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ABSTRACT

Introduction: Chronic pain is a major healthcare issue. It is debilitating and often occurs simultaneously with other health issues (Murray et al., 2013; Shmagel et al., 2016). The SPADE symptom cluster (sleep disturbance, pain interference, anxiety, depression, and low energy/fatigue) is common in chronic low back pain (cLBP) patients and may interact with their disability (Alamam et al., 2019; Davis et al., 2016; Tavares et al., 2019).

Methods: This cross-sectional study utilized data from the Pain Registry for Epidemiological, Clinical, and Interventional Studies and Innovation (PRECISION). The PROMIS-29 v2.0 was used to assess SPADE symptoms, and the Roland-Morris Disability Questionnaire was used to measure disability. The Spearman-Rho correlation between each SPADE symptom and disability was calculated. The correlations were then tested for significant differences and ranked in order of strongest to weakest correlation. Lastly, groups were assigned based on the number of presenting symptoms and tested for between-groups differences in mean disability.

Results: Each of the five SPADE symptoms and the composite SPADE score were all positively and significantly correlated with disability. Pain Interference was most strongly correlated with disability. SPADE comorbidity was related to disability.

Conclusion: SPADE symptoms greatly increase disability in chronic low back pain patients.

Keywords: Chronic Low Back Pain, Disability, Sleep Disturbance, Pain Interference, Anxiety, Depression, Fatigue

THE SPADE SYMPTOM CLUSTER AND

PHYSICAL DISABILITY IN CHRONIC

LOW BACK PAIN PATIENTS

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I would like to offer my deepest gratitude to Cathleen Kearns, who was monumentally important as a member of my committee and as my internship supervisor at the Osteopathic Research Center (ORC). She provided continued support and went out of her way to guide me throughout the entirety of the practicum. Dr. Licciardone, a committee member and the principal investigator of the PRECISION Pain Research Registry, is also owed my gratitude for his role in teaching me about research practices and statistics, as well as his assistance in my data analysis.

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LIST OF ABBREVIATIONS

ORC: Osteopathic Research Center

SPADE: Sleep Disturbance, Pain Interference, Anxiety, Depression, and Low Energy/Fatigue

cLBP: Chronic Low Back Pain

RMDQ: Roland-Morris Disability Questionnaire

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CHAPTER 1. INTRODUCTION

This Clinical Research Management practicum was completed at the Osteopathic Research Center (ORC) in the Department of Family Medicine at the University of North Texas Health Science Center in Fort Worth, TX. My supervisor and site mentor was Cathleen Kearns. Dr. Deanna Cross was my major professor. Dr. John Licciardone, Dr. Stephen Mathew, and Dr. Patricia Gwirtz served as advisory committee members.

My 26-week, 40 hours per week, internship was completed between May and November of 2019 at the ORC. As a project coordinator, daily tasks included data collection, appointment scheduling and management, and other logistical items necessary for the Pain Registry for Epidemiological, Clinical, and Interventional Studies and Innovation (PRECISION).

My practicum project focused on the relationship between psychosocial quality of life factors—specifically the SPADE symptom cluster (Sleep disturbance, pain interference, anxiety, depression, and fatigue)—and disability in chronic low back pain (cLBP) patients. Previous studies demonstrate that the SPADE symptom cluster and cLBP are major healthcare concerns and commonly comorbid (Shmagel et al., 2016; Davis et al., 2016). There is also evidence that SPADE symptoms and disability due to low back pain are associated (Kanstrup et al., 2014; Tavares et al., 2019). My project had three primary goals: 1) measure the correlations between SPADE symptoms and disability due to low back pain, 2) test for significant differences between those correlations to determine if some are more closely related to disability than others, and 3) examine whether the number of presenting SPADE symptoms is a main effect for disability.

The baseline surveys for the PRECISION Pain Research Registry include the PROMIS-29 v2.0 and Roland-Morris Disability Questionnaire. These instruments were chosen to measure

SPADE symptom presentation and disability, respectively. Spearman rank correlations, a single-sample test of H_0: $\rho_{12} = \rho_{13,}$ and a one-way ANOVA were performed in order to accomplish the aforementioned goals of the study.

CHAPTER II. INTERNSHIP SUBJECT

Background and Literature

Chronic low back pain (cLBP) is common and debilitating. In 2010, cLBP had a point prevalence of 13.1% in the United States (Shmagel et al., 2016). A global review found that in 2012, cLBP had a point prevalence of 11.9% and a one-month prevalence of 23.2%. These rates increased over time (Manchikanti et al., 2014). cLBP was found to be the leading cause of disability in the United States in 1990 and 2010.

Individuals who suffer from cLBP often suffer from multiple comorbidities. Studies show the existence of symptom clusters in cLBP patients (Shmagel et al., 2016). cLBP patients had increased odds of suffering from depressive symptoms, sleep disturbance, obesity, and multiple medical diagnoses (Shmagel et al. 2016). These medical conditions can also contribute to disability. For example, Major Depressive Disorder (MDD) was the second leading cause of disability in 2010 (Murray et al., 2013). Clusters of behavioral, psychosocial, and medical symptoms are an important area of cLBP research (Shmagel et al. 2016).

Because cLBP patients often have other symptoms, it is important to investigate these comorbid conditions. The SPADE symptom cluster—comprised of sleep disturbance, pain interference, anxiety, depression, and fatigue (also called low energy)—has emerged as a common and problematic set of complications in chronic pain patients. One study of general musculoskeletal chronic pain patients found the rates of sleep disturbance, pain interference, anxiety, depression, and fatigue were 60.4%, 80.8%, 42.6%, 37.1%, and 73.3%, respectively (Davis et al., 2016). Only 10.9% of patients examined presented with only pain interference and no other SPADE symptoms. Another study of individuals with chronic painful chemotherapy-

induced peripheral neuropathy found that patients often experience SPADE symptoms in clusters: 10.2% of participants reported no SPADE symptoms, 23.7% experienced one, 11.9% experienced two, 28.8% experienced three, 20.3% experienced four, and 5.1% experienced all five (Knoerl et al., 2018). They also found that sleep disturbance/fatigue and anxiety/depression were the symptom pairs most likely to co-occur (Knoerl et al., 2018).

To date, there have been few studies that have examined the SPADE symptom cluster in cLBP patients, but there are studies that support a link between SPADE symptoms and disability in other pain patient populations. Insomnia, a sleep-related pathology that could cause sleep disturbance, was found to explain a significant amount of functional disability in pediatric chronic pain patients (Kanstrup et al., 2014). Depressive symptoms were found to predict pain-related disability in children that developed chronic pain after a new acute musculoskeletal pain complaint (Holley et al., 2017). Similar studies have been conducted in patients with acute or subacute low back pain. An improvement in sleep quality was associated with improvement in pain-related disability in a sample of patients from the Spanish Back Pain Research Network (Kovacs et al., 2018). Anxiety, depression, and fatigue were all found to be associated with pain-related disability in Brazilian medical students with low back pain (Tavares et al., 2019).

Several of the SPADE symptoms have been examined in cLBP patients specifically. A prospective cohort study in a Saudi population found that pain intensity at baseline, combined with higher fear avoidance-work and older age, predicted higher disability one year later (Alamam et al., 2019). The same study also found that pain intensity at the 12-month follow-up was explained by higher disability at baseline (25.7% explained), which highlights the bidirectional nature of the SPADE/disability relationship. Anxiety and depression, grouped

together, were also found to be correlated with disability among an elderly veteran population with cLBP in the United States (Weiner et al., 2018).

Although recent efforts have been made to standardize cLBP research methods (Deyo et al, 2014), there is still a considerable amount of variance in existing literature. The aforementioned cLBP studies were conducted all over the world, from the United States (Shmagel et al., 2016) to Spain (Kovacs et al., 2018) to Saudi Arabia (Alamam et al., 2019). SPADE pathologies were measured in several different ways. Sleep was examined as insomnia (Kanstrup et al., 2014), sleep quality (Kovacs et al., 2018), or fatigue (Tavares et al., 2019). Depression was measured with a single question (Tavares et al., 2019) or a 20-item survey (Holley et al., 2017). Even disability, the common variable of interest in these studies, was measured with several different tools like the Arabic Oswestry Disability Index (Alamam et al., 2019) or Roland-Morris Disability Questionnaire (Tavares et al., 2019). These differences in research populations and methods make it difficult to compare and generalize results (Shmagel et al. 2016), but they also show that chronic low back pain is a global problem with similar consequences in diverse populations.

Specific Aims

The problem I aim to address is that the correlation between SPADE symptom presentation and the effect of comorbidities on disability are not clear due to inconsistency in cLBP research methods. There is also a need for a study that looks at all five SPADE symptoms in cLBP patients. In order to provide such clarity, my project has three specific aims.

Specific Aim #1: Measure the correlation between SPADE symptoms and physical disability.

Hypothesis #1: All five SPADE symptoms will be significantly and positively correlated with disability in chronic low back pain patients.

Specific Aim #2: Determine which SPADE symptoms are most closely associated with physical disability by testing whether the correlations differ from each other.

Hypothesis #2: Depression and pain interference will be most strongly associated with disability.

Specific Aim #3: Examine whether the number of SPADE symptoms that an individual presents with affects disability. Specify the rates of SPADE symptom presentation and comorbidity within chronic pain patients.

Hypothesis #3: Individuals presenting with more SPADE symptoms will have greater disability.

Significance

The long-term treatment of chronic pain is generally ineffective (Bredow et al., 2016). This increases the importance of pain management practices, yet the majority of patients with cLBP develop disability or report symptoms related to psychosocial quality-of-life measures (Weiner et al., 2018). This project will help clarify the relationship between those complications and create a foundation for future research to improve pain management practices.

Materials and Methods

Population

This study utilized data from the Pain Registry for Epidemiological, Clinical, and Interventional Studies and Innovation (PRECISION), which had 577 individuals suffering from chronic and subacute low back pain in the Dallas/Fort Worth metroplex at the time of data analysis on September 10th, 2019 (Licciardone, 2018). Inclusion criteria were 21 – 79 years of

age, self-reported low back pain for at least three to six months, self-reported low back pain on at least half the days of the last six months, and report having a physician that could provide treatment for low back pain. Exclusion criteria were pregnancy, incarceration, or institutionalization (Licciardone, 2018). These criteria comply with the NIH Research Task Force definition of cLBP (Deyo et al, 2014). Of the 577 PRECISION participants, 519 met the inclusion criteria and did not meet the exclusion criteria for chronic low back pain. Table 1 provides descriptive statistics for the sample. Table 2 provides descriptive statistics for their pain.

Table 1. Sample Descriptive Statistics

	N	Frequency	Percent
Gender	519		
Male		151	29.1%
Female		368	70.9%
Race	519		
American Indian or Alaskan Native		10	1.9%
Asian		5	1.0%
Black or African American		146	28.1%
Native Hawaiian or Pacific Islander		3	0.6%
White		355	68.4%
Ethnicity	519		
Hispanic or Latino		67	12.9%
Not Hispanic or Latino		452	87.1%
Education Level	519		
No high school diploma		33	6.4%
High school graduate or GED		98	18.9%
Some college, no degree		145	27.9%
Occupational/technical/vocational program		29	5.6%
Associate's degree		40	7.7%
Bachelor's degree		109	21.0%
Master's degree		52	10.0%
Professional school degree (e.g., physician, dentist, attorney)		5	1.0%
Doctoral degree (e.g., Ph.D)		8	1.5%
Smoking Habit	519		
Current smoker		107	20.6%
Used to smoke, but have now quit		161	31.0%
Never smoked		251	48.4%

	N	Minimum	Maximum	Mean	Std. Dev.
Age (y)	519	21	79	53.4	12.2
Height (in)	489*	55	77	66.2	3.9
Weight (lb)	489*	85	463	207.2	53.8
BMI	489*	16.6	70.5	33.4	8.4

*Height and weight data were missing for 30 subjects because it was not collected at the onset of the study

Table 2. Pain Descriptive Statistics

	N	Frequency	Percent
Widespread Pain	519		
Not at all		192	37.0%
A little bit		189	36.4%
A lot		138	26.6%
Low Back Pain Duration	519		
3 – 6 Months		8	1.5%
6 Months – 1 Year		24	4.6%
1 – 5 Years		149	28.7%
>5 Years		338	65.1%
Low Back Pain Operation	519		
Yes, one operation		38	7.3%
Yes, more than one operation		36	6.9%
No		445	85.7%
Work Loss Due to Low Back Pain	519		
Yes		203	39.1%
No		316	60.9%

	N	Minimum	Maximum	Median	IQR
Numerical Rating Scale*	519	0	10	6	3
RMDQ	519	0	24	15	9

*NRS survey item asks participants, "In the past 7 days, how would you rate your low-back pain on average? Rate your pain as a number from 0 to 10"

	N	Minimum	Maximum	Median**	IQR
Composite SPADE Score	519	37.7	76.4	56.2	10.3
Sleep Disturbance	519	32	73.3	56.1	9.3
Pain Interference	519	41.6	75.6	62.5	8.1
Anxiety	519	40.3	81.6	53.7	21.1
Depression	519	41.0	79.4	51.8	17.9
Fatigue	519	33.7	75.8	57.0	13.6

**Median was chosen for central tendency because several of the SPADE scores were not normally distributed.

Data Collection

As part of their baseline survey, PRECISION subjects completed the PROMIS-29 v2.0 and the Roland-Morris Disability Questionnaire (RMDQ). These were used to measure the presentation of SPADE symptoms and physical disability, respectively.

The Patient-Reported Outcomes Measurement Information System (PROMIS) was developed to assess well-being in physical, mental, and social domains of health (Cella et al., 2007). The PROMIS-29 v2.0 utilizes the PROMIS item bank in order to "assess pain using a single 0–10 numeric rating item and seven health domains" (Hays et al., 2018, p. 1885). The health domains include the SPADE symptoms. Each domain is comprised of four items. Each item has five response options and thus returns a value from 1 to 5. The four items in each domain are then totaled to yield a score ranging from 4 to 20, with high scores representing worse severity (Hays et al., 2018). The scores for each domain are then normalized so that 50 represents the mean and 55 signals clinically significant impairment, defined as one half standard deviation above the mean. This study used the measures from appropriate PROMIS-29 v2.0 domains to assess presentation of the SPADE symptoms: sleep disturbance, pain interference, anxiety, depression, and fatigue. The PROMIS four-item scales for anxiety and depression have shown internal validity as well as convergent validity with other measures of anxiety and depression (Kroenke et al., 2014).

The RMDQ is a 24-item self-report questionnaire that measures physical disability due to low-back pain (Roland & Morris, 1983). It is scored by totaling the number of items that a patient believes are applicable to him or her and thus can range from 0 to 24, with higher scores representing higher levels of disability.

Statistical Analysis

Six Spearman-rank correlations between RMDQ and the five SPADE symptoms plus the composite SPADE score were completed using IBM SPSS Statistics software (version 25). Spearman-rank was the chosen test because the RMDQ scores were found to not be normally distributed via the Kolmogorov-Smirnov test. The PROMIS-29 v2.0 domain score for one symptom and the RMDQ score served as the variables in each test.

After finding the Spearman Rho correlation coefficients, Equation 1 was used to test for differences between them. It is a single sample test of H_0: $\rho_{12} = \rho_{13}$ (Kleinbaum, 2008).

Equation 1.

$$z = \frac{(r_{12} - r_{13})\sqrt{n}}{\sqrt{(1 - r_{12}^2)^2 + (1 - r_{13}^2)^2 - 2r_{23}^3 - (2r_{23} - r_{12}r_{13})(1 - r_{12}^2 - r_{13}^2 - r_{23}^2)}}$$

A new variable, named SPADE comorbidity, was created that divided subjects into groups determined by how many presenting SPADE symptoms they had. Significant symptom presentation was defined as a normalized score ≥55. The SPADE comorbidity values served as the groups for a one-way ANOVA that tested for between-groups differences in the dependent variable: disability. Given that there are five SPADE symptoms, an individual could have zero, one, two, three, four, or five presenting symptoms. SPADE comorbidity therefore had six values. The ANOVA tested whether the number of presenting SPADE symptoms was a main effect for disability. If the ANOVA found a significant difference, Fisher's LSD was used for post-hoc testing.

The Bonferroni correction was used to reduce the chance of Type 1 errors. The six correlations were thus tested at an alpha level of .0083. Equation 1 was used 10 times, so it was

tested at a significance of .005. Post-hoc testing for the ANOVA, which entailed 15 tests, set alpha at .003.

Results

Correlations Testing

All five SPADE symptoms were positively and significantly correlated with disability. Table 3 shows the Spearman's Rho for each SPADE symptom's correlation with RMDQ disability. Pain interference had the highest Spearman's Rho at .752. Fatigue, anxiety, and depression were closely grouped in the middle at .483, .444, and .439, respectively. Sleep disturbance had the lowest Spearman's Rho at .386. All five correlations, as well as the correlation for the composite SPADE score (.638), were found to be significant at the .0083 level. Figures 1-6 are scatterplots that display the values for the RMDQ and SPADE symptoms scores. The red line on each plot is drawn at the level of significant SPADE symptom impairment i.e. a score of 55.

Table 3. Correlations Between RMDQ Disability and SPADE Symptoms

SPADE Symptom	Spearman's Rho	P-value
Composite	.638*	<.001
Sleep Disturbance	.386*	<.001
Pain Interference	.752*	<.001
Anxiety	.444*	<.001
Depression	.439*	<.001
Fatigue	.483*	<.001

*Correlation is significant after the Bonferroni correction

Figure 1. Plot of RMDQ vs. Composite SPADE

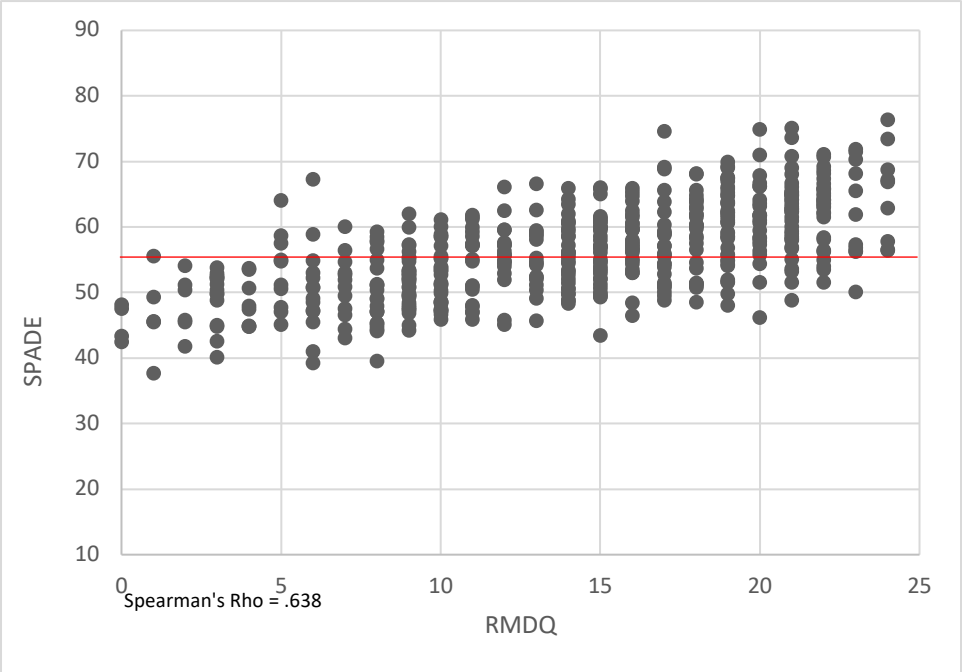


Figure 2. Plot of RMDQ vs. Sleep Disturbance

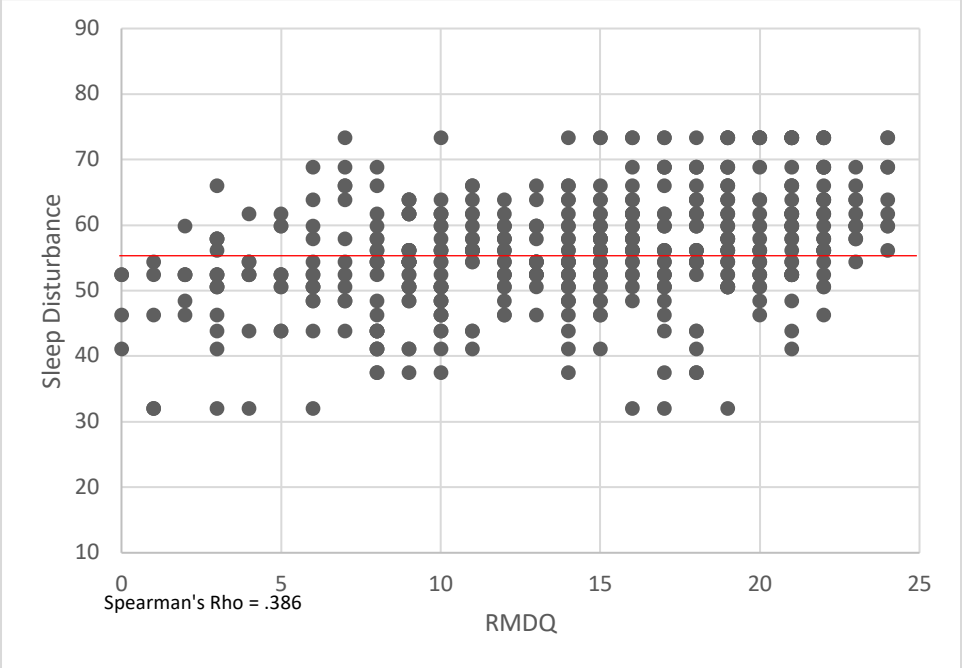


Figure 3. Plot of RMDQ vs. Pain Interference

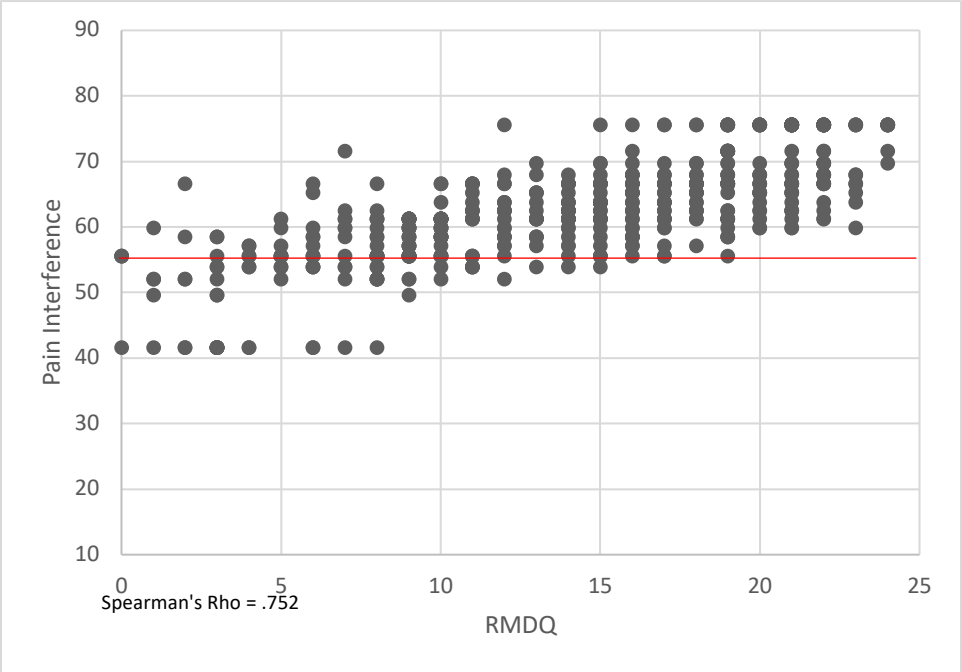


Figure 4. Plot of RMDQ vs. Anxiety

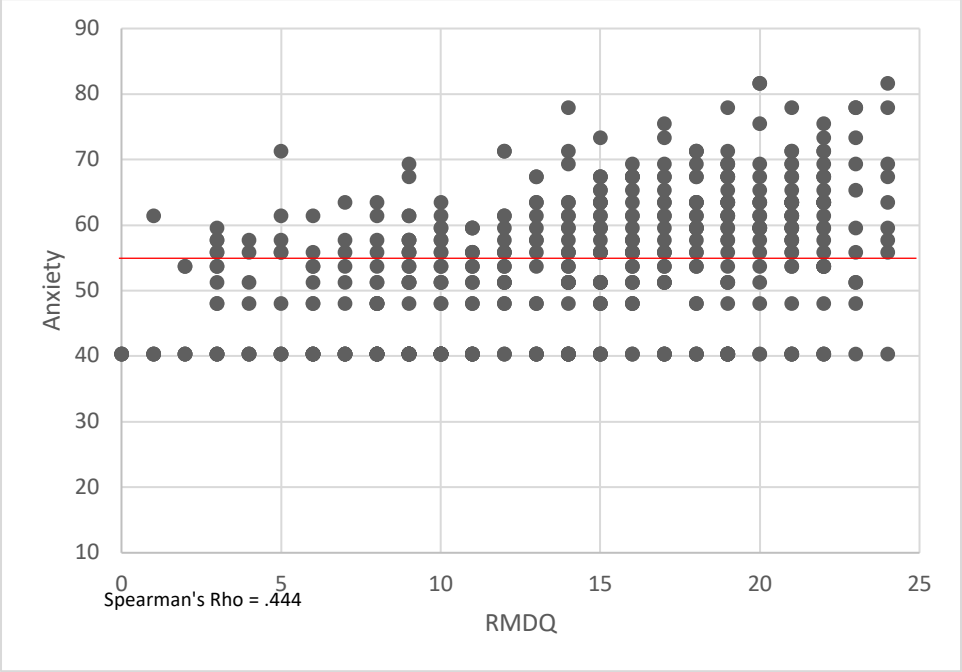


Figure 5. Plot of RMDQ vs. Depression

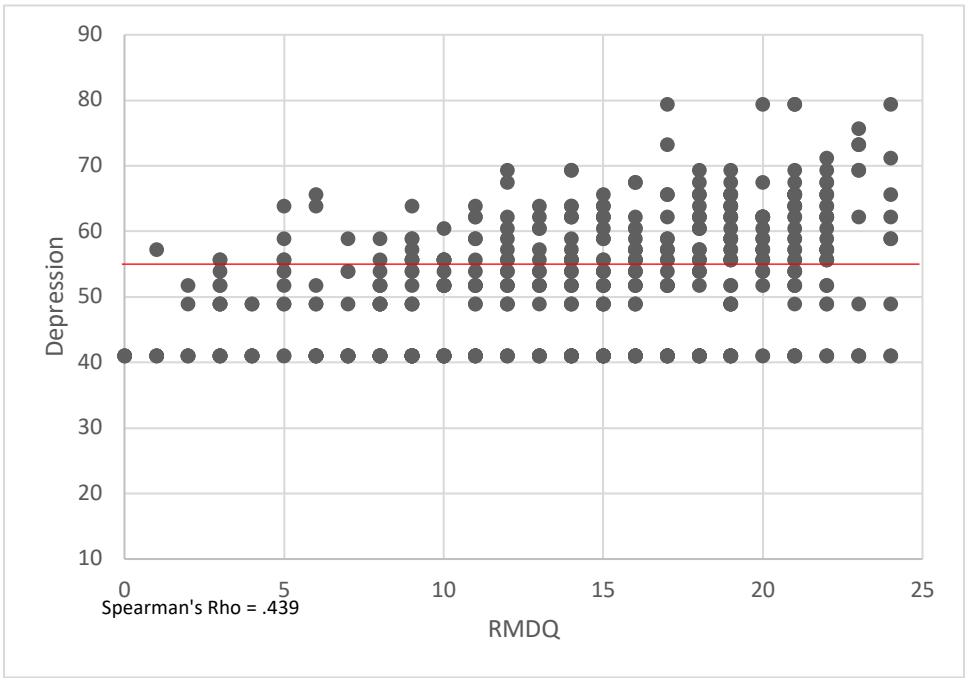
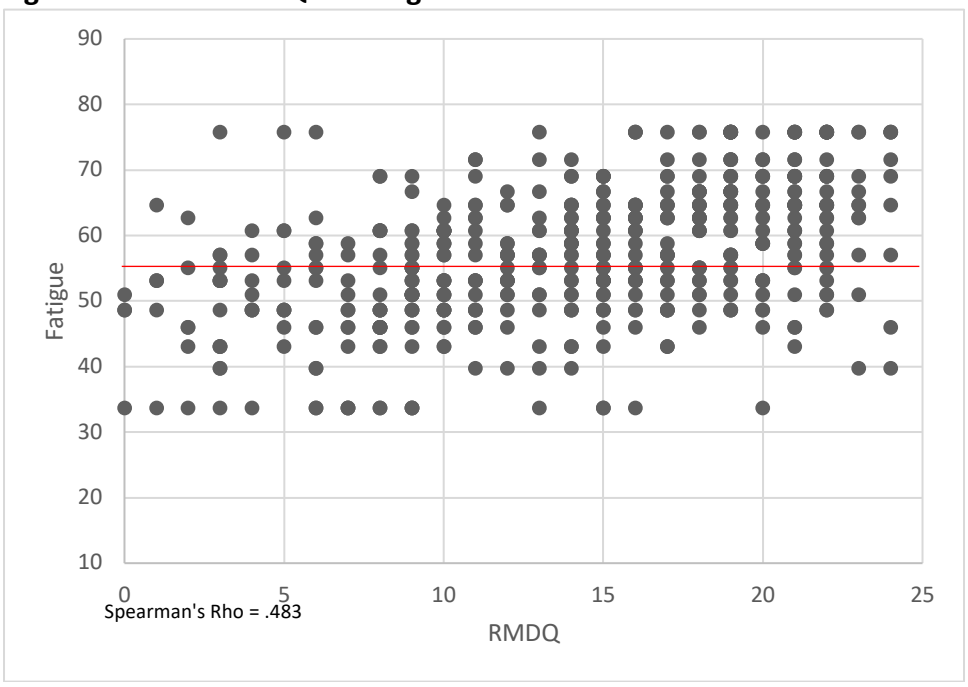


Figure 6. Plot of RMDQ vs. Fatigue



Testing for Differences in the Correlations

Each SPADE symptom was correlated with disability with the descending order of strength being: pain interference, fatigue, anxiety, depression, and sleep disturbance. However, before concluding that this order is true, the correlations must be tested on the assumption that they are equivalent (H_0: $\rho_{12} = \rho_{13}$). The results yielded by Equation 1 are shown in Table 4. Pain interference was more strongly correlated with disability than the other four SPADE symptoms, but no other significant differences were found.

Table 4. Z-Scores Showing Differences Between RMDQ/SPADE Symptom Correlations

	ρ_{13}			
ρ_{12}	Sleep Disturbance	Pain Interference	Anxiety	Depression
Pain Interference	9.78*			
Anxiety	1.28	8.81*		
Depression	1.13	9.12*	0.17	
Fatigue	2.43	8.82*	1.04	1.18

*Correlations differ significantly after the Bonferroni correction

SPADE Comorbidity

The mean RMDQ score for registrants with no presenting SPADE symptoms was 5.21. The mean increased to 9.67 for participants with one presenting symptom, 12.94 for two, 14.84 for three, 15.83 for four, and 18.55 for participants presenting with all five SPADE symptoms. Figure 7 displays the mean RMDQ score for each level of SPADE comorbidity. A one-way ANOVA was performed to test for differences between the groups. It found that significant differences did exist between the mean RMDQ scores of the six groups (p-value < .001). Fisher's LSD was used for post-hoc testing. Only two pairs of means were not significantly different: those of individuals that had comorbidity scores of 2 and 3 and those of individuals with scores of 3 and

4. Table 5 shows the results of the post-hoc testing. Table 6 provides information on the clustering of SPADE symptoms.

Figure 7. Mean Disability by Number of Presenting SPADE symptoms

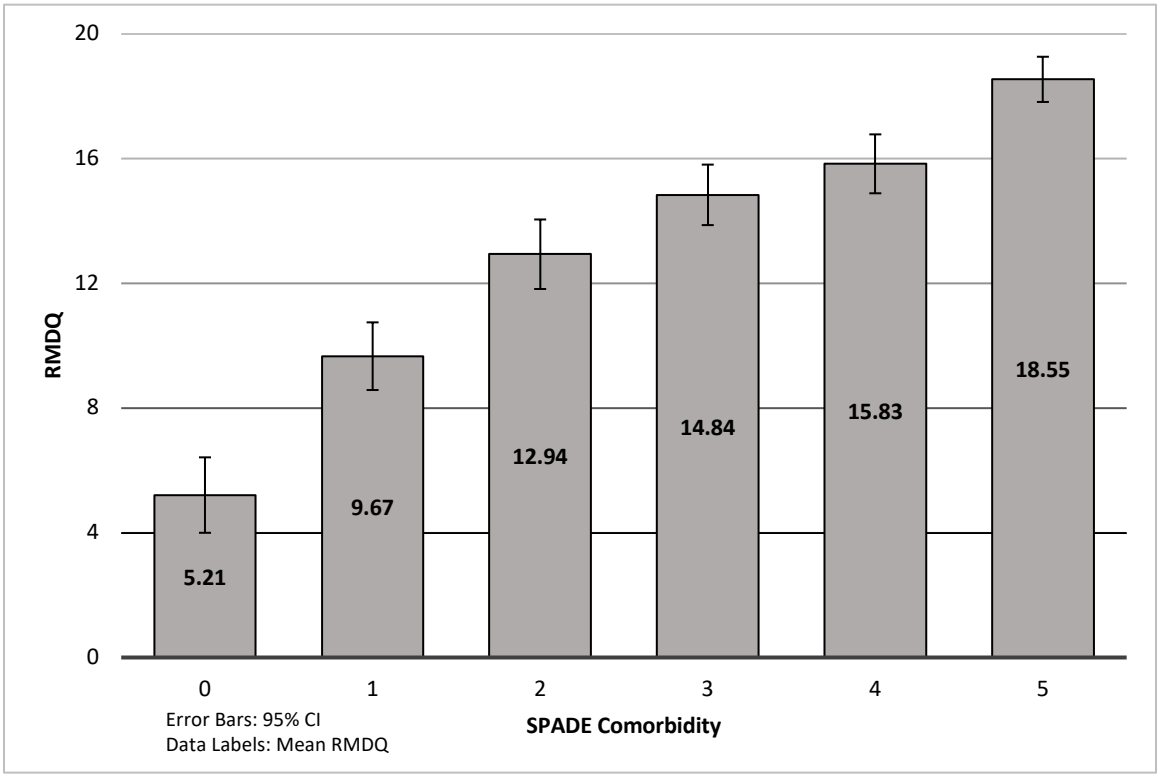


Table 5. SPADE Comorbidity Post-hoc Testing

	Fisher's LSD				
	Comorbidity				
Comorbidity	0	1	2	3	4
1	<.001*				
2	<.001*	<.001*			
3	<.001*	<.001*	.005		
4	<.001*	<.001*	<.001*	.13	
5	<.001*	<.001*	<.001*	<.001*	<.001*

*Means differed significantly after Bonferroni correction

Table 6. Clustering of SPADE Symptoms

	SPADE Symptom 1				
Comorbid Symptom 2	Sleep Disturbance (n = 282)	Pain Interference (n=462)	Anxiety (n=259)	Depression (n=212)	Fatigue (n=318)
Sleep, n (%)		264 (57.1)	170 (65.6)	138 (65.1)	219 (68.9)
Pain, n (%)	264 (93.6)		246 (95.0)	203 (95.8)	305 (95.9)
Anxiety, n (%)	170 (60.3)	246 (53.2)		180 (84.9)	202 (63.5)
Depression, n (%)	138 (48.9)	203 (43.9)	180 (69.5)		176 (55.3)
Fatigue, n (%)	219 (77.7)	305 (66.0)	202 (78.0)	176 (83.0)	
# of Comorbid Symptoms	Sleep Disturbance (n = 282)	Pain Interference (n=462)	Anxiety (n=259)	Depression (n=212)	Fatigue (n=318)
1, n (%)	8 (2.8)	67 (14.5)	2 (0.8)	0 (0.0)	4 (1.3)
2, n (%)	34 (12.1)	87 (18.8)	21 (8.1)	9 (4.2)	35 (11.0)
3, n (%)	71 (25.2)	101 (21.9)	39 (15.1)	29 (13.7)	78 (24.5)
4, n (%)	61 (21.6)	99 (21.4)	89 (34.4)	66 (31.1)	93 (29.2)
5, n (%)	108 (38.3)	108 (23.4)	108 (41.7)	108 (50.9)	108 (34.0)

Discussion

This study sought to examine the relationship between SPADE symptoms and disability by measuring their correlation, testing for differences between those correlations, and examining whether the number of presenting symptoms affects disability. The results yielded three important findings.

The first is that each SPADE symptom is significantly and positively associated with disability. This was hypothesized and supported by each Spearman-rank correlation yielding a p-value of <.001. Previous research had already shown a correlation between SPADE symptoms and disability (Murray et al., 2013; Kovacs et al., 2018; Tavares et al., 2019), but had used a wide variety of populations and methods. This study serves to validate those findings and support their generalizability. This is an imperative step for cLBP research and clinical application. In a systematic review of cLBP research examining which factors predict

rehabilitation outcomes, van der Hulst et al. (2005, p. 813) stated that the variability in cLBP research methods makes it "difficult to draw a final conclusion about prognostic factors of treatment outcome." That statement is supported by the general ineffectiveness of cLBP treatments. An investigation of cLBP treatment guidelines found that only four guidelines (out of seventeen total and nine that met inclusion criteria) met specific quality criteria but that even those had areas of weakness (Chetty, 2017). In order to improve the poor treatment outcomes for cLBP patients, it is necessary to standardize research methods and validate existing literature.

The study also sought to determine which SPADE symptoms were most strongly correlated with disability. Based on Spearman's Rho, pain interference had the strongest correlation (.752), followed by fatigue (.483), anxiety (.444), depression (.439), and finally sleep disturbance (.386). However, hypothesis testing with Equation 1 found few significant differences between them. Pain interference was found to be more strongly correlated with disability than the other four SPADE symptoms. No other significant differences existed. Thus, the second important finding of this study is that pain interference is more strongly correlated with disability than the other four SPADE symptoms, but that the other four cannot be ranked.

It was hypothesized that pain interference and depression would be most strongly correlated with disability. Pain interference is conceptually similar to disability and there is overlap in their measures so the high level of correlation was expected. Depression was also thought to be strongly associated with disability because it was found to be the second leading cause of disability in the United States, trailing only chronic low back pain (Murray et al., 2013). The researchers considered that the two conditions may interact to worsen disability in a

population with both, but these results demonstrate that depression was not more strongly correlated with disability in cLBP patients than sleep disturbance, anxiety, or fatigue.

The third important finding of this study is that the number of presenting SPADE symptoms an individual has affects their disability. Figure 7 shows a steady increase in mean disability as SPADE comorbidity increases. A one-way ANOVA returned a significance of <.001 for between groups differences. Post-hoc testing of Fisher's LSD found that only two pairs of groups were not significantly different; comorbidity scores of 2 and 3 were not significantly different, and neither were scores of 3 and 4. Every other difference between the mean disability scores of the SPADE comorbidity groups was significant.

This final result that SPADE comorbidity affects disability is the novel contribution of this study and the most compelling for future research. As Shmagel et al. (2017, p. 1694) stated, "the clustering of behavioral, psychosocial, and medical issues should be considered in the care and rehabilitation of Americans with cLBP." This study suggests that the quality of life in cLBP patients presenting with multiple SPADE symptoms may be improved by treatments that target those symptoms via a reduction in physical disability. Even if their pain cannot be cured, improvement in one or more SPADE symptoms may lead to improved physical functioning.

The main limitations of this study are that it did not account for treatment of cLBP nor the natural progression of the disease. All data was collected from the baseline study for PRECISION participants, who enter the study with different causes of and treatments for their chronic low back pain. Table 2 shows the diversity of their experiences with cLBP. Factors like duration of the disease or frequency of pain may affect disability or SPADE symptoms, or both, and are thus potential confounding variables. A second limitation of the study is that its sample

may not be representative of the general population. For example, it was heavily skewed towards the female gender (70.9%). There may be issues when generalizing these results to a larger population. Finally, it should also be noted that this study has all the limitations of a cross-sectional study.

Summary and Conclusions

Chronic low back pain is a major healthcare issue. It is debilitating and often occurs simultaneously with other health issues (Murray et al., 2013; Shmagel et al., 2016). The SPADE symptom cluster (sleep disturbance, pain interference, anxiety, depression, and low energy/fatigue) is common in chronic low back pain (cLBP) patients and has been previously linked with disability (Alamam et al., 2019; Davis et al., 2016; Tavares et al., 2019).

This cross-sectional study utilized data from the Pain Registry for Epidemiological, Clinical, and Interventional Studies and Innovation (PRECISION) to evaluate the relationship between SPADE symptoms and disability. Each SPADE symptom and the composite SPADE score was found to be positively and significantly correlated with disability. Pain Interference was most strongly correlated with disability. The number of presenting SPADE symptoms did have an effect on average disability.

CHAPTER III. INTERNSHIP EXPERIENCE

Description of Internship Site and Internship Experience

Internship Site

The internship was conducted at the Osteopathic Research Center (ORC) in the Department of Family Medicine at the University of North Texas Health Science Center in Fort Worth, Texas. John Licciardone, DO, MS, MBA is the executive director of the ORC. Ms. Cathleen Kearns serves as the research assistant director. Samantha Johnson is the lead research coordinator. Nicole Phillips, PhD is the director of genomic research. Vishruti Pandya is a research coordinator and student employee. I interned as a project coordinator alongside one other intern, Savannah Cooper.

The primary ORC study during my internship was *The Pain Registry for Epidemiological, Clinical, and Interventional Studies and Innovation (PRECISION).* The goal of the registry is to collect genetic, biomarker, and survey data that can serve as a foundation for research studies on subacute and chronic low back pain. Saliva and blood samples were collected for each subject at the time of enrollment from participants (blood samples were halted for remote participants after the transition to REDCap Cloud). Quarterly surveys that collected self-reported demographic, medical, and psychosocial data were also completed by each registry participant.

During my internship, there was one active sub-study: *Using Health-related Quality of Life Measures to Optimize Chronic Pain Management through Patient Engagement: A Preliminary Registry-based Trial (PRECISION Pain Research Registry),* otherwise referred to as

the SPADE sub-study. PRECISION participants qualified for the SPADE sub-study if they showed significant impairment in the SPADE cluster on the PROMIS-29 in either their baseline, 3-month, 6-month, or 9-month encounter for PRECISION, and if they met the definition for having chronic low back pain. If qualified, consented, and enrolled, subjects completed two encounters. Subjects were randomized to one of two groups. The first group was given the results of the SPADE portion of the PROMIS-29 along with an interpretation guide. One month later, during their second encounter, the first group completed a survey. The second group was not given anything at the first encounter and then were provided their SPADE scores with the interpretation guide at their second encounter.

Internship Experience

I began my internship in May of 2019 during a transition period for the ORC. Due to growth in the PRECISION Registry, the decision had been made to transition from using Qualtrics for data collection and paper records for operations management to using REDCap Cloud (RCC) for both. During my onboarding and training, there was no online system available for use because RCC was in the midst of programming our services and migrating data for previously enrolled subjects. Enrollment was suspended to allow for data migration and all surveys were completed by phone or in person, with all data being recorded on paper. During this time, my primary role was to assist in data collection and re-consenting subjects with a new consent form that informed them of the protocol changes associated with the transition. I also completed several projects like de-identifying the paper and electronic records of a previously completed sub-study: *The Safety and Efficacy of Opioids in Patients with Low Back Pain: A*

Registry-Based Cohort Study to Compare Single- and Multi-Gene Approaches to Precision Medicine Prescribing vs. Usual Care (IPS).

In June, I attended didactic sessions led by Dr. Licciardone. He taught me, Savannah, and the ORC's new student research fellows about the PRECISION protocol, clinical research practices, and statistics. During this time, I also developed my research project proposal.

REDCap Cloud finished developing our new online system in early August. At that point, subjects that preferred to complete their surveys online were able to do so. The ORC staff was able to spend less time completing surveys and instead focused on finishing the transition by inputting the data previously collected on paper into REDCap, cleaning up subject profiles on REDCap and Greenphire (the compensation service used at ORC), re-opening enrollment for PRECISION, and starting enrollment for the SPADE substudy. Cathy, Samantha, Savannah, Vishruti, and I also worked closely to develop processes that fit our new online system. For example, we divided duties for monitoring and compensating the participants that completed surveys online and had no scheduled contact with the staff.

Several weeks after opening RCC, the transition was over. We settled into a routine and were comfortable working with the new system. At this point, my daily tasks centered on tracking reports and managing our survey calendar. Each day, I pulled a report from RCC that would detail which participants were 20 days into their 30-day window to complete their survey. I was tasked with reminding online participants about the survey and ensuring their completion in the remaining ten-day window. As subjects screened and consented to enroll in PRECISION, I also put together and mailed their saliva sample collection kit and Greenphire ClinCard as well as tracked the return of the saliva kit. Twice per week I was tasked with

compensating participants that completed surveys remotely. My other daily tasks were phone surveys and managing the Outlook calendar we use to track appointments.

In mid-September, ORC began to push for expansion. One of the primary reasons for switching to RCC and remote consenting (via DocuSign) was to allow for remote enrollment across the state and easier data management to accommodate more participants. I assisted in recruitment efforts and sometimes took on additional responsibilities to allow other staff members to spend more time on recruitment.

Journal Summary

The Daily Activity Journal in Appendix A details the work I completed each day. It reflects the daily tasks that I detailed previously in the description of my internship experience.

APPENDIX A: DAILY ACTIVITY JOURNAL

Week 1 Daily Activity Log

5/28 Tuesday

- Review protocol, work on paper topic
- Work on paper topic, deliver papers to IRB

5/29 Wednesday

- Work on paper topic and statistical testing
- Assist Samantha with filing/binder organization
- Sent home early due to storm

5/30 Thursday

- File protocol in binder
- Develop paper topic—genetic factors and anxiety/depression?
- Meeting with Dr. Licciardone—introduction, discuss practicum
- Summaries for Samantha
- Rescheduling calls

5/31 Friday

- Rescheduling calls
- Schedule reconsents
- IPS Deidentification
- Schedule reconsents

Student signature: Noah Hendrix Date: 6/17/19

Mentor signature: Cathleen M. Kearns Date: 6-17-19

Week 2 Daily Activity Log

6/3 Monday

- Move office
- Didactic—Introduction to ORC, PRECISION, Fellowship program
- Visit Help Desk about canvas issues
- Meet with Dr. Cross—paper topic, discuss genetic research
- IPS Deidentification

6/4 Tuesday

- Genetics research
- Didactic—PRECISION recruitment overview
- Deidentification
- Meet with Cathy—discuss practicum and upcoming ORC activity (redcap, IPS)
- IPS Deidentification

6/5 Wednesday

- Deidentification
- Meet with Cathy—discuss paper topic (SPADE and disability)

6/6 Thursday

- Research for committee meeting
- IPS Deidentification

6/7 Friday

- IPS Deidentification
- Work on meeting presentation
- Committee meeting—project proposal
- IPS Deidentification

Student signature: Noah Hendrix Date: 6/17/19

Mentor signature: Cathleen M. Kearns Date: 6-17-19

Week 3 Daily Activity Log

6/10 Monday
- Paper topic research
- Didactic—library research
- Doctor appointment
- Staff meeting—reconsenting, ramifications of woman withdrawing consent

6/11 Tuesday
- Finish IPS deidentification

6/12 Wednesday
- Literature review for paper proposal

6/13 Thursday
- Literature review for paper proposal
- Statistical testing for paper proposal

6/14 Friday
- Finish paper proposal
- Meet with Cathy—discuss proposal, what to gain from practicum, budgeting
- Reformat and finalize proposal for Dr. Cross

Student signature: Noah Hendrix Date: 6/17/19

Mentor signature: Cathleen M. Kearns Date: 6-17-19

Week 4 Daily Activity Log

6/17 Monday

- Finalize and send proposal to Dr. Cross
- Rescheduling
- Reconsent appointment
- Rescheduling
- Meet w/ Dr. Hodge
    - Discuss application strategy and letter of recommendation
- Meet w/ Dr. Cross
    - Discuss proposal draft, need to beef up literature review, clearly state hypothesis, elaborate on why it's important, confirm statistical tests

6/18 Tuesday

- Install SPSS at Help Desk
- Didactic—Data management
    - SPSS variable view lesson, SPSS data view lesson
- Work on Project proposal—rewrite importance/hypothesis section, statistics testing research (comparing coefficient of determination?)
- Staff meeting
    - Paper surveys in order to avoid missed appointments while transition to redcap continues
    - No loss to followup during this period
- Discuss statistics with Vishruti, will followup tomorrow

6/19 Wednesday

- SPSS Practice ahead of didactic
- Practice reconsenting ahead of supervised session w/ Samantha
- Reconsent and 15 month survey w/ Samantha
- Reconsent w/ Samantha
- Read about bootstrapping and bivariate correlations
- Reconsent w/ Dina
- Try to install bootstrap fix for SPSS

6/20 Thursday

- Protocol and consent form review
- Practice consenting with Samantha and Dina
- Reconsent and 6 month survey
- Rewrite Problem/Hypothesis section of proposal to reflect changes in statistical testing (bootstrapping)
- Proposal rewrite—methods, measures, statistical analysis, sample, reflect Dr. Cross's feedback

6/21 Friday

- Finish proposal rewrite, send to Dr. Cross
- Didactic—roundtable topic discussion, article discussion, SPSS lesson
- Staff meeting—redcap
- Meet w/ Dr. Licciardone—discuss statistics
- Meet w/ Dr. Cross—discuss proposal

Student signature: Noah Hendrix Date: 6/24/19

Mentor signature: Cathleen M. Keane Date: 8/13/19

Week 5 Daily Activity Log

6/24 Monday

- Arrive
- Presentation—Vision for the UNTHSC Research Enterprise
- Work on scheduling with Savanna
    - Mark down everyone coming up on missed visits
    - Install printer and
- Clin card replacement

6/25 Tuesday

- Arrive and go to GSBS to meet with Carla, but she was unavailable
- Prepare 30 spit kits for mailing later
- Staff meeting about potential move
- Finish 30 spit kits
- Read about Google Voice and VoIP
- Talk with Vishruti and learn about the excel projects she's been working on
- Work on finishing all surveys nearing missed visit status (i.e. those that need to be done by next Friday)

6/26 Wednesday

- Research on VoIPs
- Set up google voice for test run
- 3 month survey
- VoIP research
- 3 month survey
- STARS training session: Post-Award Information
    - Discussion of scenarios involving grant awards and how they can be used
- 3 month survey

6/27/19 Thursday

- Prepare charts for the day
- Didactic sessions—fellow project presentations and discussions
- Discuss VOIP and automated SMS with Cathy
    - Needs to be HIPAA compliant
    - Need to potentially have a lot of minutes
    - She would like the calls to appear from one or two numbers associated with the university
- Phone calls for people that need to be done by next week
- Draft email to Mr. Tissera
- Reconsent and 6 month survey
- Work on proposal presentation and final draft for tomorrow

6/28 Friday

- Review from previous day and prepare surveys/charts for later
- Didactic sessions—fellow project presentations and discussion
- Fellowship lunch with Dr. Licciardone
- Meeting with Dr. Aryal
    - Talk about how to compare correlation coefficients
    - Use equation he provided
- Staff meeting
    - Update on space
- Read about new statistics test

Student signature: Noah Hendrix Date: 6/28/19

Mentor signature: Cathleen M. Kearns Date: 8/13/19

Week 6 Daily Activity Log

7/1 Monday

- Finalize proposal and send to Cathy
- Annual compliance training: “Vision for the UNTHSC Resesrach Enterprise”
- Survey calls
- Send proposal to committee

7/2 Tuesday

- Surveys and voicemails/emails to set up appointments
- 3 month followup surveys
- Work on scheduling

7/3 Wednesday

- Move offices and setup
- In person reconsent and survey

7/4 Thursday

- 4th of July

7/5 Friday

- Several online surveys
- Insert online consent forms into PDF charts

Student signature: Noah Hendrix Date: 7/5/19

Cathleen M. Kearns

Mentor signature: _____ Date: 8/13/19

Week 7 Daily Activity Log

7/8 Monday

- Phone surveys due to REDCap transition
- Scheduling of surveys due through next week
- Insert consent forms into Subject Charts from DocuSign

7/9 Tuesday

- Phone surveys due to REDCap transition
- Scheduling of surveys due through next week
- Insert consent forms into Subject Charts from DocuSign

7/10 Wednesday

- Insert reconsents in subject charts
- Staff meeting—REDCap opening soon
- Gather quotes for new Macbooks, notebooks, and docking stations
- Put together all the charts for the afternoon surveys
- In person survey
- Discuss idea for community event in the spring
- Survey call and charting
- Finish inserting reconsents into subject charts

7/11 Thursday

- Phone/paper surveys due to REDCap transition
- Work on community event plan

7/12

- Phone/paper surveys due to REDCap transition
- Prep charts for next week
- Some more brainstorming for community event

Student signature: Noah Hendrix Date: 7/12/19

Mentor signature: Cathleen M. Kenny Date: 8/13/19

Week 8 Daily Activity Log

7/15 Monday

- Phone surveys due to REDCap transition
- Scheduling of surveys due through next week
- Staff meeting

7/16 Tuesday

- Phone surveys due to REDCap transition
- Scheduling of surveys due through next week

7/17 Wednesday

- Survey calls and charting
- Survey scheduling calls

7/18 Thursday

- Phone/paper surveys due to REDCap transition
- Work on community event plan

7/19

- Phone/paper surveys due to REDCap transition
- Prep charts for next week
- Introductory research on remote blood collection

Student signature: Noah Hendrix Date: 7/19/19

Cathleen M. Kearns

Mentor signature: _____ Date: 8/13/19

Week 9 Daily Activity Log

7/22 Monday

- Several phone surveys (REDCap transition) and reconsents
- Staff Meeting
- Prepare some remote blood collection research for Cathy

7/23 Tuesday

- Phone surveys due to REDCap transition
- Schedule appointments through next week

7/24 Wednesday

- Work on new technology hardware quote
- Send email for hardware exception request form
- Phone survey due to REDCap transition

7/25 Thursday

- Phone surveys due to REDCap transition
- Schedule appointments through next week

7/26 Friday

- Phone surveys due to REDCap transition
- Schedule appointments through next week
- Prep charts for next week

Student signature: Noah Hendrix Date: 7/26/19

Cathleen M. Kearns

Mentor signature: _____ Date: 8/13/19

Week 10 Daily Activity Log

7/29 Monday

- Day off for move

7/30 Tuesday

- Catch up after day off
- Phone surveys due to REDCap transition
- Schedule appointments through next week

7/31 Wednesday

- Phone surveys due to REDCap transition
- Schedule appointments through next week

8/1 Thursday

- Phone surveys due to REDCap transition
- Schedule appointments through next week
- Discuss REDCap management with Cathy

8/2 Friday

- Phone surveys due to REDCap transition
- Schedule appointments through next week
- Talk to Box about cloud needs and getting a quote

Student signature: Noah Hendrix Date: 8/2/19

Cathleen M. Kearns

Mentor signature: _____ Date: 8/13/19

Week 11 Daily Activity Log

8/5 Monday

- Phone surveys due to REDCap transition
- Schedule appointments through next week
- Discuss REDCap transition

8/6

- REDCap training
- Upload Subject Charts to REDCap

8/7 Wednesday

- Finish uploading subject charts to REDCap
- Make phone calls for voided consent forms and doubled 12 month survey
- Discuss data adjudication, management and protocols meant to preserve integrity of data
- Upload birthday, initials, token #, and screening ID

8/8 Thursday

- Upload birthday, initials, token #, and screening ID
- Complete surveys electronically
- Unpack books
- Enter phone survey data into redcap

8/9 Friday

- Enter data into REDCap
- In person survey and reconsent
- Upload birthday, initials, token #, and screening ID

Student signature: Noah Hendrix Date: 8/16/19

Mentor signature: Cathleen M. Kenny Date: 8/13/19

Week 12 Daily Activity Log

8/12 Monday

- Phone surveys
- Weekly meeting with Cathy: schedule thesis defense and data analysis with Dr. Licciardone
- Enter data into redcap

8/13 Tuesday

- Phone surveys
- Finish data entry into redcap

8/14 Wednesday

- Phone surveys
- Input birthday, ID #, and initials in redcap

8/15 Thursday

- Finish inputting birthday, ID #, and initials in redcap
- Phone surveys

8/16 Friday

- REDCap data management discussion
- Prepare and mail flyers for NIH Certification of Confidentiality
- REDCap SPADE walkthrough

Student signature: Noah Hendrix Date: 9/3/19

Cathleen M. Kenny

Mentor signature: _____ Date: 9/3/19

Week 13 Daily Activity Log

8/19 Monday

- SPADE Training
- 20 and 30 day followup calls
- Work to finish catch up calls from redcap transition
- PRECISION Surveys

8/20 Tuesday

- 20 and 30 day lapsed reports
- Follow up compensation
- Phone surveys

8/21 Wednesday

- 20 and 30 day lapsed reports
- Phone surveys
- Prepare saliva kits for mailing

8/22 Thursday

- 20 and 30 day lapsed reports
- Follow up compensation
- Phone surveys

8/24 Friday

- 20 and 30 day lapsed reports
- Phone surveys
- Baseline and enrollment training

Student signature: Noah Hendrix Date: 9/3/19

Cathleen M. Kenner

Mentor signature: _____ Date: 9/3/19

Week 14 Daily Activity Log

8/26 Monday
- 20 and 30 day lapsed reports
- PRECISION Surveys

8/27 Tuesday
- 20 and 30 day lapsed reports
- Follow up compensation
- Work on project while REDCap is down due to upgrade
- Prepare saliva collection kits for mailing

8/28 Wednesday
- 20 and 30 day lapsed reports
- Work on project while REDCap is down due to upgrade

8/29 Thursday
- 20 and 30 day lapsed reports
- Follow up compensation
- PRECISION Surveys
- Prepare saliva collection kits for mailing
- SPADE consenting

8/30 Friday
- 20 and 30 day lapsed reports
- PRECISION Surveys
- Prepare saliva collection kits for mailing

Student signature: Noah Hendrix Date: 9/3/19

Mentor signature: Cathleen M. Kenny Date: 9/3/19

Week 15 Daily Activity Log

9/2 Monday

- UNTHSC Closed for Labor Day

9/3 Tuesday

- 20 and 30 day lapsed reports
- Follow up compensation for remote visits
- Ship saliva collection kits
- Reminder calls and scheduling
- Watch Facebook marketing video series

9/4 Wednesday

- 20 and 30 day lapsed reports
- Phone survey
- Reminder calls and scheduling
- Phone survey
- Finish Facebook marketing video series

9/5 Thursday

- 20 and 30 day lapsed reports
- Follow up compensation for remote visits
- Phone surveys
- Reminder calls
- Deliver returned saliva samples to lab

9/6 Friday

- 20 and 30 day lapsed reports
- SPADE consent
- Mark ineligible SPADE subjects in Greenphire
- Prepare for data analysis meeting with Dr. Licciardone

Student signature: Noah Hendrix Date: 9/20/19

Mentor signature: Cathleen M. Kenner Date: 9/23/19

Week 16 Daily Activity Log

9/9 Monday

- 20 and 30 day lapsed reports
- Ship saliva collection kits
- New subject enrollment

9/10 Tuesday

- 20 and 30 day lapsed reports
- Follow up compensation for remote visits
- Ship saliva collection kits
- Review for data analysis with Dr. Licciardone
- Conduct data analysis with Dr. Licciardone
- Reminder phone calls for lapsed visits
- Phone survey
- Survey scheduling
- Significance testing for correlations

9/11 Wednesday

- 20 and 30 day lapsed reports
- Scheduling calls
- Work on developing first half of paper from proposal

9/12Thursday

- 20 and 30 day lapsed reports
- Follow up compensation for remote visits
- Phone survey
- Survey scheduling

9/13 Friday

- 20 and 30 day lapsed reports
- Staff meeting
- Phone surveys

Student signature: Noah Hendrix Date: 9/20/19

Mentor signature: Cathleen M. Kenny Date: 9/23/19

Week 17 Daily Activity Log

9/16 Monday

- 20 and 30 day lapsed report tracking
- Phone surveys
- Reminder calls for lapsed reports
- Discuss how to track saliva kits with Samantha

9/17 Tuesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- Phone survey
- Staff meeting to discuss carnival community event
- Contact people with saliva kits that have not yet been returned

9/18 Wednesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Phone surveys
- Graphs and tables for results section of paper

9/19 Thursday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Phone surveys
- Follow up compensation for remote visits
- Prepare 20 saliva kits
- Tables for paper and other work

9/20 Friday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Phone surveys
- Deliver returned saliva kits to lab
- Project work

Student signature: Noah Hendrix Date: 9/20/19

Mentor signature: Cathleen M. Kenny Date: 9/23/19

Week 18 Daily Activity Log

9/23 Monday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Phone surveys

9/24 Tuesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- Phone surveys

9/25 Wednesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Phone surveys
- In person saliva sample collection

9/26 Thursday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- Phone surveys

9/27 Friday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Histology TBL
- Phone surveys
- Make Dr. Licciardone's revision to thesis

Student signature: Noah Hendrix Date: 10/4/19

Mentor signature: Cathleen M. Kearns Date: 10/21/19

Week 19 Daily Activity Log

9/30 Monday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Histology exam
- Audit online charts so that paper charts can be shredded
- Phone surveys

10/1 Tuesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- Audit online charts so that paper charts can be shredded
- Phone surveys

10/2 Wednesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Meet with Dr. Cross to review thesis
- Audit online charts so that paper charts can be shredded
- Phone surveys

10/3 Thursday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- Audit online charts so that paper charts can be shredded
- Input new Clincard numbers onto spreadsheet
- Phone surveys

10/4 Friday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Input new Clincard numbers onto spreadsheet
- Phone surveys

Student signature: Noah Hendrix Date: 10/4/19

Mentor signature: Cathleen M. Kenny Date: 10/21/19

Week 20 Daily Activity Log

10/7 Monday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Phone surveys
- Audit online charts so that paper charts can be shredded

10/8 Tuesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- Prepare and mail saliva kits
- Audit online charts so that paper charts can be shredded

10/9 Wednesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Phone surveys
- Audit online charts so that paper charts can be shredded
- Prepare and mail saliva kits
- Practice thesis defense

10/10 Thursday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- Phone surveys
- Audit online charts so that paper charts can be shredded

10/11 Friday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Audit online charts so that paper charts can be shredded
- Prepare new set of 10 saliva kits so that they are ready for later

Student signature: Noah Hendrix Date: 10/21/19

Cathleen M. Kenny

Mentor signature: _____ Date: 10/21/19

Week 21 Daily Activity Log

10/14 Monday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Audit online charts so that paper charts can be shredded
- Meet with Dr. Licciardone to discuss paper

10/15 Tuesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- Audit online charts so that paper charts can be shredded
- Create scatterplots and cluster table for thesis

10/16 Wednesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Audit online charts so that paper charts can be shredded
- Phone surveys
- Phone call with KLTY to discuss community event

10/17 Thursday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- Audit online charts so that paper charts can be shredded
- Contact subjects that have not returned saliva kit

10/18 Friday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Help set up classroom for Honors Research Class
- Prepare online recruitment brief

Student signature: Noah Hendrix Date: 10/21/19

Kathleen M. Kenna

Mentor signature: _____ Date: 10/21/19

Week 22 Daily Activity Log

10/21 Monday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Audit online charts so that paper charts can be shredded
- Phone survey

10/22 Tuesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- Phone survey

10/23 Wednesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Audit online charts so that paper charts can be shredded

10/24 Thursday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- Audit online charts so that paper charts can be shredded
- Phone survey

10/25 Friday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Practice thesis defense
- Phone survey

Student signature: Noah Hendrix Date: 11/11/19

Mentor signature: Cathleen M. Kearns Date: 11-11-19

Week 23 Daily Activity Log

10/28 Monday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Audit online charts so that paper charts can be shredded

10/29 Tuesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- Practice thesis defense

10/30 Wednesday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Audit online charts so that paper charts can be shredded
- Work on defense revisions

10/31 Thursday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Follow up compensation for remote visits
- In person surveys
- Phone survey

1/1 Friday

- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Practice thesis defense

Student signature: Noah Hendrix Date: 11/11/19

Cathleen M. Kearns

Mentor signature: _____ Date: 11-11-19

Week 24 Daily Activity Log

11/4 Monday
- Thesis Defense

11/5 Tuesday
- Out of the office to work on revisions from defense

11/6 Wednesday
- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Half day to work on revisions from defense

11/7 Thursday
- In person baseline visit
- Histology exam

11/8 Friday
- Report tracking: 20 day lapsed, 30 day lapsed, incomplete events, saliva kits
- Phone visit
- Remote visit follow-ups

Student signature: Noah Hendrix Date: 11/11/19

Kathleen M. Kenny

Mentor signature: _____ Date: 11-11-19

APPENDIX B: PROMIS-29 v2.0

PROMIS–29 Profile v2.0

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11 1	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21 2	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23 3	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53 4	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01 5	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40 6	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41 7	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53 8	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04 9	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06 10	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29 11	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41 12	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7 13	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3 14	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS–29 Profile v2.0

	Fatigue **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATEXP41 15	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40 16	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109 17	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116 18	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20 19	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44 20	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS 21	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS 22	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS 23	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS 24	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9 25	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22 26	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31 27	How much did pain interfere with your ability to participate in social activities? .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34 28	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS–29 Profile v2.0

Pain Intensity

In the past 7 days…

Global07 29	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst imaginable pain**

APPENDIX C: ROLAND-MORRIS DISABILITY QUESTIONNAIRE

When your back hurts, you may find it difficult to do some of the things you normally do.

This list contains sentences that people have used to describe themselves when they have back pain. When you read them, you may find that some stand out because they describe you today.

As you read the list, think of yourself today. When you read a sentence that describes you today, put a tick against it. If the sentence does not describe you, then leave the space blank and go on to the next one. Remember, only tick the sentence if you are sure it describes you today.

1. I stay at home most of the time because of my back.
2. I change position frequently to try and get my back comfortable.
3. I walk more slowly than usual because of my back.
4. Because of my back I am not doing any of the jobs that I usually do around the house.
5. Because of my back, I use a handrail to get upstairs.
6. Because of my back, I lie down to rest more often.
7. Because of my back, I have to hold on to something to get out of an easy chair.
8. Because of my back, I try to get other people to do things for me.
9. I get dressed more slowly then usual because of my back.
10. I only stand for short periods of time because of my back.
11. Because of my back, I try not to bend or kneel down.
12. I find it difficult to get out of a chair because of my back.
13. My back is painful almost all the time.
14. I find it difficult to turn over in bed because of my back.
15. My appetite is not very good because of my back pain.
16. I have trouble putting on my socks (or stockings) because of the pain in my back.
17. I only walk short distances because of my back.
18. I sleep less well because of my back.
19. Because of my back pain, I get dressed with help from someone else.
20. I sit down for most of the day because of my back.
21. I avoid heavy jobs around the house because of my back.
22. Because of my back pain, I am more irritable and bad tempered with people than usual.
23. Because of my back, I go upstairs more slowly than usual.
24. I stay in bed most of the time because of my back.

APPENDIX D: PRECISION PROTOCOL V16

V16 05-31-19

University of North Texas Health Science Center

Office for the Protection of Human Subjects / Institutional Review Board (IRB)

Protocol Synopsis for Research Project Involving Human Subjects

PROTOCOL INFORMATION

Title of Research Activity: *Pain Registry for Epidemiological, Clinical, and Interventional Studies and Innovation (PRECISION Pain Research Registry)*

Name of Principal Investigator: *John C. Licciardone, DO, MS, MBA*

Names of each Co-Investigator: *Robert J. Gatchel, PhD, Subhash Aryal, PhD, Nicole Phillips, PhD*

Sponsoring Agency / Company (if applicable): *Osteopathic Heritage Foundation; American Osteopathic Association; University of North Texas Health Science Center*

Sponsor's Grant Number: *OHF – N/A; AOA – 751711713 & 1911751; UNTHSC- N/A*

A. OVERALL REGISTRY SPECIFIC AIMS –

Specific Aim 1: Develop a pain research registry that will serve as a foundation for future research studies on subacute and chronic pain, particularly low back pain.

Specific Aim 2: Develop a biobank that will serve as a foundation for future research studies on low back pain.

Specific Aim 3: Conduct statistical analysis to determine the association between demographic, clinical and genetic variables and progression from subacute to chronic low back pain.

Specific Aim 4: Conduct statistical analysis to determine the association between demographic, clinical and genetic variables and recovery from chronic low back pain.

SUBSTUDY 1 SPECIFIC AIMS – Completed December 31, 2018

Specific Aim 1: Processes of medical care for low back pain. Are there differences in practice style between DOs and MDs that may be observed using patient-reported perceptions of their physician's communication style, empathy, and other dimensions of medical care, including OMT?

Specific Aim 2: Clinical outcomes of medical care for low back pain. Are there differences between DO and MD patients on reported measure of pain intensity and back-related functioning over 6 months?

Specific Aim 3: To study relationships between processes (Specific Aim1) and outcomes (Specific Aim 2) of medical care for low back pain.

SUBSTUDY 2 SPECIFIC AIMS – SPADE

Aim 1 – Primary Outcomes: Changes in SPADE Cluster Score and in its Five Component QOL Scale Scores: We hypothesize that subjects allocated to the experimental group will experience significantly better change scores over 3 months on the SPADE cluster and each of its five component Quality of Life (QOL) scales than subjects allocated to the control group, and that the group differences will meet or exceed the threshold for a medium treatment effect size (Cohen's d ≥ 0.5).

Aim 2 – Secondary Outcomes: Changes in Pain Intensity and Back-Specific Functioning: We hypothesize that subjects allocated to the experimental group will experience significantly better change scores over 3 months on a numerical rating scale for pain intensity and on the Roland-Morris Disability Questionnaire relating to back-specific functioning than the control group, and that the group differences will meet or exceed the threshold for a medium treatment effect size (Cohen's d ≥ 0.5).

Aim 3 – Subject Actions Based on QOL Report that Mediate Primary and Secondary Treatment Outcomes at 3 Months: We hypothesize that significant between-group differences in QOL, pain intensity, and back-specific functioning in the trial will be mediated by subject actions prompted by the QOL report provided to those in the experimental group, and that such mediators will persist as significant predictors in statistical analyses that control for moderator variables.

B. BACKGROUND AND SIGNIFICANCE –

OVERVIEW OF LOW BACK PAIN

Low back pain is a common health condition in the United States of America that causes considerable time lost from work, decreased quality of life and disability.

According to the *2011 Institute of Medicine Report, Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, more than 100 million Americans suffer from chronic pain, and a conservative annual estimate of the cost of chronic pain to the US economy is $560-635 billion.

Chronic pain, including low back pain, continues to be a focal area of interest of the National Institutes of Health – National Center for Complementary and Integrative Health. Thus, this research registry project and the foundation it will provide for future studies is very timely and fits well in the national pain research landscape.

C. PRELIMINARY STUDIES – Not applicable

D. INVESTIGATOR EXPERIENCE –

Dr. Licciardone's research focuses on the prevention and treatment of chronic pain. He holds the Osteopathic Heritage Foundation Distinguished Chair in Clinical Research in honor of Drs. David Richards and Benjamin Cohen, former President and Provost of the University of North Texas Health Science Center. He also directs the Osteopathic Research Center, including its PRECISION Pain Research Registry. The latter studies precision medicine and biopsychosocial approaches to pain management. He received a Midcareer Investigator Award from the National Institutes of Health (NIH), served as an expert panelist for NIH in the area of chronic pain, and completed a four-year term on its National Advisory Council for Complementary and Integrative Health. He directed the OSTEOPATHIC Trial, a five-year study funded by NIH that demonstrated substantial improvements in and recovery from chronic low back pain with osteopathic manipulation. He is presently a Co-Investigator in the $14

million Prevention of Acute to Chronic Back Pain Trial (PACBACK Trial) sponsored by NIH, and recently served on the Work Group that developed NIH's Federal Pain Research Strategy. Internationally, Dr. Licciardone has served as a consultant to the World Health Organization on regulatory and safety issues relating to osteopathy in Europe and other nations. He gave the keynote address at Advancing Osteopathy 2008, a conference celebrating the 10th anniversary of recognition of osteopaths in the United Kingdom's National Health Service, including a preconference reception with the His Royal Highness, The Prince of Wales. Dr. Licciardone is recognized by Expertscape as the leading international authority on osteopathic manipulation.

To date, he has published over 100 papers. A partial list of these publications is provided in the curriculum vitae on file with the original IRB application for this study.

E. EXPERIMENTAL DESIGN AND METHODS –

1) *Methods and Procedures*:

Potential subjects recruited for this research registry (up to 2,000 cases) will be asked to complete encounters quarterly to provide data relative to their experience with low back pain. The research team will collect data on physical, emotional and social aspects of low back pain, medications and supplements taken for any conditions, treatments for low back pain, characteristics of physicians who provide low back pain care, and characteristics of pain and pain perception. Biological samples will also be collected to explore genetic and other physical markers of low back pain.

Subjects will be encouraged to complete the consent/enrollment process and all study encounters remotely. Upon request, encounters may be scheduled in-person. Subjects who elect to complete the initial encounter in-person may complete subsequent encounters in-person, by telephone, or online. Please note the initial encounter may not be completed by telephone as it is assumed if subjects are asking for an in-person visit, they would not be comfortable with the process of consenting or returning the saliva sample remotely. Subjects will be recruited throughout the State of Texas using the mechanisms outlined in the recruitment section.

Informed consent and all other enrollment documentation will be executed using an electronic system (such as DocuSign or REDCap). The electronic consent packets will include the informed consent document, the HIPAA authorization, the W-9 form and the web-based payment system FAQ. The packets will be signed and countersigned. Subjects will be required to upload a copy of a valid government identification card that includes a photo and date of birth to confirm age and identity. Each subject will be able to download a copy of the executed consent packet once all parties complete the signing process.

Subjects will provide an email address as part of the enrollment process. If a subject does not have an email address or is not comfortable using the computer, he/she may complete the baseline visit in-person and complete subsequent encounters by telephone. All electronic systems are HIPAA-compliant and password-protected. Only the appropriate key personnel will have access to subjects' personal identifiable information.

For the baseline encounter, 24 months, 48 months and 72 months post-enrollment, subjects will be asked to complete a longer survey that includes questions about pain perception, medications taken for other medical conditions and side effects related to the medications they take. Subject compensation will be $50 for completion of the baseline, 24-month, 48-month and 72-month surveys.

Subsequent study encounters at 3 months, 6 months, and 9 months will be compensated $25. Compensation for the 12-month, 36-month and 60-month encounters will increase to $30 based on the length of the surveys.

Post-enrollment encounters at 15, 18, 21, 27, 30, 33, 39, 42, 45, 51, 54, 57, 63, 66, and 69 months will

be compensated $10.

Compensation will be provided for each encounter as outlined in the compensation schedule. Subjects will be compensated using a web-based payment system (such as Greenphire). The web-based payment system is HIPAA-compliant, and only the appropriate key personnel have access to subjects' personal identifiable information stored in the system. Instructions for using debit card will be provided to each subject.

Because compensation for several milestone encounters have been increased, all active subjects who are not lost to follow-up or those who have not withdrawn, will need to be re-consented. Current and future re-consents will be completed electronically. Subjects may also request to re-consent in-person.

For re-consents that are completed in conjunction with a quarterly visit, the subject will receive only the compensation for that scheduled visit. If a subject is asked to re-consent at a time that is not aligned with a quarterly visit, the subject will be compensated $10.

All compensation will be reported and taxed in accordance with institutional, state and federal guidelines.

A completed IRS W-9 form is required to receive compensation. If a subject chooses not to complete the W-9 form, he or she may still choose to participate in the study, but will not be compensated for participation. This is clearly explained in the consent document.

Subjects completing the consent process remotely will be mailed a card and cardholder agreement. The card does not have any value until funds are loaded following completion of the encounter.

Study personnel will register the payment card once receipt is confirmed and approve all payments. Confirmation may be confirmed by tracking of packages sent via courier service, by email or by telephone. Subjects will interact with MasterCard customer support to resolve any issues related to the use of the card.

Form A replaces the SA Form and is given at the baseline, 24-month, 48-month, and 72-month encounters. Form B replaces the S3 form and will be used at 3-month, 6-month, and 9-month encounters. Form C will replace the S12 form and is given at 12-month, 36-month and 60-month encounters. Form D will replace the S15 form and will be used at the 15-month, 18-month, 21-month, 27-month, 30-month, 33-month, 39-month, 42-month, 45-month, 51-month, 54-month, 57-month, 63-month, 66-month, and 69-month encounters.

Telephone encounters are available upon request for all but the initial baseline visit as some subjects enrolled in the study are not comfortable using the computer. Study coordinators read to these subjects during in-person and telephone visits and mark the answers in the electronic data capture system on the subjects' behalf. Prospective subjects may screen to determine if they qualify to enroll in the research registry by completing the SQ form electronically, by telephone or in-person. The online screening questionnaire is programmed to determine if a prospective subject passes or fails the screening based on responses to the questions. Prospective subjects will be told if they are eligible for the study or not, immediately after submitting the screening form. The screening questionnaire requires contact information to be included before the prospective subject is told whether they qualify for the study or not. If a prospective subject chooses not to share contact information, they may close the survey (SQ) without submitting it and no data will be retained. Prospective subjects will be told via instructions included in the online screening tool that their responses to the screening questionnaire will be retained. If prospective subjects fails the screening, they may opt to be contacted at a later date to reassess eligibility for this research registry or for future research projects. They may also opt out of future contact. Identifiable information (contact information) will be retained for all people who pass or fail the screening for the research registry if they provide that information and submit the screening survey. A script will be used when contacting prospective subjects who passed the screening and

request to complete the initial baseline visit in-person.

For those that passed the screening and chose to complete the encounter electronically a series of tasks are required. After subjects view the FAQ video that provides details about the study, subjects will be asked to indicate they are ready to enroll. Other options include, requesting contact with a study coordinator or choosing not to enroll in the study. Once the prospective subject elects to enroll, a link to the consent packet will be displayed for them to click. The consent packet is completed electronically, signed and countersigned. Once the packet is completed, the subject will be able to download a PDF copy. The subject will receive a link to the saliva FAQ video. After the staff receives the completed consent packet, the saliva kit will be mailed to the subject. Once the subject returns the saliva kit to study personnel, the subject will officially be enrolled in the study and the baseline survey link will be sent via email using the automated electronic system. Subjects will be compensated for the baseline visit after all segments of the visit have been completed.

If subject chooses to complete the baseline visit in-person, it will be scheduled as soon as feasible given available appointments, ideally within two to three weeks of the participant passing the screening.

The questions included in study surveys are primarily drawn from the following:

- NIH minimum dataset for chronic low back pain
- PROMIS Quality of Life Measures
- Roland-Morris Disability Questionnaire
- Pain Catastrophizing Scale
- Pain Self-Efficacy Scale Questionnaire
- Items related to diagnosed medical comorbidities
- Communication Behavior Questionnaire
- Consultation and Relational Empathy Measure
- Patient Satisfaction Questionnaire
- Pain Sensitivity Questionnaire
- Comprehensive pharmacological treatments
- Drug Adverse Events
- History of Medical Conditions Inventory
- Use of opioids/NSAIDS for low back pain
- Physician information

Each subject will be asked to complete these questionnaires. The electronic survey requires subjects to answer the questions in one session. The three-hour time frame listed for the initial encounter is the longest it has taken a subject to complete the visit. Most subjects who are comfortable using the computer take less than an hour to complete the survey portion of the encounter. We have left the description of the time for the initial visit at three hours for those subjects who do need that long to complete the encounter. We also recognize that as we move to remote collection of saliva samples, it will take subjects a range of time to complete that task and to take the saliva package to a courier service if pickup is not available in their area. Each subject will be assigned a unique identifying number that will be used to store that person's responses in the electronic data capture system. As PRECISION transitions to the new electronic data capture system paper charts and other paper study documentation will no longer be used and all information will be stored electronically in the secure, HIPPA-compliant, cloud-based space that will host the survey data. These documents and study data are only accessible by approved key personnel. Once conversion of all documents have been validated, paper charts will be de-identified and destroyed.

For baseline visits completed in person, subjects will be asked to provide a saliva sample for genetic analysis as well as a blood sample. Certified phlebotomists will draw up to 30 ml (approximately two tablespoons) of blood for biochemical and genetic analysis. Blood samples will be marked with a unique identifier and transported to the genetics facility in the Center for BioHealth. No personal identifiable information will be stored with the blood sample.

For subjects completing the baseline visit remotely, PRECISION will not be collecting blood samples because of challenges of processing and shipping the blood samples in a cost-effective manner. The only genetic samples collected from remote subjects will be saliva samples. A kit with specific instructions will be sent to the subject via courier with a prepaid return label included. Subjects will have access to an instructional video that outlines the process for collecting and returning the saliva sample. We anticipate it will take subjects approximately two to three hours to complete the remote baseline encounter once all components are included. Subjects who complete the baseline encounter remotely and in-person will be given the same compensation as the time involved is the same, but is allocated differently based on the tasks required.

All saliva samples will be delivered to the genetics facility in the Center for BioHealth, where they will be stored and analyzed. All genetic samples will be coded with a unique identifying number. Laboratory personnel will not have access to personal identifiable data for any subjects. Genetic samples, biomarker samples and responses to research registry questionnaires will be used for analyses as indicated in the specific aims for the research registry project and for this and future substudies as indicated. Biological samples will also be analyzed in future studies related to low back pain and other conditions related to pain.

Occasionally, study personnel may need to contact research registry participants between study encounters to clarify study-related data.

Subjects may be invited to participate in other future research projects based on specific information provided during study encounters. Subsets of participants may be invited based on the specific aims and inclusion/exclusion criteria for future studies. Future studies will not be pursued without express approval from the IRB. A re-contact clause is included in the informed consent document. Contact would be made by the subject's preferred method of communication. Subjects may choose to receive study information using multiple methods of communication.

Inclusion Criteria (Study Population 1, "Cases")

To participate in the research registry, subjects must be:

- 21 years old to 79 years old (documented by an original, valid, government-issued photo identification provided at the baseline encounter)
- Report having low back pain for at least two months; **AND** report having low back pain for at least half of the days for the past two months
- Able to understand informed consent
- Speak and respond to questions asked in English as no translation services will be available
- Provide information about medications taken (self-report only)
- Must report having a physician, must be able to tell study staff if physician is a MD or DO, and must report having this physician for a period of at least one to three months

Exclusion Criteria (Study Population 1, "Cases")

To enroll in the research registry, subjects must not be:

- Pregnant (self-report only)
- Incarcerated or institutionalized

Women who report being pregnant during the screening will not be considered eligible to enroll in the research registry, however, a woman who reports being pregnant after enrolling in the research registry will be permitted to remain in the research registry.

A detailed explanation of laboratory analysis for the genetic samples and data confidentiality are included in the appropriate sections below.

Participants may withdraw from the research registry at any time and, upon written request to the PI, may ask to have their data, and genetic and biomarker samples discarded. Subjects may also ask that they not be contacted further, but may choose to allow the research team to continue to use data provided up to that point and to continue to use the genetic/biomarker samples and corresponding data. Both of these options are clearly described in the main informed consent document for the research registry.

Additional Study Population – (Study Population 2, "Controls")

Data collection for up to 2,000 control subjects (Total for research registry is 4,000 subjects – 2,000 cases and 2,000 controls) will be conducted remotely using the electronic system and the same process as PRECISION subjects. Control subjects may request an in-person visit at the UNT Health Science Center. These control subjects will be recruited using the same venues as subjects with low back pain. They will complete the screening form CON-SQ electronically, by telephone or in-person.

Just as with PRECISION subjects (Population 1), control subjects (Population 2) will complete the appropriate screening questionnaire. Control subjects completing the encounter remotely will provide a saliva sample, and control subjects completing the encounter in-person will provide blood samples in addition to saliva samples as outlined for Population 1. The control subjects will be compared to subjects with low back pain on self-reported measures, genetic measures and biomarker measures.

Control subjects will be compensated $50 for this visit using a web-based payment system (such as Greenphire). Each control subject will be asked to complete an IRS W-9 form.

Subjects will not specifically be told that they are control subjects. They will be recruited to a health status study.

Inclusion Criteria for (Study Population 2, "Controls")

- 21 years old to 79 years old (documented by an original, valid, government-issued photo identification provided at the baseline encounter)
- Report that pain in any area of their body is experienced less than half the days of the past two months
- Able to understand informed consent
- Speak and respond to questions asked in English as no translation services will be available
- Provide information about medications taken (self-report only)
- Must report having a physician, must be able to tell study staff if physician is a MD or DO, and must report having this physician for a period of at least one to three months

Exclusion Criteria for Control Subjects (Study Population 2)

Control subjects must not be:

- Pregnant (self-report only)
- Incarcerated or institutionalized

Please note there is a separate screening form for control subjects (CON-SQ), a separate baseline survey (CON-Baseline), a separate consent (Version C-3), and separate advertisements (Health Status – Tell Us About Your Health). All documents are marked HEALTH STATUS instead of PRECISION. Subject recontact clauses, data storage and confidentiality, compensation, genetic analysis and biomarkers, and other study processes will be handled as outlined in this protocol for subjects with low back pain (Population 1).

Substudy 2: SPADE (New Substudy)

Subjects for substudy 2 will be selected from PRECISION Pain Research Registry participants

based on their responses to specific questions and their scores on specific questionnaires at a quarterly visit that occurs at either the baseline, 3-month, 6-month or 9-month encounter. This study focuses on various Quality of Life (QOL) measures including sleep disturbance, pain interference with activities, anxiety, depression, and low energy/fatigue (SPADE). Subjects must have a SPADE cluster score ≥55 to be eligible for this study and must be categorized as having chronic low back pain based on their survey responses at their most recent quarterly encounter. A separate consent form (SPADE substudy Consent) will be completed by each subject within approximately two weeks of the quarterly visit where he/she were determined to be eligible for the substudy. Subjects participating in this substudy will be randomly assigned to an experimental or control group. Approximately 146 subjects (73 in the experimental group and 73 in the control group) will be recruited to this substudy. Each subject in the experimental group will receive a graph of the individual components of the SPADE score that may be shared with his or her physician. They will also receive an interpretation guide. Three months later, the subjects randomized to the experimental group will complete a survey to evaluate how the information in the graph may have improved his or her qualify of life. Subjects in the experimental group will be compensated $25 for the first substudy encounter where consent is signed and the graph is provided with instructions for use. At their next quarterly visit, they will be paid $10 in addition to their quarterly visit compensation for completing the additional short survey that will take approximately 10-15 minutes. Subjects who consent to participating in this study that are randomized to the control group will receive $25 when they sign the consent document but will not receive the graph of their SPADE score or the interpretation guide. Instead, they will be given the graph in conjunction with their next quarterly visit, at which time, they will receive $10 in addition to the compensation for their scheduled quarterly encounter. Subjects randomized to the control arm of this substudy will not complete the additional survey. Subjects will be invited to participate in the substudy if they are completing their baseline, 3-month, 6-month or 9-month encounter as these are the only encounters that offer the opportunity to complete surveys that provide the requisite outcomes data.

Inclusion Criteria (Substudy 2)

To participate in this substudy, subjects must:

- Be categorized as having chronic low back pain
- Have a SPADE cluster score of ≥55

Exclusion Criteria (Substudy 2)

To participate in this substudy, subjects must not:

- Be categorized as having subacute low back pain
- Have a SPADE cluster score < 55

2) Data Analysis and Data Monitoring:

Statistical analyses will be performed for the baseline and follow-up surveys, as well as for the genetic and biomarker data. Demographic, clinical, and relevant genetic/biomarker data will be merged to facilitate analyses of the primary hypotheses outlined herein. These analyses may include basic descriptive statistics as well as analytical statistics to assess the primary hypotheses and other secondary hypotheses as indicated by the data.

3) Data Storage and Confidentiality:

Data collected through the cloud-based electronic data capture and study management system will be periodically downloaded into a database such as SPSS or SAS for statistical analysis. Since each subject will be assigned a unique identifying number, research data will be stored by each subject's unique identifying number in a secure, password-protected, HIPAA-compliant electronic system that is only accessible by approved key personnel. All data previously downloaded from Qualtrics will be kept on computer hard drives, external hard drives, or secure servers in password-protected areas.

The PI and the research assistant director will have administrator access to the research management and electronic data capture system. They will define roles for other users and will restrict write access based on each staff member's job duties. Only key personnel will have access to the system. The system provides a date/time stamp as well as identifies which user made modifications. Permission to modify data will be very limited and on an as needed basis only. An example of data that may need to be modified includes updating a subject's contact information or correcting the spelling of a drug name in the list of medications that each subject completes at various time points.

Genetic and biomarker samples will be stored at temperatures of minus 20 degrees Celsius while they are being used for various processes short-term. Long-term, samples will be stored in a minus 80 degrees Celsius freezer. The secure freezer is housed in the genetics facility. Only authorized key personnel will have access to the samples from research registry participants. Saliva samples will be collected using ORAGENE Discover collection vials. One vial will be collected per subject, and the vial will be identified with a barcode that corresponds to the subject's unique identifying number. Once the sample is processed for long-term storage, that tube will be identified using a label with the same barcode used on the collection vial.

Blood will be collected as outlined in other parts of the protocol and will be transported to the genetics facility in the Center for BioHealth, where trained key personnel will centrifuge the blood and separate it into serum, plasma and the buffy coat. A portion of subject's blood sample will be stored as whole blood. These samples will be stored in the secured freezer until they are processed. All procedures will be completed in accordance with the institution's biosafety policy.

Genetic data will be stored on a stand-alone computer in the genetics facility in the Center for BioHealth. All genetic data will be kept by the unique identifying number assigned to each subject, and will be stored in a password-protected file. Because personnel in this work group are accustomed to working with genetic data for criminal cases, they are trained to follow security requirements set forth by the Federal Bureau of Investigation. Only authorized key personnel will have access to genetic data.

Because genetic information will eventually be derived from this research registry, we intend to seek a certificate of confidentiality from the National Institutes of Health to offer an additional layer of protection of our participants' privacy and confidentiality.

Biomarker data will be stored on a secured computer in the department. All data will be assigned a unique number, and will not be stored with personal identifying information.

All potentially clinically-relevant genetic data are generated for research purposes only, and will not be provided to the participants or their healthcare provider.

4) Setting:

PRECISION Pain Research Registry will be using an electronic data capture and study management system for all subjects, whether they are new or currently active subjects. Subjects will be encouraged to complete all encounters, including the consent process and the baseline encounter remotely. Subjects who are not comfortable using a computer or who do not have access to a computer may request an in-person visit to complete the consent process and baseline encounter. In this case, all

remaining study visits would be conducted by phone unless the subject specifically requests to complete subsequent encounters in-person. In-person visits are conducted at the UNT Health Science Center. Subjects who initially consent in-person may also re-consent in-person. In-person or phone encounters or re-consents may be converted to online encounters at any time by notifying study personnel.

5) Laboratory Methods and Facilities:

Saliva samples for genetic analysis will be processed for long-term storage and stored in the genetics facility in the Center for BioHealth. These samples will be collected using ORAGENE Discover collection vial for collection and stabilization of saliva samples. Collection vials for saliva and blood, as well as any subsequent sample storage tubes will be coded with a personal unique identification number to protect confidentiality of the genetic and biomarker data.

DNA will be extracted from samples using automated and manual extraction methods appropriate for the sample types. DNA samples will be quantified to determine the amount of nuclear or mitochondrial DNA. Portions of the DNA obtained from the various sample types will be amplified using the polymerase chain reaction for DNA sequence data, autosomal, Y chromosomal, mitochondrial DNA, insertions, deletions, and other SNP DNA markers under development for genetic analysis. These methods include but are not limited to DNA sequencing, autosomal STR typing using commercially available STR typing kits, or in-house designed STR assays and genetic typing with new SNPs and or insertion/deletion panels. SNP testing will include markers within genes that affect drug metabolism and genotypes at these loci. This information, along with data on copy number variation of relevant genes, will be used to infer individual metabolizer status of commonly used pharmaceuticals based on published literature and validated guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC). DNA fragments and sequence data may be visualized by capillary electrophoresis using an Applied Biosystems 3130*xl* and/or 3500*xl* Genetic Analyzer (Applied Biosystems, Foster City, CA), real-time PCR using an Applied Biosystems 7300/7500, or other relevant techniques. Mitochondrial haplotype data will be compiled and analyzed using the GeneCodes Sequencher™ 4.7 software. Autosomal and Y STR data will be compiled and analyzed using either the Applied Biosystems GeneMapper ID software or in-house developed software. Genetic data will be maintained in electronic format on password protected secure computers or servers maintained in the genetics facility. The data will only be shared with authorized key personnel via a secure file sharing service or FTP site.

Any and all of the biological samples collected or data generated from this research registry may be used in future studies to evaluate, compare, and validate technologies for DNA extraction, phenotypic traits, repair, WGA, amplification, typing, sequencing, purification, robotics, expert systems, Laboratory Information Management Systems and other genetic analysis techniques. Routine laboratory procedures may be performed by offsite contractors provided the samples are de-identified prior to the work being performed. Archived saliva samples and isolated DNA will be stored indefinitely or until exhausted.

6) Estimated Period of Time to Complete the Study (Study Population 1):

Encounter	Tasks	Estimated Time to Complete	Compensation
Baseline	Execute informed consent; provide a valid photo id; complete baseline survey (Form A); provide biological samples for genetics and biomarker analysis; obtain information about medications and supplements. This encounter (including informed consent) may be completed remotely or in-person. Subjects completing the visit remotely will provide saliva samples while subjects completing the encounter in-person will also	Up to 3 hours	$50

	provide blood samples.		
Months 3, 6 and 9	Update contact information; complete survey (Form B); obtain information about medications and supplements. Encounter may be completed electronically, by telephone or in-person.	30 minutes to 1 hour	$25
Months 12, 36, and 60	Update contact information; complete survey (Form C); obtain information about medications and supplements. Encounter may be completed electronically, by telephone or in-person.	30 minutes to 1 hour	$30
Months 15, 18, 21, 27, 30, 33, 39, 42, 45, 51, 54, 57, 63, 66 and 69	Update contact information; complete survey (Form D). Encounters may be completed electronically, by telephone or in-person.	15-20 minutes	$10
Months 24,48, and 72	Update contact information; complete survey (Form A). Encounters may be completed electronically, by telephone or in-person.	45 minutes to 1 hour	$50

Estimated Period of Time to Complete the Study (Study Population 2):

Encounter	Tasks	Estimated Time to Complete	Compensation
Baseline	Execute informed consent; provide a valid photo id; complete baseline survey (Form CON-Baseline); provide biological samples for genetics and biomarker analysis. This encounter (including informed consent) may be completed remotely or in-person. Subjects completing the visit remotely will provide saliva samples while subjects completing the encounter in-person will also provide blood samples.	Up to 3 hours	$50

Estimated Period of Time to Complete the SubStudy (Substudy 2):

Encounter	Tasks	Estimated Time to Complete	Compensation
Primary (Enroll)	Execute informed consent. Complete primary REDCap survey (SPADE Form); Subjects randomized to the experimental group will be provided with a SPADE score graph and an interpretation guide. Subjects randomized to the control arm will not receive the graph/guide at this encounter.	10-20 minutes	$25
Secondary (Exit)	Subjects that were randomized to the experimental arm of the substudy will complete the SPADE survey. Subjects randomized to the control group will not complete the SPADE survey but will receive the SPADE score graph and an interpretation guide.	10-20 minutes	$10

F. HUMAN SUBJECTS –

1) ***Description of Subjects***:

We intend to recruit up to 4,000 subjects (2,000 subjects with low back pain and 2,000 control

subjects) for this research registry project.

We plan to recruit participants 21 years of age to 79 years of age from the UNT Health Science Center clinics and from the Dallas-Fort Worth Metroplex using such methods as flyers, community events and venues, social media, electronic communications such as email, websites, online advertising, newspapers and other media outlets, and referrals from local physicians. We plan to recruit participants from across the State of Texas using predominantly social media and internet-based platforms, but we will also use more traditional methods such as those outlined here for local recruitment.

Women who report being pregnant during the screening process will not be considered eligible to enroll in the research registry, however, a woman who reports being pregnant after enrollment will be permitted to remain in the research registry.

We aim to recruit a racially and ethnically diverse group of subjects that generally follows the demographics reported for the State of Texas in the most recent United States census. Please see targeted enrollment table below for a specific breakdown.

We do not intend to recruit from vulnerable populations.

2) ***Sample Size:***

Up to 4,000 subjects (2,000 subjects with low back pain and 2,000 control subjects) will be enrolled in the initial phase of this research registry.

3) ***Describe both Inclusion / Exclusion Criteria:***

Inclusion Criteria for Subjects with Low Back Pain (Study Population 1)

To participate in the research registry, subjects must be:

- 21 years old to 79 years old (documented by an original, valid, government-issued photo identification provided at the baseline encounter)
- Report having low back pain for at least two months; **AND** report having low back pain for at least half of the days in the past two months
- Able to understand informed consent
- Speak and respond to questions asked in English as no translation services will be available
- Provide information about medications taken (self-report only)
- Must report having a physician, must be able to tell study staff if physician is a MD or DO, and must report having this physician for a period of at least one to three months

Exclusion Criteria for Subjects with Low Back Pain (Study Population 1)

To enroll in the research registry, subjects must not be:

- Pregnant (self-report only)
- Incarcerated or institutionalized

Inclusion Criteria for Control Subjects (Study Population 2):

- 21-years-old to 79-years-old (documented by an original, valid, government issued photo identification provides at baseline encounter)
- Report that pain in any area of their body is experienced less than half the days of the past two months
- Able to understand informed consent
- Speak and respond to questions asked in English as no translation services will be available
- Provide information about medications taken (self-report only)
- Must report having a physician, must be able to tell study staff if physician is a MD or DO, and

must report having this physician for a period of at least one to three months

Exclusion Criteria for Control Subjects (Study Population 2)

Control subjects must not be:

- Pregnant (self-report only)
- Incarcerated or institutionalized

Minors under the age of 21 will not be included as low back pain is not prevalent in this population and clinical guidelines for pediatric patients should be based exclusively on pediatric populations. Pregnant women will not be enrolled in the research registry if they report being pregnant at the time of screening as their back pain may be self-limiting based on physiological changes during the pregnancy. Women who report being pregnant after enrollment will be permitted to remain in the research registry. People over 79- years old will not be enrolled to help protect their identity within aggregated data sets. If enrolled, the relatively small number of such older subjects may potentially enable research staff to identify them based on their age and unmask their research data. However, enrolled subjects will not be dis-enrolled after reaching 79 years of age.

We do not intend to recruit from vulnerable populations.

4) ***Describe intended gender, age range, and intended racial and ethnic distribution for subjects with low back pain and control subjects:***

Race/Ethnicity	Targeted Enrollment
African American (Black)	508
American Indian / Native American	40
Asian	200
Caucasian (White)	3168
Native Hawaiian / Pacific Islander	4
Other /Unknown	80
Ethnicity	**Targeted Enrollment**
Hispanic/Latino	1576
Not Hispanic/Latino	2424
Gender	**Targeted Enrollment**
Female	2012
Male	1988

The age range of participants for this research registry includes adults age 21-years-old to 79-years-old at the time of enrollment.

5) ***Identify the source(s) from which you will obtain your study population:***

Participants may be recruited from the UNT Health Science Center clinics and from the Dallas-Fort

Worth Metroplex using such methods as flyers, newspapers and other media outlets, community events and venues, social media, electronic communications such as email, websites and online advertising, and referrals from local physicians. We plan to use a broad-based approach to recruiting subjects for this research registry.

6) ***Describe Plans for Recruitment of Subjects:***

We intend to recruit up to 4,000 subjects (2,000 subjects with low back pain and 2,000 control subjects) using UNT Health Science Center clinics and from the Dallas-Fort Worth Metroplex using such methods as flyers, community events and venues, social media, electronic communications such as email, websites, online advertising, newspapers and other media outlets, and referrals from local physicians. We plan to recruit participants from across the State of Texas using predominantly social media and internet-based platforms, but we will also use traditional methods such as those outlined here for local recruitment.

In addition to posting flyers in the waiting area of local clinics (DFW Metroplex), study personnel may approach people in the waiting room, briefly describe the research registry and offer the person a flyer with study information to share with friends and family. Study personnel would not be asking for any personal health information, nor would they be asking if that individual had low back pain. Study personnel would seek approval from the clinic manager prior to employing this strategy.

We plan to seek referrals to the research registry from physicians throughout the DFW Metroplex and across the State of Texas using written correspondence, digital correspondence, telephonic communication, advertisements, and social media. We plan to recruit directly from the community using a broad approach including having a presence at community events and venues, developing events such as town hall meetings where community members are invited to the UNT Health Science Center campus, posting and advertising on social media, advertising on websites, running newspaper and other media advertisements, and broadly distributing flyers in a wide range of venues.

G. RISK/BENEFIT ANALYSIS –

1) Level of Risk / Description of Benefit:

The level of risk to participants in this research registry is a minor increase over minimal risk. There is no direct benefit to participants recruited for this research registry.

2) Describe How the Anticipated Benefit Justifies the Risk:

The risk to participants in this research registry is a minor increase over minimal risk. There is no direct benefit to participants in research registry. However, the study may lead to a better understanding of the natural progression of low back pain and, potentially, toward better targeting of treatments in the future.

3) Describe how the anticipated benefit of this research is at least as favorable to the subjects as that to be received by available alternative approaches for the subjects:

There are no interventions in the main research registry, however, Substudy 2 does include an intervention that entails providing subjects randomized to the experimental arm of the study with a graph of specific quality of life measure that may be shared with their health care provider. Future benefits of the research registry and any substudies may include developing a better understanding of the natural course of low back pain, which may lead to better or more personally targeted treatments.

4) Describe any potential RISKS OR DISCOMFORTS in detail. Use evidence from clinical and/or animal studies to evaluate the level of potential hazards associated with participation in the research protocol. Indicate the methods for detecting adverse reactions. Describe the procedures for protecting against or minimizing potential risks (e.g., confidentiality, reputational injury, direct injury or harm to subject, etc.) and assess their effectiveness. Discuss why the risks to the subjects are reasonable in relation to proposed benefits to mankind. Be sure to describe any anticipated adverse events that might occur during the course of the study.

A risk to subjects in this research registry may be a potential loss of confidentiality if their genetic data is requested by the judicial system or by an insurer. In addition to the data safeguards in place, we intend to seek a certificate of confidentiality to prevent us from being required to disclose such genetic data to outside agencies or parties once such data it is generated in our study.

Subjects may also experience embarrassment if they are unable to read or complete the forms on computer or mobile device. The research coordinator will be very sensitive to subjects who need assistance in order to alleviate any embarrassment.

Subjects may experience bruising or soreness at the site of the blood draw. Occasionally, a subject may feel lightheaded during or after a blood draw. Certified laboratory phlebotomists will be drawing the blood, and are trained to address these issues.

H. PAYMENT/COMPENSATION –

Subjects with low back pain (Study Population 1) will receive compensation for time and travel as follows: Baseline visit - $50; 3-, 6- and 9-month 9 encounters - $25; 12-, 36-, and 60-month encounters - $30; 24-, 48-, and 72-month encounters - $50; and 15-, 18-, 21-, 27-, 30-, 33-, 39-, 42-, 45-, 51-, 54-, 57-, 63-, 66-, and 69-month encounters - $10. Compensation is based on survey length for each encounter, and will be made via a secure, web-based payment system.

Control subjects (Study Population 2) will receive compensation for time and travel as follows: Baseline visit - $50.

Subjects completing Substudy 2 will receive $25 compensation at the initial encounter and $10 additional compensation at the final encounter, which will be in conjunction with their next quarterly visit.

I. SUBJECT COSTS –

The only anticipated costs to subjects for this pain research registry is the transportation cost if a subject chooses to visit the UNTHSC campus to complete any of the study visits. The cost is minimal, and subjects will receive compensation sufficient to cover any travel expenses incurred. Subjects completing the study remotely may incur costs if they need to deliver samples remotely to the courier service for return to the study team instead of being able to contact the courier service for a pickup. Finally, if subjects choose to receive payment confirmation messages via text, they may incur costs for the text messages based on the parameters of their cell phone service plan.

J. Historical Protocol Modifications

- Substudy 1 for subjects 1-51 only: Data collected for the substudy includes asking subjects several questions related to their relationship with the physician who treated them for their low back pain. Questions focused on physician communication styles, empathy and patient satisfaction with care. Use of these questions was previously approved by the IRB under this protocol and were added to the baseline survey beginning with subject number 52. The same information was collected for

subjects 1-51. A separate consent (AOA Substudy Consent) was completed by each subject. The subject would then be asked to complete the online survey (Form AOA1) in addition to the survey for that visit. Subjects did not receive any additional compensation for completing this survey.

Please note this substudy survey has been completed as outlined above and is no longer in use as of February 2018.

- The research registry will no longer manage subjects using paper documentation, this will include paper consent, HIPAA, IRS W9 along with enrolling by U.S. Postal Service, and completing survey by paper.
- Initial study payments were provided via Walmart physical or e-gift cards, all payments have been transitioned to a web-based payment system.
- If potential subject did not provide required documents at the baseline visit, a one-time payment of $10 would be given to avoid undue hardship in covering time and travel cost. This has been eliminated as most subjects will consent and enroll remotely. Subjects choosing to complete the baseline visits in-person will be instructed to bring the appropriate documents and information prior to the visit. Historically, we have only used this payment structure a few times each year, so we do not feel that eliminating the payment option creates a hardship for subjects.

K. LIST OF KEY PERSONNEL –

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