulmonary morbidity). To assess the first objective, eCO and child cotinine, a biological marker of nicotine exposure, were utilized. The majority eCO were in the normal or nonsmoking range. According to eCO and parental self-report, only six of the 31 children (19%) were exposed to secondhand smoke. However, salivary cotinine indicated 24 of the 27 participants (88%) were exposed in some capacity to SHSe, with cotinine levels greater than .15 ng/mL.

To assess the second objective, children completed spirometry to assess pulmonary functioning and medical information was collected through a medical chart review. Contrary to the hypothesized relationship of SHSe and health outcomes, no associations between SHSe and increased health care utilization, sickle cell disease morbidity, or estimates of pulmonary morbidity were observed. Additional information regarding caregiver nicotine/tobacco history

and perceptions of harm were examined using descriptive statistics. Eight caregivers reported smoking 100 cigarettes or more in their lifetime and the majority of caregivers had never tried electronic cigarettes (n = 24), or nicotine replacement therapy (NRT; n = 30). Related to perceptions of harm, 11 caregivers perceived electronic cigarettes as safer than traditional tobacco cigarettes.

Overall, the findings in this study partially support the findings in the three previous studies examining SHSe in youth with sickle cell disease (i.e., West et al., 2003, Glassberg et al, 2012, Cohen et al., 2013), with several exceptions. First, West and colleagues (2013) found that self-, caregiver-, and physician-reported SHSe via questionnaire and medical chart review were indicative of increased medical utilization and pulmonary morbidity in youth with SHSe. However, in the present study, self-, caregiver-, and physician-reported SHSe were poor indicators of actual SHSe, with the majority of ratings indicating no exposure. This similar to other studies with a majority sample of African American (see Wilson, Kahn, Jhoury, & Lanphear, 2005), which report lower reported exposure to SHSe. Second, in the present study no correlations between SHSe (i.e., cotinine or eCO) and negative health outcomes/medical utilization were observed. Glassberg and colleagues (2012) identified that sickle cell crises and increased asthma morbidity related to SHSe significantly increased emergency department utilization and the frequency of the previously mentioned health outcomes. However, the present study found no correlations between SHSe, asthma morbidity, decreased pulmonary functioning, or sickle cell crises. Lastly, the findings of Cohen and colleagues (2013), which identified that 44% of patients reported a history of SHSe, and 29% reported current SHSe, were again, not upheld in the present study. Only 22.58% of the current sample reported any SHSe, however 24 of the 27 cotinine samples (88%) indicated SHSe. Cohen and colleagues (2013) also identified a relationship between SHSe and increased airway obstructive via spirometry. The findings in the present study only identified increased airway obstructive in 38% of children, regardless of SHSe

or a previous physician diagnosis of asthma.

The present study highlights some important considerations. First, 24 of the 27 children in the present study were exposed to SHSe or secondhand vapor (SHVe) via salivary cotinine. Interestingly, seven caregivers endorsed household exposure via traditional tobacco cigarettes and two caregivers endorsed electronic cigarettes use (secondhand vapor; SHVe). Despite the relatively low levels of cotinine exposure (i.e., majority of cotinine values between .15 ng/mL and 1 ng/mL), it is important to note that there is no safe level of SHSe/SHVe (United States Surgeon General Report, 2006; Wilson, Klein, Blumkin, Gottlieb, & Winickoff, 2011; Oono, Mackay, & Pell, 2011). According to the United States Surgeon General Report (2006), nearly 22 million children (60%) in the United States aged 3 -11 cotinine to be exposed to SHSe. This exposure increases the rates of sudden infant death syndrome, acute respiratory infections, and increases asthma morbidity (United States Surgeon General Report, 2006), regardless of the level of SHSe. A recent study found even higher SHSe rates than the documented SHSe rates in the United States Surgeon General Report (2006). The National Health and Nutrition Examination Survey (NHANES; Wilson et al., 2011) found that 73% of children are exposed to SHSe. Wilson and colleagues (2011) also document that this exposure is not limited to caregiver smoking, but that house-type (e.g., apartment, duplex, and detached or single-family homes) may increase the amount of SHSe. Interestingly, Wilson and colleagues (2011), identified a stratified increase in SHSe via cotinine related to the type of housing, with children living in apartment complexes having greater increases in SHSe than children who lived in detached or single-family homes. In the present study, no information on housing-type was included, and the high prevalence of SHSe may be indicative of SHSe/SHVe due to seepage through a wall or through shared ventilation systems in an apartment or duplex.

The high prevalence of SHSe in the present study may also be a result of the lax tobacco control policies within the state in which the study was conducted. Findings from the literature show that stronger policies or a greater coverage of state-level smoke-free policies are associated

with a lower prevalence of adult smoking (Eriksen & Cerak, 2008; International Agency for Research on Cancer, 2009; Dinno & Glantz, 2009). Dove et al. (2010) used cross-sectional data from NHANES and found that children from non-smoking homes living in counties with extensive coverage of smoke-free air laws had lower cotinine levels than similar children living in counties without smoke-free laws. Additionally, tobacco use trends in the United States indicate significant SHSe for children from lower socioeconomic and educational households (Hiscock, Bauld, Amox Fidler, & Munafo, 2012). Despite the decline of smoking uptake and SHSe throughout the United States, SHSe continues to remain a potential problem among lower socioeconomic and education households (Escobedo & Peddicord, 1997; Garfinkel, 1997). Notably, in the present study, a large portion of the caregivers in the present sample were high school graduates (45.20%), had government assisted (e.g., Medicaid/Medicare; 35.50%) or no insurance (9.7%), were single parents (51.70%), and made less than $30,000 (60.00%). Additionally, it should be noted that several studies have identified that African American have higher levels of cotinine (e.g., Benowitz et al., 1994, 2009; Perez-Stable et al., 1998, Knight et al., 1996; Wilson, Kahn, Khoury, & Lanphear, 2005). It is unclear if these differences are due to type of tobacco products used (e.g., menthol cigarettes, cigarillos; Kabat et al., 1991) or differences in metabolizing tobacco/nicotine products (Benowitz et al., 1994, 2009; Perez-Stable et al., 1998).

Despite the important findings of this study, the results are limited in generalizability due to the low sample size (n= 31) and the cross-sectional design. Additionally, the low sample size and the high prevalence of SHSe prevented the utilization of inferential statistics. However, the ability to increase this sample size was limited in that only four of the 35 caregiver approached declined. Despite these limitations, the present study has several advantages over previous studies in that it was employed in a regular clinic setting and it was the first study to obtain biochemical confirmation of SHSe (i.e., cotinine). This study also highlighted the benefit of salivary cotinine to measure SHSe as opposed to more traditional methods of determining SHSe (cotinine versus eCO). The findings in the present study show that SHSe may not be attributed to a primary

caregiver per se, but may be a result of household SHSe from a variety of other sources.

Overall, the present study highlights the need for future studies to evaluate SHSe in youth with sickle cell disease. Based on the findings in the present study, SHSe appears to be a significant concern with 88% of the sample having detectible cotinine levels, which is only obtainable from tobacco/nicotine exposure, via salivary EIA analysis. Due to a lack of eCO and self-, parent-, and physician-reported SHSe, it is recommended that future studies utilize other forms of biochemical verification, such as salivary or serum cotinine, to assess for SHSe. Future studies utilizing a larger sample size and a longitudinal design are also needed to assess trends among health related outcomes such as pulmonary morbidity, increased emergency department utilizations, and sickle cell crises.

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# APPENDICES

# Appendix A
# REVIEW OF THE LITERATURE

# REVIEW OF LITERATURE

## Chapter Overview

Sickle Cell Disease: Description and Disease Implications

### Nature and Etiology of Sickle Cell Disease

In the United Statues, the exact number of people living with SCD is unknown (National Heart, Lung, and Blood Institute, 2009). However, the Center for Disease Control and Prevention (CDC), in collaboration with the National Institutes of Health (NIH) and 7 states (i.e., California, Florida, Georgia, North Carolina, New York, Michigan and Pennsylvania) have combined efforts to establish a prevalence rate of children and adults living with SCD. The CDC (2014) and NIH (2009) estimate that SCD affects 90,000 to 100,000 Americans, occurs among 1 out of every 500 Black or African-American births, and in about 1 out of every 36,000 Hispanic-American births. It is estimated that sickle cell trait (SCT) occurs among about 1 in 12 Blacks or African Americans.

SCD includes a collection of autosomal recessive genetic disorders involving the abnormal production of hemoglobin. In SCD, red blood cells are short-lived and brittle, assuming a "sickled" shape that hinders their ability to effectively deliver oxygen throughout the body (Barakat, Nicolaou, O'Hara, & Allen, 2009). In addition, impaired red blood cells often aggregate to occlude other smaller blood vessels and significantly reduce the amount of oxygenated blood to the lungs and other organs (Serjeant, 1997). Variants of the disease range in severity from the most severe, homozygous (HbSS), to heterozygous SCD, which is associated with benign symptoms (Barakat, Nicolaou, O'Hara, & Allen, 2009). Individuals who carry SCT generally do not experience symptoms associated with the disease (Rees et al., 2003). Due to the advancement of treatment and early neonatal testing, mortality rates associated with SCD and SCT have

declined significantly in the past twenty years (Platt et al., 1994), However, individuals diagnosed with SCD/SCT continue to have life expectancy rates below the general population (Platt et al., 1994).

Children and youth diagnosed with SCD face numerous chronic symptoms, ranging from stroke and pulmonary hypertension to more common side effects such as acute chest syndrome and acute pain associated with vaso-occlusive episodes, also known as sickle cell crises (CDC, 2014). Acute chest syndrome, a leading cause of death marked by pulmonary infiltrate, fever and respiratory distress (Vichinsky et al., 2000), is a life-threatening complication of SCD that causes chest pain, fever and difficulty breathing and can be caused by a lung infection or by a sickle cell crisis. A sickle cell crisis occurs when the sickle cells block blood flow and decrease oxygen delivery to vital organs (NIH, 2015). Sickle cell crises can occur without warning and cause sharp and intense stabbing or throbbing pain throughout the body (NIH, 2015). A crisis can be a result of acute illness, extreme temperature changes, stress, and dehydration (NIH, 2015). Often it is difficult to pinpoint the specific catalyst of a sickle cell crisis, but literature over the past decade has found that exposure to and use of tobacco may exacerbate and potentially increase the likelihood of having a sickle cell crisis (e.g., West et al., 2003).

Tobacco decreases oxygen flow to the lungs and can affect tissues throughout the body. It can cause lung infection and permanent lung damage, such as chronic obstructive pulmonary disease (COPD) and emphysema (Control & Prevention, 2013). In children and youth with SCD, short-term and long-term lung problems are more common such as pulmonary infection and asthma (NIH, 2015). In nonsmokers, the damaging effects of SHSe has on health is well documented (e.g., Helsing, Sandler, Comstok, & Chee, 1988; Albulhosn, Morray, Llewellyn, & Redding, 1997). For children and youth with sickle cell, exposure to tobacco smoke can cause

blood vessels to become smaller, which can lead to a pain crisis (West et al., 2003). An additional hazard of SHSe occurs when the nicotine in secondhand smoke attaches to hemoglobin, lowering the oxygen level in the blood, and subsequently triggering a sickle cell crisis (St. Jude Children's Research Hospital, 2012). Despite the specific dangers to children and youth with SCD, little to no research has been conducted examining the specific impact secondhand smoke exposure (SHSe) has on health outcomes. More importantly, no studies, to our knowledge, have used objective measures to identify SHSe in a cross-sectional study sample. Therefore, understanding the specific impact SHSe has on children and youth with SCD is imperative. In the following sections, we will review the three primary studies that have been published to-date examining SHSe in SCD.

## Secondhand Smoke Exposure in Sickle Cell Disease

### Study 1: West et al., 2003

The purpose of the current study was to determine whether children and adolescents ($n$ = 52, $M_{Age}$ = 12.6 years; $SD$ = 3.5 years) with SCD exposed to SHSe at home ($n$ = 22; 42%) had more sickle cell crises than those who lived in nonsmoking households. A research assistant blinded to the participants' family smoking history (smoker versus nonsmoker) retrospectively examined the medical record of each participant during the two years prior to participating in the study (1998-2000). Total hospital costs, length of stay, outpatient visits, fetal hemoglobin levels, and asthma or other pulmonary illnesses were calculated for each participant. SHSe was determined during a survey of the primary caretaker and the patient if the patient was 7 or older and a smoking household was determined if the primary caregiver or the patient identified anyone living in the home who smokes tobacco products either outside or inside the home during the two year prior to the study visit.

Using a Wilcoxon rank sum test to compare the number of sickle cell crises (including acute chest syndrome and stroke), the number of hospitalized days, total hospital cost, and total number of outpatient visits, West et al., (2003) found that children with SHSe had significantly more inpatient sickle cell crises (exposed: $M_{Age}$ = 3.7, *SD* = 5.7; nonexposed: $M_{Age}$ = 1.7, *SD* = 3.5; *p* = .02) and more hospitalized days (exposed: $Days_M$ = 23.4, *SD* = 51.1; nonexposed: $Days_M$ = 9.3, *SD* = 23.4, p = .48). No significant difference was observed between outpatient visits and total hospital costs. Using poisson regression, controlling for age and sickle cell type, SHSe were independently associated with more inpatient sickle cell crises and those patients diagnosed with homozygous S sickle cell anemia (West et al., 2003).

The findings from West and colleagues (2003) provides a foundation linking the known biological and dose-dependent effects of SHSe as a potential mechanism for increasing the exacerbation of sickle cell crises in children/youth diagnosed with SCD. Overall, West et al. (2003), found that children and youth with SCD with SHSe were more likely to have acute sickle cell crises requiring hospitalization and greater hospital costs than those who were not exposed, suggesting that SHSe may influence the severity of SCD. In fact, West and colleagues (2003) found that patients with SHSe had 1.9 times the risk of a sickle cell crisis than did unexposed patients. The limitations for West et al. (2003) included obtaining SHSe via self- and patient-report only and using retrospective chart review. The present study will address these limitations partly by imploring a more direct quantitative measure of SHSe (i.e., cotinine and NNAL measurement), which will determine whether the association of SHSe with inpatient sickle cell crises demonstrates a dose-response pattern.

Study 2: Glassberg et al. (2012)

Glassberg and colleagues (2012) sought to examine clinical, social and environmental

factors that may increase emergency department intakes (ED) among children and youth with SCD. They examined ED visit between 2004 and 2010 associated with SCD ED pain and acute chest syndrome admissions in Canada, England, France and the United States. For the purpose of the present study, only the results for the United States will be discussed. T-tests, chi-square tests, and multivariable negative binomial regression models were used to examine mean differences/proportions and adjusted rate ratios for ED visits, with separate models for pain ED visits and acute chest ED visits (Glassberg et al., 2012). Covariates included age, sex, sickle cell genotype, asthma diagnosis (e.g., self-report verified via medication documentation in electronic medical chart), fetal hemoglobin percent and SHSe via in-home smokers. Eight hundred and ten youth ($M_{Age}$ =8.71, $Age_{Range}$ = 6.88-10.83; 51.4% male; 97.8% Black or African American; 70.5% on Medicaid; *M* = $20-29,999; 53.7% below poverty line) were included in the ED analyses for pain and acute chest syndrome admission (Glassberg et al., 2012).

Overall, a previous diagnosis of asthma was associated with a 28% increase in the frequency of ED visits for pain (rate ration [RR] = 1.28; 95% confidence interval [CI] = 1.04-1.58, p = .02). Using a multivariable model, income below the deferral poverty line was associated with a 31% increase in ED visits for pain (RR = 131, 95% CI = 1.04-1.64, p = .02). Similar to the findings of West et al. (2003), the two variables associated with increased risk of ED visits for acute chest syndrome were asthma and SHSe (Glassberg et al., 2012). Exposure to SHSe within the home was associated with a 73% increase in the rate of ED utilization for acute chest syndrome (RR = 1.73, 95% CI= 1.09-2.74, p = .02) and a physician diagnosis of asthma was associated with a 60% increase in ED visits for acute chest syndrome (RR = 1.60, 95% CI = 1.03-2.49, p = .04).

While SHSe was associated with a greater increase in the occurrence of acute chest

syndrome, asthma was the only variable associated with increased ED utilization for both *pain* and *acute chest syndrome*. More specifically, the presence of a household tobacco smoker was associated with a 73% increase in acute chest syndrome events when compared to those that did not have a household exposure. Thus, there are strong data regarding the association between SHSe and increase asthma morbidity (e.g., Chilmonczyk, et al., 1993; Strachan & Cook, 1998), and there are emerging data about its association with SCD morbidity (West et al., 2003; Cohen, DeBaun, Blinder, Strunk, & Field, 2010). These data strengthen the evidence that SHSe is associated with SCD morbidity, particularly lung disease. The limitations of Glassberg and colleagues (2012) include retrospective report regarding past SHSe via patient and self-report only. The present study improves on these findings partly by using quantitative measures of SHSe (i.e., cotinine and NNAL measurement), which will determine whether the association of SHSe with acute chest syndrome ED visits demonstrates a dose-response pattern.

Study 3: Cohen et al. (2013)

Cohen et al. (2013) employed a cross-sectional analysis of 252 children, ages 4 to 20-years-old ($n$ = 126, $M_{Age}$ = 11, $Age_{Range}$ = 4-18, 52% male), with asthma and sickle cell anemia (SCA) to examine spirometry, specifically airway obstruction, bronchodilator responsiveness and SHSe from three sites, including Missouri, Ohio, and London, England. Parents of children with SCA were asked questions about past and present in-home SHSe. Using logistic regression models to examine associations between SHSe and airway obstruction and bronchodilator responsiveness, Cohen and colleagues (2013) found that roughly 108 of the 245 children (44%) self-reported a history of exposure to SHSe and 71 of the 245 (29%) reported current exposure to SHS. Additionally, results of the logistic regression found that of those children with SHSe, SHSe during infancy and preschool periods were associated with *poorer* spirometry results. More

specifically, these children had poorer forced expiratory flow (i.e., the speed of air coming out of the lungs during the middle portion of a forced expiration), decreased midexpiratory phase/FVC ratio (i.e., the ratio of speed of air and force of air coming from the lungs), and increased airway obstruction and increased bronchodilator responsiveness (i.e., a phenotypic characteristic of chronic obstructive pulmonary disease; Cohen et al., 2013). Further, the $FEV_1$/FVC value was below the lower limit of normal observed levels in healthy black children, with more reports of daytime cough/wheezing during physical activity, and nighttime cough/wheezing causing awakening (Cohen et al., 2013). Overall, Cohen et al. (2013) demonstrates that early SHSe is associated with airway obstruction in children with SCA. Similar to Glassberg et al. (2012) and West et al. (2012), limitations of this study included utilization of caregiver- and self-report only of SHSe.

The Current Study

To address the limitations and to expand on the findings of West et al. (2003), Cohen et al. (2013), and Glassberg et al. (2012) the present study aimed to be the first to objectively measure SHSe via salivary cotinine, establish prevalence of SHSe in youth with SCD/SCA and preliminarily investigate the likelihood of a dose-response relationship between salivary cotinine and negative health events (i.e., increased ED use, increased occurrence of sickle cell crises and acute chest syndrome). Thirty-one caregiver-child dyads were recruited during a regularly scheduled clinic visit. Children will provided a saliva sample, completed a measure of lung functioning (i.e., spirometry) and exhaled carbon monoxide test. Self-report measures asked caregivers about their history of nicotine use Information regarding number of clinic visits, health care utilization and illness characteristics will be collected via electronic medical chart review.

Specific Aims

**Aim 1**: Identify any differences in health care of children diagnosed with sickle cell in families who smoke versus those who are nonsmokers.

**Aim 2**: To identify any physical effects of secondhand smoke on kids with sickle cell (i.e., spirometry and salivary cotinine) compared to children who are not exposed to secondhand smoke.

## Chapter Summary

Despite public smoking bans, and the knowledge regarding the dangers of SHSe, this continues to be a significant problem of children and youth with caregivers that use tobacco products. Due to the limited research to date and the lack of cross-sectional and objective measurements, the present study aimed to address a significant gap in the current literature. A first-step is needed to understand 1) the prevalence of SHSe in SCD; 2) the impact SHSe may have on important health outcomes such as sickle cell crises, ED visits, and pulmonary functioning, and 3) insight into the level of salivary cotinine in youth/children with SCD. The present study aimed to address these questions and provide support for future investigations examining SHSe in SCD.

Appendix B
MEASURES

Demographic Form
Nicotine and Tobacco Questionnaire

**Demographics**

Child Sex: F M Child Age:_____ Child Date of Birth:_____

Person Completing Form (relationship to child): _____

Parent Sex: F M Parent Age:_____ Parent Date of Birth:_____

Address: _____

Phone number: _____

Ethnicity of Child: ____ Caucasian ____ Latino/Latina
____ African American ____ Chicano/Chinana
____ Asian ____ Middle Eastern
____ Pacific Islander ____ American Indian
____ Other (Please specify: _____)

Child's Place of Birth: _____ Child's Primary Language: _____

Mother's Age:_____ Father's Age:_____

Mother's Education:
____ High school graduate
____ College graduate
____ Masters degree
____ PhD, JD, MD
____ other
(please specify:_____)

Father's Education:
____ High school graduate
____ College graduate
____ Masters degree
____ PhD, JD, MD
____ other
(please specify:_____)

Ethnicity of Mother: ____ Caucasian ____ Latino/Latina
____ African American ____ Chicano/Chinana
____ Asian ____ Middle Eastern
____ Pacific Islander ____ American Indian
____ Other (Please specify:_____)

Ethnicity of Father: ____ Caucasian ____ Latino/Latina

____ African American ____ Chicano/Chinana

____ Asian ____ Middle Eastern

____ Pacific Islander ____ American Indian

____ Other (Please specify:_____)

Mother's occupation:_____

Father's occupation:_____

Approximate family income:

____ < $10,000 ____ $41,000-50,000

____ $10,000-20,000 ____ $51,000-60,000

____ $21,000-30,000 ____ > $60,000

____ $31,000-40,000

Parent's Marital Status: ____ married ____ separated ____ divorced

____ mother passed away ____ father passed away ____never married

Are you CURRENTLY covered by any of the following types of health insurance or health coverage plans?

1. Insurance through a current or former employer or union
2. Insurance from an insurance company
3. Medicare, for people 65 and older, or people with certain disabilities
4. SoonerCare (Medicaid), Medical Assistance, Insure Oklahoma, or any other kind of government assistance plan for those with low incomes or disability
5. Indian Health Service
6. Any other type of health insurance or health coverage plan. Specify: _____
7. No health insurance

-777. DON'T KNOW/NOT SURE
-999. REFUSED
-888. N/A

Is your CURRENT residence in a rural (e.g., a geographic area that is located OUTSIDE cities and towns) or urban (e.g., a geographic area located INSIDE cities and towns) area?

1. YES (rural)

0. NO (urban)

-777. DON'T KNOW/NOT SURE
-999. REFUSED
-888. N/A

Was your PREVIOUS residence in a rural (e.g., a geographic area that is located OUTSIDE cities and towns) or urban (e.g., a geographic area located INSIDE cities and towns) area?

1. YES (rural)

0. NO (urban)

-777. DON'T KNOW/NOT SURE
-999. REFUSED
-888. N/A

How long is your commute to your primary care physicians' office?

_____ Hours _____ Minutes

-777. DON'T KNOW/NOT SURE
-999. REFUSED
-888. N/A

**Nicotine and Tobacco Questionnaire**

1. **Have you smoked at least 100 regular cigarettes in your lifetime?**
   1. Yes
   2. No

2. **Do you now smoke regular cigarettes?**
   1. yes, everyday
   2. yes, some days
   5. Not at all

**3. Please select which answer best describe your experience with the following products**?

**A. Smokeless chewing tobacco (e.g., Skoal, Copenhagen)**

1. Never tried, not even once
2. Tried it before
3. Use occasionally
4. Use daily

**B. Dissolvable tobacco (Ariva, Stonewall, Camel Orbs, Camel sticks or strips)**

1. Never tried, not even once
2. Tried it before
3. Use occasionally
4. Use daily

**C. Snus (Marlboro Snus, Camel Snus)**

1. Never tried, not even once
2. Tried it before
3. Use occasionally
4. Use daily

**D. Roll-your-own cigarettes**

1. Never tried, not even once
2. Tried it before
3. Use occasionally
4. Use daily

**E. Smoking tobacco from a hookah or waterpipe**

1. Never tried, not even once
2. Tried it before
3. Use occasionally
4. Use daily

**F. Electronic cigarettes or e-cigarettes (e.g., BluCig, SmokeTip, ProSmoke, NJoy)**

1. Never tried, not even once
2. Tried it before
3. Use occasionally
4. Use daily

**G. Nicotine replacement products (e.g., nicotine gum, patch, lozenge, or inhaler)**

1. Never tried, not even once
2. Tried it before
3. Use occasionally
4. Use daily

**H. Regular tobacco cigarettes (e.g., Marlboro, Camel, Winston, Newport)**

1. Never tried, not even once
2. Tried it before
3. Use occasionally
4. Use daily

**4. Which if any of these products are safer than regular cigarettes? Select all that apply.**

1. Smokeless, chewing tobacco (e.g., Skoal, Copenhagen)
2. Dissolvable tobacco (Ariva, Stonewall, Camel Orbs, Camel sticks or strips)
3. Snus (Marlboro Snus, Camel Snus)
4. Roll-your-own cigarettes
5. Smoking tobacco from a hookah or waterpipe
6. Electronic cigarettes or e-cigarettes
7. Nicotine replacement products (nicotine gum, patch, lozenge, inhaler)

**5. What was the first tobacco product you ever tried?**

1. I've never tried any tobacco product, not even once.
2. Regular tobacco cigarettes (e.g., Marlboro, Winston, Kool, Camel, etc.)
3. Smokeless, chewing tobacco (e.g., Skoal, Copenhagen)
4. Dissolvable tobacco (Ariva, Stonewall, Camel Orbs, Camel sticks or strips)
5. Snus (Marlboro Snus, Camel Snus)
6. Roll-your-own cigarettes
7. Smoking tobacco from a hookah or waterpipe
8. Electronic cigarettes or e-cigarettes
9. Nicotine replacement products (nicotine gum, patch, lozenge, inhaler)

**6. How many people in your home…**

a. Smoke regular cigarettes _____

b. Use an e-cigarette _____

c. Use a tank system _____

d. Use *both* regular cigarettes and an e-cigarette/tank system _____

**7. On a scale from 0-10, where 0="not at all harmful", and 10="extremely harmful", how harmful to your health do you think the following are?**

| Product | Harm Rating |
|---|---|
| Electronic Cigarettes | |
| Tank System | |
| Regular Cigarettes | |
| Smokeless Tobacco | |

| | |
|---|---|
| Nicotine Gum | |
| Nicotine Patch | |
| Nicotine Lozenge | |
| Nicotine inhalator | |
| Chantix | |
| Wellburtin/Zyban | |
| Marijuana | |
| Hookah | |
| Snus | |

8. **On a scale of 1 – meaning not at all important and 10 – meaning extremely important, how important do you feel it is to quit using nicotine products_____?**

9. **On a scale of 1 – meaning not at all confident and 10 – meaning extremely confident, how confident are you that you could quit using nicotine products_____?**

10. **Please list the order in which you have tried the following products (write 0 or leave blank if you have never tried a product):**

| Product | Rank Order |
|---|---|
| Electronic Cigarettes | |
| Tank System | |
| Regular Cigarettes | |
| Smokeless Tobacco | |
| Nicotine Gum | |

| | |
|---|---|
| Nicotine Patch | |
| Nicotine Lozenge | |
| Nicotine inhalator | |
| Chantix | |
| Wellburtin/Zyban | |
| Marijuana | |
| Hookah | |
| Snus | |

Appendix C
TABLES

Table 1. Caregiver Demographics

| Variable | Percent |
|---|---|
| **Age (years; M (SD))** | 37.58 (8.54) |
| **Relationship to Child** | |
| Father | 12.9% |
| Mother | 87.10% |
| **Ethnicity** | |
| African American | 90.30% |
| White | 3.20% |
| Middle Eastern | 6.5% |
| **Annual Family Income** | |
| 0 – 20,000 | 33.30% |
| 21,000 – 40,000 | 33.40% |
| 41,000 – 50,000 | 16.70% |
| 60,000 or Greater | 16.70% |
| **Education Level** | |
| High school graduate | 45.20% |
| College graduate | 32.30% |
| Master level graduate | 6.50% |
| Undisclosed | 16.10% |
| **Martial Status** | |
| Married | 46.70% |
| Separated | 10.00% |
| Divorced | 6.70% |
| Never Married | 36.70% |
| **Primary Insurance** | |
| Private | 7.40% |
| Employer Provided | 33.30% |
| Medicare | 7.40% |
| SoonerCare or Medicaid | 40.70% |
| No Insurance | 11.10% |

Note. Percent of participants reported, unless otherwise noted.

Table 2. Child Demographics.

| Variable | Percent |
|---|---|
| **Age (years; M (SD))** | 9.00 (4.48) |
| **Gender** | |
| Male | 41.90% |
| Female | 58.10% |
| **Ethnicity** | |
| African American | 90.3% |
| White | 3.20% |
| Middle Eastern | 6.50% |
| **Sickle Cell Type** | |
| SS | 45.20% |
| SC | 41.90% |
| S/Beta 0 | 3.20% |
| HgbS/HgbD | 3.20% |
| HgbS/Beta+Thalassemia | 3.20% |
| Unspecified | 3.20% |

Note. Percent of participants reported, unless otherwise noted.

Table 3. Medical Information and Biochemical Data

| Variables | M (SD) |
|---|---|
| **Caregiver Exhaled CO** | 3.93 p.p.m. (4.54 p.p.m.) |
| **Child Exhaled CO** | 4.35 p.p.m. (2.68 p.p.m.) |
| **Child Previous Diagnosis of Asthma (Percent diagnosed)** | 35.50% |
| **Child Cotinine** | .92 ng/mL (1.28 ng/mL) |
| **Number of Emergency Department Visits** | |
| 30 days | .32 (.65) |
| 365 days | 1.52 (2.47) |
| **Number of Sickle Cell Crises** | |
| 30 days | .19 (.48) |
| 365 days | 1.0 (2.05) |
| **Number of Acute Chest Syndrome Occurrences** | |
| 30 days | .06 (.25) |

Note. CO = Carbon Monoxide; p.p.m. = parts per million; ng/mL = Nanogram/milliliter; means (standard deviation), unless otherwise noted.

Table 4. Correlations

| Variables | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Child Gender** | 1 | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Child Age** | .312 | 1 | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Child Cotinine** | -.072 | -.301 | 1 | --- | --- | --- | --- | --- | --- | --- | --- |
| **Caregiver Gender** | .063 | .000 | .045 | 1 | --- | --- | --- | --- | --- | --- | --- |
| **Caregiver Age** | .020 | .487** | -.166 | -.420* | 1 | --- | --- | --- | --- | --- | --- |
| **SC Type** | -.313 | -.001 | .078 | -.042 | -.025 | 1 | --- | --- | --- | --- | --- |
| **PAD** | -.190 | .351 | -.162 | -.117 | .181 | -.147 | 1 | --- | --- | --- | --- |
| **EDV** | .325 | .058 | -.028 | -.106 | .097 | -.200 | .257 | 1 | --- | --- | --- |
| **ACS** | .223 | -.295 | -.114 | .101 | -.112 | -.193 | .080 | .686** | 1 | --- | --- |
| **SCC** | .350 | -.139 | .094 | -.046 | -.037 | -.187 | .125 | .863** | .730** | 1 | --- |
| **Former/ Current Smoker** | .202 | .184 | .482* | -.213 | .284 | -.060 | .179 | .048 | -.155 | .071 | 1 |

Note. **= Correlation is significant at the 0.01 level (2-tailed). *=Correlation is significant at the 0.05 level (2-tailed). SC = Sickle Cell. EDV = Emergency department visits. ACS = Acute Chest Syndrome. SCC = Sickle Cell Crises. PAD = Previous Asthma Diagnosis. EDV, ACS, and SCC were documented in the medical record within 30 days of participation date. Former/Current Smokers were defined as those who endorsed having 100+ cigarettes in their lifetime.

Table 5. Caregiver-Reported Nicotine and Tobacco Use/Perceptions

| Variables | Frequency (Percent) |
|---|---|
| **More than 100+ Cigarette in Caregiver's Lifetime** | |
| No | 23 (74.20%) |
| **Current Regular Smoker** | |
| No | 27 (87.10%) |
| Occasionally | 2 (6.50%) |
| **Ever Tried (Yes)** | |
| Snus | 1 (3.20%) |
| Hookah | 2 (6.50%) |
| Electronic Cigarettes | 7 (22.50%) |
| Nicotine Replacement Therapy | 1 (3.20%) |
| Regular Cigarettes | 6 (19.40%) |
| **Safer Than Regular Cigarettes (Yes)** | |
| Skoal | 4 (12.90%) |
| Dissolvable Tobacco | 0 |
| Snus | 1 (3.20%) |
| Roll Your Own Cigarettes | 0 |
| Hookah | 1 (3.20%) |
| Electronic Cigarettes | 11 (35.50%) |
| Nicotine Replacement Therapy | 9 (29.00%) |
| **First Tobacco Product Tried** | |
| Regular Tobacco Cigarettes | 13 (41.90%) |
| Smokeless Tobacco | 2 (6.50%) |
| Nicotine Replacement Therapy | 1 (3.20%) |
| Never Tried Tobacco | 15 (48.40%) |
| **Number of People Who Use Tobacco/Nicotine** | |
| Regular Cigarettes | 7 (22.60%) |
| Electronic Cigarettes | 1 (3.20%) |
| Tank Electronic Cigarette | 3 (9.70%) |
| Regular Cigarettes and Electronic Cigarettes | 0 |
| **Perception of Relative Harm (Mean (SD))** | |
| Electronic Cigarettes | 6.42 (4.26%) |
| Tank Electronic Cigarette | 7.33 (3.94%) |
| Regular Cigarettes | 9.26 (2.50%) |
| Skoal | 8.23 (3.43%) |
| Nicotine Gum | 6.23 (4.33%) |
| Nicotine Patch | 5.97 (4.29%) |
| Nicotine Lozenge | 5.97 (4.35%) |
| Nicotine Inhalator | 6.35 (4.30%) |
| Chantix | 6.77 (4.07%) |
| Wellbutrin | 7.20 (3.86%) |

| | |
|---|---|
| Marijuana | 7.81 (3.51%) |
| Hookah | 8.17 (3.20%) |
| Snus | 8.29 (3.33%) |

Note. Perception of Relative Harm was ranked on a scale from 0 (not at all) to 10 (extremely).

Appendix D

University of Oklahoma Health Sciences Center IRB Approval

Oklahoma State University IRB Approval

The UNIVERSITY of OKLAHOMA

## Institutional Review Board for the Protection of Human Subjects

### Initial Submission – Expedited Approval

**Date:** July 08, 2015

**IRB#:** 5608
**Approval Date:** 07/08/2015
**Expiration Date:** 06/30/2016

**To:** Theodore L Wagener, PhD

**Study Title:** A Preliminary Investigation of Psychosocial Effects in Sickle Cell

**Reference Number:** 640149

**Collection/Use of PHI:** Yes

**Expedited Criteria:** Expedited Category 7

On behalf of the Institutional Review Board (IRB), I have reviewed and granted expedited approval of the above-referenced research study. Study documents (e.g. protocol, consent, survey, etc.) associated with this submission are listed on page 2 of this letter. To review and/or access the submission forms (e.g. application, review response form) as well as the study documents approved for this submission, click *My Studies*, click to open this study, under *Protocol Items*, click to view/access the current approved *Application*, *Informed Consent*, or *Other Study Documents*.

**If this study required routing through the Office of Research Administration (ORA), you may *not begin your study yet*, as per OUHSC Institutional policy, until the contract through ORA is finalized and signed.**

As principal investigator of this research study, you are responsible to:

- Conduct the research study in a manner consistent with the requirements of the IRB and federal regulations 45 CFR 46 and/or 21 CFR 50 and 56.
- Request approval from the IRB prior to implementing any/all modifications.
- Promptly report to the IRB any harm experienced by a participant that is both unanticipated and related per IRB policy.
- Maintain accurate and complete study records for evaluation by the HRPP Quality Improvement Program and, if applicable, inspection by regulatory agencies and/or the study sponsor.
- Promptly submit continuing review documents to the IRB upon notification approximately 60 days prior to the expiration date indicated above.

In addition, it is your responsibility to obtain informed consent and research privacy authorization using the currently approved, stamped forms and retain all original, signed forms, if applicable.

If you have questions about this notification or using iRIS, contact the IRB @ 405-271-2045 or irb@ouhsc.edu.

Sincerely,

Martina Jelley, MD, MSPH
Chairperson, Institutional Review Board

1000 Stanton L Young Blvd, LIB 176, Okla City, OK 73117 (FWA 00007961)

# Institutional Review Board Authorization Agreement

**Name of Institution or Organization Providing IRB Review** (Designated IRB):
Board of Regents of the University of Oklahoma Health Sciences Center

**IRB Registration #**: IRB00000741
**Federalwide Assurance (FWA) #:** FWA00007961

**Name of Institution Relying on the Designated IRB** (Deferring Institution):
Oklahoma State University **FWA #**: FWA0000493

The Officials signing below agree that Oklahoma State University may rely on the OUHSC IRB for review and continuing oversight of its human subjects research described below:

( ) This Agreement applies to all human subjects research covered by Deferring Institution's FWA.

(x) This Agreement is limited to the following specific protocol(s):

Name of Research Project: A Preliminary Investigation of Psychosocial Effects in Sickle Cell (IRB #5608)
Name of Principal Investigator: Theodore Wagner, PhD
Sponsor or Funding Agency: N/A
Award Number, if any: N/A

(_) Other(*describe*):_____

**Responsibilities of Designated IRB and Deferring Institution**

1. The review performed by the Designated IRB will meet the human subject protection requirements of the Deferring Institution's OHRP-approved FWA.
2. The Designated IRB will follow its written procedures for reporting its findings and actions related to the covered research to appropriate officials at the Deferring Institution.
3. Relevant minutes of IRB meetings will be made available to the Deferring Institution upon request.
4. The Deferring Institution remains responsible for ensuring compliance with the Designated IRB's determinations and with the Terms of its OHRP-approved FWA.
5. The Deferring Institution will be responsible for reviewing and approving HIPAA Authorizations, HIPAA Waivers, and other issues relying on a Privacy Board.
6. This Agreement must be kept on file by both parties and provided to OHRP upon request.

Either party may terminate this Agreement upon 30 days' written notice to the other. Upon termination, the Designated IRB will no longer be responsible for the oversight of the Deferring Institution's research. For five years following termination, the parties shall continue to protect and maintain each other's designated confidential and proprietary information in confidence.

Signature of Signatory Official (Designated IRB)

Jason R. Sanders Date: 12-10-15

Jason R. Sanders, M.D.
Interim Sr. Vice President & Provost

Template Version Date: 10/23/2015

Signature of Signatory Official (Deferring Institution)

Date: 11/18/15

Print Full Name: Kenneth W. Sewell
Institutional Title: Vice President for Research

VITA

Alayna Pauline Tackett

Candidate for the Degree of

DOCTOR OF PHILOSOPHY

Thesis: A PRELIMINARY INVESTIGATION OF THE BIOLOGICAL EFFECTS OF SECONDHAND SMOKE EXPOSURE IN YOUTH DIAGNOSED WITH SICKLE CELL DISESAE

Major Field: Clinical Psychology

Biographical:

Education:

Completed the requirements for the Doctor of Philosophy in Clinical Psychology at Oklahoma State University, Stillwater, Oklahoma in May 2016.

Completed the requirements for the Master of Science in Clinical Psychology at Oklahoma State University, Stillwater, Oklahoma in May 2014.

Experience: Graduate Research Assistant to Larry L. Mullins, Ph.D., Oklahoma State University, August 2012-Present; Graduate Research Assistant to Theodore L. Wagener, Ph.D., Breathe Lab, Oklahoma University Health Sciences Center, August 2012-Present; Clinical experience through Psychological Services Center Oklahoma State University, August 2012- Present.

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