The Prevalence of Chronic Symptoms and their Association with Quality of Life in People with Malignant Hyperthermia Susceptibility

by

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Background: Malignant hyperthermia susceptibility (MHS) is a skeletal muscle disorder leading to potentially life-threatening reactions in the presence of triggers, most often, volatile anesthetic drugs. MHS is caused by mutations in the *RYR1*, *CACNA1S*, and *STAC3* genes, but the genetic cause remains unknown in about half of patients. Although Malignant Hyperthermia is a well-known acute event, scarce literature about quality of life (QoL) of MHS patients suffering from chronic symptoms affects the ability to provide them with appropriate care, leading to patient frustration for healthcare providers being unable to determine the etiology of their symptoms. The purpose of this study was to describe the reported symptoms and quality of life and their association in individuals that have MHS.

Methods: Participants were recruited through the North American Malignant Hyperthermia Registry (NAMHR) for a descriptive, cross-sectional study. Participants were included in the study if they were eighteen years of age or older, and were diagnosed as MHS by documented mutation in either *RYR1* or *CACNA1S* genes, or by a positive muscle contracture test. Sample characteristics, PROMIS pain intensity, PROMIS neuropathic pain, PROMIS nociceptive pain, RAND SF-36 and Chronic MH Symptoms questionnaires were sent to potential participants.

Results: One hundred and thirty-seven individuals were contacted about the study. Twenty-two (16.1%) participants identified by NAMHR reported back with study interest. All 22 identified participants were mailed study questionnaires, of which, 19 (86.4%) responded. PROMIS pain t-

score varied between individuals (PROMIS pain intensity minimum T-score 30.7, maximum T-score 56.3; PROMIS neuropathic pain minimum T-score 36.2, maximum T-score 66.4; PROMIS nociceptive pain minimum T-score 30.3, maximum T-score 68.9). Participants reported muscle cramping, pain and noted thermoregulation dysfunction as MHS symptoms. There was no statistical evidence to show bleeding tendencies in MHS population. RAND SF-36 QoL demonstrated lower QoL compared to general population of similar age means.

Conclusions: Individuals with chronic MHS symptoms have an association with QoL decrease. Comorbid conditions compound symptom reporting. Limited understanding of chronic symptoms impedes quality care in MHS patients by delayed detection and symptom treatment. Additional studies are needed to refine understanding and increase awareness.

Table of Contents

List of Tables

Preface

This study was made possible from my Undergraduate Research Mentorship Program (URMP) qualitative research work. It was through this study that I realized there was a significant gap in scholarly literature regarding persons with chronic malignant hyperthermia manifestations. I would like to thank my URMP team Dr. Barbara Brandom, Dr. Madison Betsker, Dr. Laurel Miner, Mr. Ensar Tota, and Dr. Richard Henker, for including me in this project and for giving me the tools to pursue research.

I would like to acknowledge and thank my committee members for this study, Dr. Barbara Brandom, Dr. Elizabeth Schlenk, and Dr. Susan Sereika. I appreciate the time you made to meet with me to discuss this project as your comments kept this study on track. Thank you to my external reviewer, Dr. Carlos Ibarra for your helpful responses and malignant hyperthermia expertise. Additionally, I would also like to acknowledge Amy Gunnett from the North American Malignant Hyperthermia Registry for helping me with the participant recruitment and Blair Powell for looking over my calculations on Excel. The feedback from this entire team has not only led to my academic enrichment, but has given this study a strong foundation.

Lastly, but not least, I would like to thank my thesis advisor Dr. Richard Henker. You have been my motivating support throughout this project. I am ever thankful for you lending your ear during the difficult and emotional times of this project. Your professionalism, experience and knowledge will forever stick with me. This project would not have been possible without significant team guidance—it truly takes a village.

1.0 Introduction

1.1 Background

Malignant hyperthermia susceptibility (MHS) is a skeletal muscle disorder predisposing to potentially life-threatening reactions triggered by volatile anesthetic drugs. MHS inheritance was first described as autosomal dominant with incomplete penetrance by Denborough et al. in 1962 following anesthesia-related deaths in the index case's pedigree (Denborough et al., 1962). Approximately one in 400 persons in the general population might be genetically predisposed to malignant hyperthermia. On the other hand, the incidence of MH crises ranges from one case per every 10,000 to 250,000 (Gonsalves et al., 2013; Rosenberg et al., 2015). Most mutations conferring MHS are located in the *RYR1* gene on chromosome 19. *RYR1* gene mutations are also associated with other skeletal muscle disorders such as central core disease and King-Denborough syndrome. Other loci responsible for MH predisposition are *CACNA1S* in chromosome 1 and *STAC3* in chromosome 12.

Pathogenic genetic changes predisposing to MH result in dysregulation of calcium homeostasis in skeletal muscle, mediated by a dysfunction of the sarcoplasmic reticulum calcium release channel ryanodine receptor *RYR1*. When exposed to triggers such as volatile anesthetic agents or succinylcholine, MHS individuals may develop a hypermetabolic state as a result of excessive calcium release from the sarcoplasmic reticulum, leading to rhabdomyolysis. MH hypermetabolic signs include increased oxygen consumption and carbon dioxide production, raise in core temperature, and muscle rigidity, tachycardia, mixed acidosis, elevation of serum creatine kinase, myoglobinemia and hyperkalemia, which may result in serious complications and death if

left untreated (Rosenberg et al., 2015). A prompt team response, scavenging the trigger agents and early administration of intravenous dantrolene are key for a favorable outcome. After surviving an acute MH episode, patients need to be sent to the intensive care unit for continuous treatment and careful monitoring.

Due to the life-threatening nature of the disorder, acute MH crises grab more attention than mostly unrecognized chronic repercussions of the MHS condition. Individuals are made aware of the disorder after an adverse anesthetic event occurred to themselves or, most often, to a relative. Literature about chronic symptoms of MHS individuals is scarce. MHS patients with chronic muscle symptoms may be misdiagnosed with other musculoskeletal disorders such as fibromyalgia. Chronic symptoms may include muscle rigidity or cramping, exercise intolerance, heat intolerance, diaphoresis and pain. Additionally, European investigators have reported increased bleeding in a small MHS cohort (Lopez et al., 2016).

This study follows a qualitative study by Betsker et al. (2021) that examined 7 MHS diagnosed participants. Interviews by phone were transcribed and analyzed for thematic analysis. Each participant was sent a chronic MH symptoms instrument, data were then compared to the interview transcriptions. The following themes were noted by our research team (Betsker et al., 2021): increased muscle pain, "*Charlie horses now and then…I guess I didn't link to exercise,"* thermoregulation abnormalities, *"I do sweat in a non-lady like way,"* fear related to MHS, *"I will do anything I can to not be put under. Like I don't care if I have to bite a bullet, to not be put under, you know I am terrified, terrified,"* and use of alternative therapies to treat MHS symptoms, *"the one thing I did try was to increase my fluid intake and my electrolyte intake."* This investigation uses the chronic MH symptoms instrument from the Betsker et al study in order to better understand and quantify the chronic symptoms MHS individuals experience on a daily basis.

1.2 Purpose

The purpose of this quantitative, descriptive study was to describe chronic symptoms and health-related quality of life in individuals that are MHS by listing reported chronic MHS symptoms, determining QoL with the RAND SF-36 instrument, using the PROMIS instruments to describe pain symptoms, and detailing how chronic MHS symptoms are associated with QoL.

1.3 Specific Aims

This study explores symptoms and health-related QoL of individuals with MHS. The specific aims of this study were to:

1. Describe reported symptoms. What are the reported symptoms that MHS individuals experience on a chronic basis?

2. Describe QoL in patients with MHS that have chronic symptoms with use of PROMIS pain (intensity, neuropathic and nociceptive pain) and RAND SF-36 instruments with relation to the general population.

3. Describe the association of symptoms with health-related QoL and pain in participants that are MHS compared to the general population and to a population of individuals with similar comorbid disease processes.

2.0 Methods

2.1 Design

This study employed a cross-sectional design. Recruitment began August 1, 2021 and ended December 31, 2021. This study identified participants using convenience sampling. Descriptive statistics were used to summarize symptoms. Participants who met inclusion criteria were sent a study link with six instruments in order to associate chronic MHS symptoms with QoL.

2.2 Sample

This study was approved by the Human Research Protection Office (21030027) on June 25, 2021. Participants were recruited from the NAMHR research registry that includes hundreds of individuals diagnosed MHS. Eligibility criteria were ≥18 years of age, had either a caffeine-halothane contracture test (CHCT) diagnostic of MHS or documentation of a MH causative mutation in either *RYR1* or *CACNA1S* genes. CHCT has a high specificity and moderate sensitivity to MH and is the only generally recognized contracture test to diagnose MH in the United States (Allen et al., 1998). Participants were excluded from recruitment if they were younger than 18 years of age, or had no pathologic confirmation of MHS risk. Individuals that met study criteria were sent a recruitment letter by NAMHR. Those who expressed interest were instructed to respond back to NAMHR. NAMHR identified 137 individuals who met criteria; recruitment letters were sent to all identified participants. Twenty-two of the 137 participants indicated interest

in participating in this research study. The twenty-two participants who expressed interest were emailed a link to an online survey using REDCap or were mailed a hard copy of the survey, if requested. All participant data stored in REDCap servers were de-identified and given a unique study identification number. Any identifiable data was securely stored in a separate file folder in a locked file drawer in a locked office.

2.3 Measurement

Participants that consented to the study were asked to complete six surveys. The survey were grouped into sections: demographics and sample characteristics, chronic MH symptoms, general quality of life (RAND Healthcare SF-36), general pain (PROMIS), neuropathic pain (PROMIS), pain intensity (PROMIS). RAND Healthcare SF-36 is a general quality of life instrument that includes eight sections: physical health, physical role limitations, bodily pain, general health perceptions, energy/fatigue, social functioning and emotional role limitations.

2.3.1 Demographics and Clinical Characteristics

Demographic information and sample characteristics included: age, gender/gender identity, number of children, healthcare appointments made in a year, known comorbid health issues, length of MH diagnosis, and known MHS familial history. Reported comorbid conditions were grouped into categories. Since this study aimed to understand chronic MHS symptoms, this information was gathered to determine if there were any confounding variables.

2.3.2 PROMIS Pain Instruments

The Patient Reported Outcomes Measurement Information System (PROMIS) was developed by the National Institute of Health (NIH), as a precise measurement tool for health status such as symptoms and QoL. Each instrument has been rigorously tested and refined for reliability and validity based on studies involving broad symptomologies from disease processes and on individuals without disease. Pain Intensity, Neuropathic Pain Quality, and Nociceptive Pain Quality instruments are considered universal and non-disease specific and were used in this study to assess pain. For this study, in attempt to decrease participant confusion, the nociceptive pain instrument was labeled as "general pain" when loaded in REDCap. Individuals self-assessed their symptoms over the previous seven days. The PROMIS Pain Intensity, Neuropathic Pain, and Nociceptive Pain Quality instruments were scored using the HealthMeasures Scoring Service. The standard general population reference T-score is 50 with a standard deviation of 10. Mean T-scores one or more standard deviations above the normed T-score indicate increased perceptions of pain. Mean T-scores one or more standard deviations below the normed T-score indicate lower perceptions of pain.

2.3.3 RAND SF-36 Health Survey

The RAND SF-36 Health Survey was used to measures health status across eight health domains: physical functioning, pain, role limitations due to health, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy and fatigue, and general health. An Excel spreadsheet was created to score the RAND SF-36 in a two-step process according to RAND scoring instructions. First, using the RAND scoring guide, numeric values

were recorded given their scoring key. Each item was given a score between 0 and 100 in which 100 represents highest function or no lost function. Second, individual questions were grouped according to eight categories (physical function, physical role limitation, emotional role limitation, energy/fatigue, emotional well-being, social functioning, pain and general health) and averaged. Any missing data was replaced with an arbitrary value and was not taken into account during scoring.

2.3.4 MH Chronic Symptoms

Due to the scarcity of studies conducted on MH chronic symptoms, this instrument was created to capture overall MHS symptoms. The instrument was created by Dr. Barbara Brandom from her experiences working with MHS patients during her time as the director of the NAMHR. The MH chronic symptoms instrument was created and used for a qualitative study describing chronic MHS symptoms (Betsker et al., 2021). This instrument describes general symptoms experienced by persons with MHS, including muscle cramping, temperature regulation, bleeding and bruising. This instrument also describes occupation and home environments that may trigger MHS symptoms, and treatments that may have been implemented due to symptom expression. Although the MHS symptoms instrument has no general population norms in which to compare, data means, medians, range and standard deviation were analyzed. The instrument used ordinal point scale to determine reported symptom frequency (not at all, a little bit, somewhat, quite a bit, and very much). Muscle symptoms (muscle pain without cramping, muscle cramping for no clear reason, and muscle stiffness) along with thermoregulation (increased body temperature for no reason, increased perspiration compared to others, took longer to cool off compared to others) were analyzed.

2.4 Statistical Analysis

2.4.1 Analysis Software and Servers

Data were collected using Research Electronic Data Capture (REDCap) surveys. REDCap is a secure data capturing tool hosted by Clinical and Translational Science Institute (CTSI) at the University of Pittsburgh. Instrument data were securely stored on REDCap data management servers and exported for quantitative analysis. Individual data were exported into and analyzed using IBM© SPSS© Statistics version 28.0.1.1 software. Outputs, syntax and SPSS data files were stored on the OneDrive cloud on University of Pittsburgh servers.

2.4.2 Quantitative Analysis

Data were first screened for any anomalies (e.g., outliers, missing data, violations of any statistical assumptions) that may invalidate the results from the planned analysis. No outliers were identified in any of the instruments; however, the small sample size limits power for analysis. Descriptive statistics were used to summarize demographics, clinical characteristics of pain, reported MHS symptoms, and RAND SF-36 QoL domains. Due to this study's small sample size, a side-by-side comparison of central tendency and variability of the RAND SF-36 were compared to general population norms and to a similar musculoskeletal disease population.

Comorbid conditions are a confounding variable that contribute to the development of chronic symptoms that are directly related to MHS. Participants were asked to list diagnosed comorbid diseases. Comorbid diseases were grouped into the following categories: hypertension, thyroid disease, diabetes, allergies/sinusitis, musculoskeletal problems, liver disease, cancer,

respiratory problems, heart disease, core disease, cataracts, and gastrointestinal disease. The data were used to compare to the general population with similar comorbid conditions.

Frequency of muscle complaints (muscle cramping, muscle cramping with pain, and muscle stiffness) showed normal distribution. Frequency of thermoregulation changes (increased perspiration and increased cooling off time) were normally distributed.

RAND SF-36 domains were correlated with PROMIS pain T-scores using Two-tailed Pearson product-moment correlation coefficient. Significance was set to 0.05 for two-sided hypothesis testing. Higher pain scores should associate to lowered QoL scores.

3.0 Results

One hundred and thirty-seven subjects were recruited by the NAMHR. All participants from the NAMHR had previously indicated an interest in participating in research studies. Twenty-two participants were identified by NAMHR and contacted by University of Pittsburgh investigators. All participants were emailed a REDCap survey link. Seven participants of the 22 were mailed a physical copy of the instruments per participant request. Nineteen participants completed the REDCap survey: twelve online and seven by hard copy. Of 19 participants, 13 reported female and 6 reported male gender. The mean age was 65.9 $\pm$ 9.9. Seventeen participants (89.5%) reported other family members shared MHS diagnosis.

Table 1 Demographic and Clinical Characteristics of the Sample

Characteristics	n (%) or Mean $\pm$ SD (Min-Max)
Sex	
Male	6 (31.6)
Female	13 (68.4)
Age (years)	65.9 $\pm$ 9.9 (51-84)
Number of children	
0	3 (15.8)
1	4 (21.1)
2	9 (47.3)
3	3 (15.8)
Number of healthcare appointments per year	
1-2	6 (31.5)
3-4	5 (26.3)
5-6	4 (21.1)
7+	4 (21.1)
Years since MH diagnosis	29.5 $\pm$ 11.2 (10-52)

Family history of MHS	
Yes	17 (89.5)
No	2 (10.5)

3.1 Aim 1: Describe symptoms reported by participants with MHS

3.1.1 Pain

For the nineteen participants reporting, pain intensity had a mean T-score of 46.4, neuropathic pain had a mean T-score of 46.2 and nociceptive pain had a mean T-score of 46.9. There was no missing participant data. Scores lower than the normed population indicates less perceived pain and a higher score indicates more perceived pain. For pain intensity one (5.3%) scored lower than the norm, eighteen (94.7%) scored at the normed mean. For neuropathic pain eight (42.1%) scored lower than the normed mean, one (5.3%) scored higher than the normed mean, and ten (52.6%) scored at the normed mean. For nociceptive pain three (15.7%) scored lower than the normed mean, three (15.7%) scored higher than the normed mean and thirteen (68.4%) scored at the normed mean. Table 2 shows descriptive analysis of PROMIS T-scores for Pain intensity, neuropathic pain and nociceptive pain.

Table 2 PROMIS Pain T-Scores (n=19)

PROMIS Instrument	T-scores		
	Minimum	Maximum	Mean (SD)
Pain intensity[1]	30.7	56.3	46.4 (6.6)
Neuropathic pain[2]	37.2	66.4	46.2 (9.0)
Nociceptive pain[3]	30.3	68.9	46.9 (10.8)

[1]Pain Intensity 3a v1.0

[2] Neuropathic Pain 5a v2.0
[3] Nociceptive Pain 5a v2.0

3.1.2 Muscle and Body Temperature Symptoms

Chronic MHS symptoms examined in this study were muscle cramping, stiffness, perceived elevations of body temperature, and perceptions of increased cooling down time. Muscle cramping (mean 2.5), muscle cramping with pain (mean 2.8) and muscle stiffness (mean 2.8) reported symptoms were reported. The majority of participants (n=13, 68.4%) did not indicate elevations in core body temperature raises for no reason. However, participants did identify increased perspiration and cool off time as symptoms. Increased perspiration (mean 2.5) and increased cooling off time (mean 2.9) were reported. All category means for muscle and thermoregulation symptoms fall between "a little bit" and "somewhat." Table 2 shows frequency analysis for muscle and thermoregulation symptoms. There was no missing participant data.

Table 3 Chronic MHS Symptoms

	Frequency (%)				
Symptom	Not at all	A little bit	Somewhat	Quite a bit	Very much
Muscle pain without cramps	3 (15.8)	8 (42.1)	4 (21.1)	3 (15.8)	1 (5.3)
Cramped muscles for no reason	3 (15.8)	6 (31.6)	4 (21.1)	3 (15.8)	3 (15.8)
Muscle stiffness	5 (26.3)	3 (15.8)	6 (31.6)	1 (5.3)	4 (21.1)
Increased body temperature for no reason	13 (68.4)	4 (21.1)	2 (10.5)	0 (0)	0 (0)
Increased perspiration	6 (31.6)	4 (21.1)	5 (26.3)	1 (5.3)	3 (15.8)
Takes longer to cool off	3 (15.7)	6 (31.6)	4 (21.1)	2 (10.5)	4 (21.1)

3.1.3 Bleeding

There were few cases of increased bleeding tendencies. Two (10.5%) participants reported frequent (1-5) nosebleeds per year. Nine (47.4%) reported frequent bruising. Ten (52.6%) participants reported bruising occurred in exposed and unexposed sites (eight (42.1%) exposed, two (10.5%) unexposed). Seven (36.8%) reported bleeding from minor wounds. Of these seven participants, the frequency of bleeding was reported as: less than once per year (1, 5.3%), one to five times per year (2, 10.5%), and six or more times per year (4, 21.1%). One (5.3%) participant reported unexpected bleeding during a surgery.

3.2 Aim 2: Describe QoL in patients with MHS

3.2.1 QoL of Patients that are MHS

All health perception domains within the MHS sample had lower scores compared to the general population aged between 55-64 and the general population aged between 65-74. The general population aged 75 years and older scored lower in physical functioning, physical role-limitation, emotional role-limitations, energy/fatigue, social functioning and pain domains compared to the MHS sample. The MHS sample scored lower in emotional well-being and general health domains compared to the general population aged 75 and older. There was one missing data point within social functioning category. Since there were only two items within this domain, the average could not be calculated; this data point was excluded for scoring. Table 4 shows the mean and standard deviation scores for RAND SF-36.

Table 4 Descriptive Statistics for Health-related Quality of Life Based on the RAND 36-Item Short Form

Domain	Mean (SD)			
	MHS sample Ages 51-84 years (n=19)	General population Ages 55-64 years (n=269) [1]	General population Ages 65-74 years (n=442) [1]	General population Ages 75+ years (n=264) [1]
Physical functioning	59.7 (34.7)	76.24 (26.32)	69.38 (26.26)	53.20 (29.98)
Role limitation (physical)	59.2 (45.8)	73.66 (38.39)	64.54 (41.30)	45.28 (41.95)
Role limitation (emotional)	73.7 (40.9)	80.26 (34.29)	81.44 (34.56)	63.18 (42.96)
Energy/fatigue	51.8 (16.3)	60.37 (22.69)	59.94 (22.12)	50.41 (23.62)
Emotional well-being	69.1 (15.7)	75.01 (19.30)	76.87 (18.08)	73.99 (20.23)
Social functioning (n=18)	75.7 (21.2) [2]	81.37 (24.81)	80.61 (25.63)	73.89 (28.75)
Pain	61.4 (21.9)	67.51 (25.63)	68.49 (26.42)	60.88 (26.01)
General health	55.3 (24.6)	64.62 (23.37)	62.56 (22.42)	56.66 (21.21)

[1] Scores obtained from SF-36 Health Survey Manual
[2] Missing value for social functioning. This value was omitted from average

3.2.2 Comorbid Illnesses

Of 19 participants, 2 (10.5%) did not list any diagnosed comorbid diseases. In order of grouping: 7 (36.8%) reported hypertension, 6 (31.6%) reported thyroid disease, 3 (15.8%) reported diabetes, 4 (21.1%) reported allergies/sinusitis, 7 (36.5%) reported musculoskeletal problems, 2 (10.5%) reported cancer, 4 (21.1%) reported respiratory problems, 4 (21.1%) reported heart disease, 3 (15.8%) reported core disease, 1 (5.3%) reported cataracts, and 2 (10.5%) reported gastrointestinal disease.

3.2.3 Ancillary QoL Comparisons to the General Population

The participants in this study identified several chronic comorbid conditions unrelated to MHS. The top two reported comorbid conditions from the MHS group were hypertension and musculoskeletal conditions. Two groups from the general population with similar comorbid conditions were compared. Participants that reported arthritis and hypertension comorbid disease had lowest mean scores in all categories with exception of emotional role limitations. Participants scores with musculoskeletal complaints and hypertension were also lower than the mean scores of the general population. Participants that had musculoskeletal complaints generally scored 10 points higher in each category compared to participants with arthritis. Table 5 shows the MHS sample compared to the arthritis and hypertension and musculoskeletal and hypertension groups.

Table 5 Health Related QoL with Chronic Comorbid Conditions

	Mean (SD)		
Domain	MHS sample Ages 51-84 years (n=19)	Comorbid conditions arthritis and HTN (n=175) [1]	Comorbid conditions musculoskeletal complaints and HTN (n=314) [1]
Physical functioning	59.7 (34.7)	56.44 (29.19)	67.58 (25.66)
Role limitation (physical)	59.2 (45.8)	38.17 (39.40)	56.15 (41.09)
Role limitation (emotional)	73.7 (40.9)	74.84 (37.36)	73.14 (37.95)
Energy/fatigue	51.8 (16.3)	49.54 (22.13)	56.82 (21.55)
Emotional well-being	69.1 (15.7)	78.01 (19.02)	78.13 (17.16)
Social functioning	75.7 (21.2) [2]	79.74 (27.12)	87.17 (20.25)
Pain	61.4 (21.9)	55.04 (26.27)	66.57 (24.34)
General health	55.3 (24.6)	58.96 (21.42)	59.85 (20.55)

[1] Scores obtained from SF-36 Health Survey Manual

[2] Missing value for social functioning. This value was omitted from average
Note: HTN = hypertension

3.3 Aim 3: Describe the Association of Pain on QoL in Participants that are MHS

3.3.1 Relationship of Pain and QoL

Pain scores based on the PROMIS instruments were correlated with QoL based on the eight RAND SF-36 individual domains. The RAND SF-36 pain domain was strongly associated to the PROMIS pain intensity and neuropathic pain instruments, providing some validation between associations. All pain scores were negatively associated with QoL categories. Pain intensity is strongly associated with impaired physical functioning, physical role limitations, and social functioning. Neuropathic pain is strongly associated with impaired physical functioning, physical role-limitations, energy/fatigue, and social functioning. Nociceptive pain was only associated with health perception. Table 6 reports Pearson product-moment correlations between RAND SF-36 categories and the PROMIS pain instruments.

Table 6 Correlation Coefficients Between QoL Factors and Pain

	PROMIS Pain Measure		
RAND SF-36 Domains	Pain Intensity	Neuropathic Pain	Nociceptive Pain
Physical functioning	-.719*	-.805*	-.206
Role limitation (physical)	-.670*	-.661*	-.268
Role-limitation (emotional)	-.404	-.381	-.378
Energy/ fatigue	-.400	-.577*	-.257
Emotional well-being	-.389	-.413	-.420
Social Functioning	-.562*	-.565*	-.209
Pain	-.921*	-.886*	-.432

General Health	-.350	-.342	-.465*

*Correlation is significant at 0.05 (2-tailed)

4.0 Discussion

This is one of a few studies to examine chronic symptoms and QoL in individuals with MHS. While fatal MH reactions are well documented due to anesthetics provided during procedures, MHS individuals are at risk for fatal non-anesthetic MH episodes. Individuals that are MHS are at risk for events without exposure to anesthetic drugs. It is thought these may be precipitated by physical exertion (Zvaritch et al., 2019). This study focused on generalized symptoms with limited focus on exertional manifestations. Given the high rate of genetic variants in the population but rare adverse anesthetic events, it is not well understood how many individuals with MHS predisposition may have undiagnosed symptoms. Due to symptom variations, some MHS individuals may have looming minor symptoms, similar to background noise. Timelier detection of MHS individuals may occur by understanding the common background symptoms.

Due to the scarce literature on chronic MHS presentations, broader literature inclusions were searched to examine symptoms associated with QoL. One study by van Ruitenbeek et al. (2019) used the RAND SF-36 form along with other QoL questionnaires *(Functional impairment using Sickness Impact Profile, Fatigue severity using Checklist Individual Strength, Symptoms of psychopathology using SLC-90 and Hospital Anxiety and Depression Scale)* to understand QoL in individuals with various *RYR1* variant skeletal muscle disorders. van Ruitenbeek et al. (2019) concluded that individuals with permanent or episodic *RYR1* related symptoms affected QoL primarily. Diminished QoL was associated with functional limitations and fatigue (van Ruitenbeek et al., 2019). When comparing this study's RAND SF-36 measurements (n=19) to van Ruitenbeek et al. (2019) findings (n=72) participants in this study scored lower in almost all categories but were within the one standard deviation of these results.

This study was mostly larger female (68.4%) sample that may not accurately reflect the gender distribution in the MHS population. The voluntariness of the study design likely contributed to the gender disproportion. Brady et al. (2009) concluded that males were at significant higher risk for MH; of 73 MH admissions 71% were male. Another study that analyzed 129 MHS individuals after an adverse anesthetic reaction also showed male sample dominance (62.2%) (Riazi et al., 2014). Since men have higher risk, understanding the variance in symptom manifestation may help identify MHS predisposed individuals sooner.

Pain, in relation to QoL, is an important symptom to understand as it can significantly lower QoL satisfaction. While all of the mean PROMIS t-scores fell within the normal range, the individual scores show that there is variation between pain manifestations. This result indicates that pain perception related to MHS varies between individuals. Looking at the RAND SF-36 pain category, the mean (61.4) was lower than both the general (68.49) and musculoskeletal (66.57) populations. One study that used the RAND SF-36 showed a pain score of 71.2 (van Ruitenbeek et al., 2019). This result again shows that MHS populations have pain associated with MHS. The difference in scoring could be attributed to the small population size. However, it could also indicate that depending on MHS symptom expression, pain perception may vary significantly throughout the population.

Participants reported more muscle pain, cramping and stiffness in addition to perceptions of temperature dysregulation when compared to the general population of non-predisposed MHS individuals. There are limited studies that examine chronic MHS symptoms; however, it has been noted that there is an increased perception of muscle pain and stiffness thought to be related to MHS (Werneid & Brandom, 2016). MHS individuals with a MHS genetic variant may experience muscle and temperature symptoms due to excessive calcium leak on resting skeletal muscle fibers.

Meizoso-Huesca et al. (2022) examined at calcium release at *RYR1* channels in mice and suggested that continuous calcium release on resting skeletal muscle fibers promotes heat generation. This result may explain why MHS individuals experience increased perspiration, and increased length of cooling time.

Although bleeding has not been recognized as a problem for daily life, developed animal models demonstrated failure to constrict small blood vessels with MHS genetic variants (Lopez et al., 2016). Multiple questions about bleeding and bleeding tendency were presented to the participants. There was not enough evidence to show increased bleeding tendencies. It is possible that this sample was not representative of the population, due to small sample size. It is likely this population does not experience bleeding abnormalities as seen in Lopez et al. (2016); however, a study with a larger sample would be needed for confirmation.

This study shows MHS individuals have lower QoL perceptions compared to the age-matched general population. Given the increased mean age and reported comorbidities, it is difficult to determine if the lowered QoL perception is based on strict MHS symptoms or if the reported scores reflect those other comorbid conditions. To help understand how these comorbidities may facilitate lower QoL, the RAND SF-36 was compared to other populations of similar mean ages with other comorbid conditions. The top two reported comorbidities in this study were hypertension (7, 36.8%), and musculoskeletal issues (7, 36.8%). Based on these frequencies, comparisons were made to a population with osteoarthritis and hypertension, and to a population with reported musculoskeletal complaints and hypertension. Both of these comparisons showed decreases in QoL when compared to the general population. The sample size of this study was too small to statistically analyze the scores. A larger sample may help correct any possible variable confounders.

Pain intensity was inversely correlated to physical functioning, physical role limitations and social functioning. Additionally, neuropathic pain was inversely correlated to physical functioning, physical role limitations, energy/fatigue, and social functioning while nociceptive pain was inversely correlated to only general health. These findings indicate that pain intensity and neuropathic pain associate with lower QoL perceptions in MHS individuals. There is limited evidence to show nociceptive pain was associated with lowered QoL. In a study by Phillips and Trivedi (2018) pain was associated with myopathies related to CACNAIS calcium channelopathies (Phillips & Trivedi, 2018). Sansone et al. (2012) found that fatigue and pain directly impacted QOL in individuals with non-dystrophic myopathies, while van Ruitenbeek et al. (2019) showed the same correlation to *RYR1*-related specific myopathies. Although pain has been documented to lower quality of life in other channelopathies, limited studies have been conducted to assess chronic pain on QoL in individuals with MHS.

4.1 Limitations

The limitations of this study include the following. The first limitation is the study sample size. With a small sample size, statistical power and precision is reduced. Second, the sample was disproportionally female which indicates that this study does not reflect the actual population. A larger sample with more exclusionary criteria may help correct any possible bias.

Third, individuals who completed the instruments electronically by-passed more menstrual and peripartum questions in the Chronic MH symptoms instrument. The question regarding heavy menstrual flow was created as a branching logic question. By clicking yes, the participant would have access to menstrual flow and bleeding related to pregnancy questions. By clicking “no” or

"not relevant to me," the participant by-passed the remaining section and ended the survey. Due to this error, menstrual bleeding and bleeding regarding pregnancy could not be captured.

The fourth limitation is the underlying reported comorbid diseases. This study focuses on generalized symptoms such as pain, and physical limitations. Since this study reflects a higher age sample, it is likely that QoL is altered by age-related comorbidities. It is difficult to discern whether reported symptoms are from comorbid disease or from MHS. Additional observational studies with a larger sample size comparing symptom expression and QoL in those matched MHS and those without MHS, would be needed to examine the reported symptoms in order to separate age-related changes from MHS symptoms.

A fifth limitation may be due to the social isolation required by the COVID-19 pandemic. Social isolation/distancing has impacted social and mental well-being within the overall population of individuals in the United States. Since the RAND SF-36 instrument assesses social and emotional well-being, both assessments may have been altered due to the pandemic rather than MHS symptoms.

4.2 Implications

These findings can inform practice by increasing clinicians' awareness of MHS chronic symptoms. With awareness of chronic MHS symptoms, health care providers may have greater anticipation of perceived symptoms after MH events, or improved detection of MHS in previously undiagnosed patients.

4.3 Next Research Steps

Continued work with NAMHR to increase study sample size in order to refine symptom associations is recommended. Assessment of demographic characteristics should be expanded to include participant's occupation and physical residence. In Betsker et al. (2021), several participants list heat intolerance as a limiting factor to daily living. Additionally, this study showed thermoregulation dysfunction as a MHS symptom. This study determines that there are symptoms associated with QoL; however, it does not consider whether career choice or place of residence is also altered. Due to sample age, comorbid disease processes may alter pain perception and QoL. Investigation of younger MHS population may give insight into symptoms that associate with QoL without comorbid disease as a confounding variable.

5.0 Conclusion

The study demonstrates that additional research is needed for individuals with chronic MHS symptoms. Due to differing gene expression, symptoms can vary from mild to severe and associate with QoL. This study can provide a foundation for more symptom investigation and increase awareness to physicians and other healthcare professionals in order to better treat MHS individuals.

Appendix A Study Instruments

Appendix A.1 Demographics

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Demographics

Please complete the survey below.

Thank you!

What is your current age?	_____
What is your gender?	◯ Male ◯ Female ◯ Non-binary ◯ None of these (fill in text box) ◯ I prefer not to answer
I identify as	_____
How many children do you have?	_____
How often do you make healthcare appointments per year?	◯ 0 ◯ 1-2 ◯ 3-4 ◯ 5-6 ◯ 7+
Do you have any other diagnosed health problems besides malignant hyperthermia?	◯ Yes ◯ No
If yes, please list any diagnosed health problems	_____
How long have you been diagnosed as malignant hyperthermia susceptible?	_____
How were you diagnosed as malignant hyperthermia susceptible?	_____
Do you have family members that are malignant hyperthermia susceptible?	◯ Yes ◯ No
How many family members are malignant hyperthermia susceptible?	_____

Appendix A.2 Quality of Life

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General Quality of Life

Please complete the survey below.

Thank you!

1)	In general, would you say your health is:	◯ Excellent ◯ Very Good ◯ Good ◯ Fair ◯ Poor
2)	Compared to one year ago, how would you rate your health in general now?	◯ Much better now than one year ago ◯ Somewhat better now than one year ago ◯ About the same ◯ Somewhat worse than one year ago ◯ Much worse than one year ago

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

3)	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	◯ Yes/ Limited a lot ◯ Yes/ Limited a little ◯ No/ Not limited at all
4)	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	◯ Yes/ Limited a lot ◯ Yes/ Limited a little ◯ No/ Not limited at all
5)	Lifting or carrying groceries	◯ Yes/ Limited a lot ◯ Yes/ Limited a little ◯ No/ Not limited at all
6)	Climbing several flights of stairs	◯ Yes/ Limited a lot ◯ Yes/ Limited a little ◯ No/ Not limited at all
7)	Climbing one flight of stairs	◯ Yes/ Limited a lot ◯ Yes/ Limited a little ◯ No/ Not limited at all
8)	Bending, kneeling, or stooping	◯ Yes/ Limited a lot ◯ Yes/ Limited a little ◯ No/ Not limited at all
9)	Walking more than a mile	◯ Yes/ Limited a lot ◯ Yes/ Limited a little ◯ No/ Not limited at all
10)	Walking several blocks	◯ Yes/ Limited a lot ◯ Yes/ Limited a little ◯ No/ Not limited at all
11)	Walking one block	◯ Yes/ Limited a lot ◯ Yes/ Limited a little ◯ No/ Not limited at all
12)	Bathing or dressing yourself	◯ Yes/ Limited a lot ◯ Yes/ Limited a little ◯ No/ Not limited at all

Physical Health Problems:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

13)	Cut down the amount of time you spent on work or other activities	◯ Yes ◯ No
14)	Accomplished less than you would like	◯ Yes ◯ No

15) Were limited in the kind of work or other activities — ◯ Yes ◯ No

16) Had difficulty performing the work or other activities (for example, it took extra effort) — ◯ Yes ◯ No

Emotional health problems:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

17) Cut down the amount of time you spent on work or other activities — ◯ Yes ◯ No

18) Accomplished less than you would like — ◯ Yes ◯ No

19) Didn't do work or other activities as carefully as usual — ◯ Yes ◯ No

20) Social Activities:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
◯ Not at all ◯ Slightly
◯ Moderately ◯ Severe
◯ Very severe

21) Pain:
How much bodily pain have you had during the past 4 weeks?
◯ None ◯ Very Mild
◯ Mild ◯ Moderate ◯ Severe
◯ Very Severe

22) During the past 4 weeks, how much pain interfere with your normal work (including both work outside the home and housework)?
◯ Not at all ◯ A little bit
◯ Moderately ◯ Quite a bit
◯ Extremely

Energy and Emotions:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

23) Did you feel full of pep?
◯ All of the time
◯ Most of the time
◯ A good bit of the time
◯ Some of the time
◯ A little bit of the time
◯ None of the time

24) Have you been a very nervous person?
◯ All of the time
◯ Most of the time
◯ A good bit of the time
◯ Some of the time
◯ A little bit of the time
◯ None of the time

25) Have you felt so down in the dumps that nothing could cheer you up?
◯ All of the time
◯ Most of the time
◯ A good bit of the time
◯ Some of the time
◯ A little bit of the time
◯ None of the time

26) Have you felt calm and peaceful?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

27) Did you have a lot of energy?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

28) Have you felt downhearted and blue

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

29) Did you feel worn out?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

30) Have you been a happy person?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

31) Did you feel tired?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

32) Social Activities:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with you social activities (like visiting with friends, relatives, etc.)?

- ◯ All of the time
- ◯ Most of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

General Health:
How true or false is each of the following statements to you?

33) I seem to get sick a little easier than other people

- ◯ Definitely true
- ◯ Mostly true
- ◯ Don't know
- ◯ Mostly false
- ◯ Definitely false

34) I am as healthy as anybody I know

◯ Definitely true ◯ Mostly true
◯ Don't know ◯ Mostly false
◯ Definitely false

35) I expect my health to get worse

◯ Definitely true ◯ Mostly true
◯ Don't know ◯ Mostly false
◯ Definitely false

36) My health is excellent

◯ Definitely true ◯ Mostly true
◯ Don't know ◯ Mostly false
◯ Definitely false

Appendix A.3 General Pain

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General Pain

Please complete the survey below.

Thank you!

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

In the past 7 days...

1)	Did your pain feel sore?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
2)	Did your pain feel tender?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
3)	Did your pain feel achy?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
4)	Did your pain feel deep?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
5)	Did your pain feel steady?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much

Appendix A.4 Neuropathic Pain

Confidential

Neuropathic Pain

Please complete the survey below.

Thank you!

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

In the past 7 days...

1)	Did your pain feel like pins and needles?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
2)	Did your pain feel tingly?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
3)	Did your pain feel stinging?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
4)	Did your pain feel electrical?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
5)	Did your pain feel numb?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much

Appendix A.5 Pain Intensity

Confidential

Pain Intensity

Please complete the survey below.

Thank you!

Please respond to each item by marking one box per row.

In the past 7 days...

1)	How intense was your pain at its worse?	◯ Had no pain ◯ Mild ◯ Moderate ◯ Severe ◯ Very severe
2)	How intense was your average pain?	◯ Had no pain ◯ Mild ◯ Moderate ◯ Severe ◯ Very severe
3)	What is your level of pain right now?	◯ No pain ◯ Mild ◯ Moderate ◯ Severe ◯ Very severe

Appendix A.6 Chronic MH Symptoms

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Chronic MH symptoms

Please complete the survey below.

Thank you!

I had muscle pain without cramping	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
My body temperature increased for no reason	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
I got cramped muscles for no clear reason	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
Muscles in my body became stiff	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
I perspired more than others near me	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
I took longer than others to cool off	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
I changed my job because of muscle weakness	◯ Yes ◯ No
I changed my job because of the hot environment	◯ Yes ◯ No
I had to stop working completely because of muscle weakness	◯ Yes ◯ No
I moved my home because of hot weather	◯ Yes ◯ No
My symptoms got worse as I got older	◯ Yes ◯ No
I had a malignant hyperthermia episode during or after anesthesia & surgery	◯ Yes ◯ No

If you had an MH episode, how old were you when this first happened?	_____
I have been admitted to the hospital because I had high creatine kinase	◯ Yes ◯ No
If you were hospitalized because of increased creatine kinase, how old were you when this happened the first time?	_____
How many times have you been admitted to the hospital because of increased creatine kinase?	_____
I take dantrolene by mouth	◯ Yes ◯ No
Has oral dantrolene helped you?	◯ Yes ◯ No
How has oral dantrolene helped you	_____
I have found ways of helping ease my symptoms	◯ Yes ◯ No
What helps you? Please describe.	_____
Do you have frequent nose bleeds?	◯ Yes ◯ No
How many nosebleeds do you have in a year?	◯ Less than 1 ◯ 1 to 5 ◯ 6 to 12 ◯ More than 12
What is the usual duration of your nosebleed?	◯ Less than one minute ◯ 1 to 10 minutes ◯ More than 10 minutes
Where any of these treatments needed for your nosebleeds? Check all that apply.	☐ Consultation only ☐ Cauterization/ packing ☐ Antifibrinolytics ☐ DDAVP (pitressin) ☐ Transfusion of blood or plasma
Do you have frequent bruising?	◯ Yes ◯ No
Where does your bruising occur?	☐ Exposed sites ☐ Unexposed sites
What is the usual size of your bruises?	☐ less than one cm (smaller than a pea) ☐ 1 cm (size of a pea) to 5 cms (size of a lime) ☐ more than 5 cms (size of an egg or larger)

Do your bruises occur after minimal or no trauma?	◯ Yes ◯ No
How much medical attention do you need for your usual bruises? Check all that apply.	☐ None ☐ Consultation only ☐ Cauterization/ packing ☐ Antifibrinolytics ☐ DDAVP (pitressin) ☐ Transfusion of blood or plasma
Do you have bleeding from minor wounds	◯ Yes ◯ No
How many times does this happen in a year?	◯ Less than once ◯ 1 to 5 times ◯ 6 or more times
How long does bleeding from your minor wounds last?	◯ Less than 5 minutes ◯ More than 5 minutes
What treatment have you received for this bleeding? Check all that apply.	☐ None ☐ Consultation only ☐ Cauterization/ packing ☐ Antifibrinolytics ☐ DDAVP (pitressin) ☐ Transfusion of blood or plasma
Have you experienced bothersome bleeding in your mouth from: Check all that apply.	☐ Never did ☐ Tooth eruption ☐ Gums/ after brushing teeth ☐ after bites to lips or tongue
What treatment was needed for oral bleeding? Check all that apply.	☐ None ☐ Consultation only ☐ Cauterization/ packing ☐ Antifibrinolytics ☐ DDAVP (pitressin) ☐ Transfusion of blood or plasma
Have you had bleeding after extraction of a tooth?	◯ yes ◯ no extractions or no bleeding after one extraction ◯ no bleeding after at least 2 extractions
What treatment was needed for bleeding after your tooth extraction? Check all that apply.	☐ None ☐ Consultation only ☐ resuturing/ packing ☐ Antifibrinolytics ☐ DDAVP (pitressin) ☐ Transfusion of blood or plasma
Have you had bleeding from the GI tract? Select all that apply,	☐ No ☐ From an ulcer ☐ From hemorrhoids ☐ From high pressure in the liver ☐ Sudden

What treatment was needed for GI bleeding? Check all that apply.	☐ None ☐ Consultation only ☐ Cauterization/ packing ☐ Antifibrinolytics ☐ DDAVP (pitressin) ☐ Transfusion of blood or plasma ☐ Surgery
Have you had bothersome bleeding during surgery?	◯ No bleeding in at least 2 surgeries ◯ No surgery performed on me or no bleeding in 1 surgery ◯ I did have unexpected bleeding during surgery
What treatment was needed for bleeding during surgery? Check all that apply.	☐ None ☐ Consultation only ☐ Cauterization/ packing ☐ Antifibrinolytics ☐ DDAVP (pitressin) ☐ Transfusion of blood or plasma ☐ Surgical homeostasis
Have you had excessively heavy menstrual flow; menorrhagia?	◯ Yes ◯ No ◯ Not relevant to me
How many days do your menstrual periods last on average?	_____
On how many days would you have heavy menstrual flow?	_____
How many hours would pass before a new pad or tampon is needed on the days with heaviest flow?	_____
What type of feminine products do you use?	_____
What medical attention was needed for your heavy menstrual bleed (menorrhagia)? Check all that apply.	☐ None ☐ Consultation only ☐ Hormone pill use and/ or antifibrinolytics ☐ Iron therapy ☐ Dilation & curettage ☐ Transfusion of blood or DDAVP (pitressin) ☐ Hysterectomy
Have you had bleeding after giving birth?	◯ No bleeding in at least two deliveries ◯ No deliveries/ or no bleeding in one delivery ◯ Yes/ bleeding after giving birth has been a problem for me
What treatments did you need for your bleeding after giving birth? Check all that apply.	☐ None ☐ Consultation only ☐ D&C and/ or iron therapy ☐ Transfusion of blood or plasma ☐ Hysterectomy

Appendix B IRB Approval Letter

University of Pittsburgh | Institutional Review Board
Office of Research Protections

APPROVAL OF SUBMISSION (Expedited)

Date:	June 25, 2021
IRB:	STUDY21030027
PI:	Richard Henker
Title:	Evaluation of Quality of Life and Chronic Symptoms in Malignant Hyperthermia Susceptible Individuals
Funding:	None

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

Approval Documentation

Review type:	Initial Study
Approval Date:	6/25/2021
Expiration Date:	
Expedited Category	(7)(b) Social science methods

Determinations:	• Waiver of consent documentation
Approved Documents:	• Subject Demographics, Category: Data Collection; • Chronic Symptoms Reported, Category: Data Collection; • Pain Intensity, Category: Data Collection; • Neuropathic Pain Quality, Category: Data Collection; • Nociceptive Pain Quality, Category: Data Collection; • General Quality of Life, Category: Data Collection; • approval letter dated 7-22-19.pdf, Category: External Site Permission Letter; • Letter from NAMHR for Pitt study with Dr. Brandom_Shockey_Version_June 21_21.docx, Category: Recruitment Materials; • NAMHR 201701821-ICF_5.17.2019.pdf, Category: External Site Permission Letter; • Recruitment Email June 21 2021_Version_0.01 (2)rah.docx, Category: Waiver Script; • UF-NAMHR medical record release.pdf, Category: External Site Permission Letter; • Univ Pitt IRB approval for NAMHR (180124), Category: Other;

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