Living with a genetic subtype of ARVC caused by a p.S358L disease causing variant in *TMEM43*: Symptoms of anxiety, depression, and post-traumatic stress in partners of those who tested positive and have an ICD as treatment

by

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A Thesis submitted to the School of Graduate Studies in partial fulfillment of the requirements

for the degree of

Master of Science in Medicine (Clinical Epidemiology)

Memorial University of Newfoundland

May 2021

St. John's, Newfoundland & Labrador

ABSTRACT

Background: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) caused by a *TMEM43* p.S358l variant is a particularly lethal subset of the disease found in high incidence in Newfoundland and Labrador (NL). Implantable Cardioverter Defibrillator (ICD) treatment has been found to be lifesaving in this population, however ICD treatment is not without side effects which can include mental health concerns. Partners of patients with a disease, while genetically unaffected, have the potential to be impacted by the disease. Qualitative data and anecdotal knowledge within the ARVC research team indicated that there may be serious mental health concerns in all *TMEM43* family members including partners, negative relatives not just the ICD patients themselves. This study aimed to quantitatively study the prevalence of anxiety, depression, and post-traumatic stress (PTSD) symptoms in the partners of ICD patients.

Methods: Partners of ICD patients as treatment for ARVC caused by a *TMEM43* p.S358l variant were recruited. Participants completed the Zung Self Rating Anxiety Scale (SAS), Patient Health Questionnaire-9 (PHQ-9), and the PTSD Checklist for Civilians (PCL-C). Prevalences of anxiety, depression, and PTSD symptoms were described in the partners and compared with scores of ICD patients, negative relatives and the general population. Associations between partners scores and demographic and clinical data was also analyzed.

Results: Twenty-six partners participated that ranged in age from 19-69 and 54% were female. Clinically significant scores for anxiety, depression, and PTSD were found in 25%, 12%, and 65% of partners respectively. Scale score were significantly related to one another(p=0.001-p=0.016). Partners PCL-C scores were significantly positively associated with their partner with the ICD's PCL-C score($r(24)=0.593$, $p=0.002$), number of appropriate shocks experienced by their partner with the ICD($r_S(24)=0.564$, $p=0.005$), and if the partner with the ICD went on to

have a heart transplant(t(24)=3.497,*p*=0.002). Partners were found to have significantly higher(*p*=0.037) scores for PCL-C than negative relatives. Compared to the general population partners had significantly higher rates of anxiety(*p*<0.001) and PTSD(*p*<0.001).

Conclusion: The partners of ICD patients as treatment for ARVC caused by a *TMEM43* p.S358l variant are experiencing significant mental health sequale. Additional mental health supports within this population are needed. Further research to better understand these symptoms and the risk factors could better inform health care.

General Summary

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a heart disease that can result in death. In Newfoundland and Labrador (NL) there is a particularly deadly type ARVC. Most individuals with this disease are treated using an Implantable Cardioverter Defibrillator (ICD). The ICD treatment is not a cure and can have lifelong physical and mental side effects. Preliminary research indicated that all family members, including partners, could be at risk of being impacted by the disease and the treatment. Symptoms of anxiety, depression and post-traumatic stress disorder (PTSD) were measured in the partners of ICD patients in the ARVC population of NL. Significantly high levels of PTSD were found in partners. Scores of each survey were significantly associated with one another. PTSD scores of the partners were significantly associated with the severity of the disease of the partner with the ICD. The partners were found to have higher rates of PTSD and anxiety than the general population. This study indicates the need for better mental health supports for the partners in the NL ARVC population.

ACKNOWLEDGMENTS

I would like to give immense thanks to my supervisors Dr. Kathy Hodgkinson and Dr. Holly Etchegary for their support, patience, and knowledge. Their expertise and guidance has been integral to the completion of my research and this thesis.

I would also like to thank my committee member Dr. Pullman for his contributions. Notably his consultation regarding ethical considerations.

To the cardiac clinic team, Dr. Connors, Dr. Paulin, and Nurses Kory and Melissa, thank you for facilitating patient relationships and letting me into your already crowded space.

To my fellow researchers, Dr. Magda Orzylowski and Natalie Butt. Magda, thank you for your expertise in mental health measures and patient follow up. Natalie, thank you for taking turns in the clinic for data collection.

To my biggest supporters, Mom and Sebastian, thank you for the unwavering encouragement and talking me off the ledge when necessary.

The biggest thanks go to the *TMEM43* families, without whom this research would not have been possible. Your resilience and willingness to consistently engage in research is incredible.

I would like to acknowledge the prior publication of several pieces of this thesis. Figure 1.1 on page 9 is reproduced for academic purposes with permissions from the publisher. Also reproduced with permission for academic purposes with permissions from publishers are Appendices 1- 3: Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia Modified Task Force Criteria, Zung Self Rating Anxiety Scale, Patient Health Questionnaire-9. Acknowledgment is also given to Dr. Hodgkinson for permissions to include a sample pedigree

from the TMEM43 population found on page 22 as Figure 4.1. Copyright material forms and publisher agreements are included in the supplementary text of this thesis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
BDI	Beck Depression Inventory
CAD	Coronary Artery Disease
CES-D	Centre for Epidemiologic Studies Depression
DAS	Dyadic Adjustment Scale
DCM	Dilated Cardiomyopathy
DNA	Deoxyribonucleic Acid
DS14	Type D Scale
FSAS	Florida Shock Anxiety Survey
HADS	Hospital Anxiety and Depression Scale
HCM	Hypertrophic Cardiomyopathy
HREB	Health Research Ethics Board
ICD	Implantable Cardioverter Defibrillator
LVAD	Left Ventricular Assist Device
MFODS	Multidimensional Fear of Death Scale
MOF SF-36	Medical Outcomes Study Short-Form 36
MRI	Magnetic Resonance Imaging
MUN	Memorial University of Newfoundland
NL	Newfoundland and Labrador
PCL-C	PTSD Checklist for Civilians
PCL-S	PTSD Checklist Specific

PHQ-9	Patient Health Questionnaire
POMS	Profile of Mood States Questionnaire
PTDS	Post Traumatic Diagnostic Scale
PTSD	Post-Traumatic Stress Disorder
RCM	Restrictive Cardiomyopathy
SAS	Zung Self Rating Anxiety Scale
SCD	Sudden Cardiac Death
SD	Standard Deviation
SF-12	Short Form Health Survey
STAI	State-Trait Anxiety Inventory
TMEM43	Transmembrane Protein 43
UK	United Kingdom
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

LIST OF APPENDICES

CHAPTER 1. INTRODUCTION

When settlers arrived in North America in the 1400's they brought with them, among other things, the nuclear family structure and foreign deoxyribonucleic acid (DNA).[1] A nuclear family is a unit that comprises two adults in a relationship and their children. Historically the definition was limited to heterosexual couples but has since been expanded to include same sex couples.[2] While many aspects of Canadian society and culture have evolved over the past 600 years, the nuclear family remains the predominant household type. Couples, with or without children, accounted for 52.3% of Canadian households in 2016.[3] In contrast to the unchanging family structure, our knowledge of genetics has evolved rapidly since the settlers' arrival; from Mendel and his peas in 1865, to the recognition of Rosalind Franklin's work which provided the crucial piece of evidence leading to the discovery of the double helix by Watson and Crick in 1953, to the human genome project in the 1990's, to today's commercially available DNA ancestry kits and the ease with which human DNA can be sequenced.[4] Included in these advancements, and likely of greatest medical impact, is the discovery of causative genes for many hereditary conditions.[5] This has allowed for predictive genetic testing, which can identify disease carriers before symptoms appear and may improve treatment of the condition.[6]

While not biologically affected by disease, a partner living with someone with a disease is in a very unique position, with a potential for impact unrelated directly to personal disease status. Unlike multi-generational households where the burden of family life, including care-giving is shared amongst multiple family members, the nuclear structure is largely independent with the couple's main support being one another. The impacts, both mental and physical, of having a partner with a disease have been studied in wide array of diseases. A meta-analysis of

the spouses of cancer patients found partners to have the same levels of anxiety as their diseased partners which were significantly higher than healthy controls.[7] Similarly, equally high levels of emotional distress were found in both individuals with Huntington's disease and their partners.[8] In a study on patients with epilepsy, higher rates of Post-Traumatic Stress Disorder (PTSD) in their partners was associated with the severity of the seizures.[9] A study on an array of diseases and disabilities found caregiving partners to be at a significantly increased risk for stroke and coronary heart disease.[10] Research on the partners of Alzheimer's patients found the partners to have declining immune function that is thought to be due to accelerated telomere erosion.[11] Research into partners' experiences, which is the focus of this thesis, is important not only to improve partners' outcomes, but also the individual with the disease. Having a supportive and healthy partner can improve both physical and psychological outcomes for the patient with a disease.[12,13]

1.1 CARDIOMYOPATHY

The function of the heart is to pump blood throughout the body. The heart consists mainly of muscle tissue (myocardium), divided into four chambers, the left and right atria (upper chambers) and the left and right ventricles (lower chambers). The right atrium receives oxygen poor blood from the body and pumps it into the right ventricle. From there, the blood is pumped into the lungs and oxygenated. The oxygen rich blood is received by the left atrium and pumped to the left ventricle and subsequently back into the body. Functioning of the heart can be impacted by a number of factors. Some examples include plaque buildup from Coronary Artery Disease (CAD) that reduces the amount of blood entering the heart or valve malfunctions that

impact the amount of blood entering the atria or ventricles. Diseases specific to the functioning of the ventricles are known as Cardiomyopathies. These diseases are defined by Maron et al. as *"a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure–related disability."*[14] These abnormalities make it harder for the ventricular myocardium to pump blood from the heart to the rest of the body. The cardiomyopathies are classified based on their morphologies into five types, Hypertrophic Cardiomyopathy (HCM), Dilated Cardiomyopathy (DCM), Restrictive Cardiomyopathy (RCM), Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) and Unclassified Myopathies.

1.2 ARVC

The human body is an intricate composition of over 37 trillion cells, each performing a specific role, with the combined effect of creating a functional human being.[15] Each cell contains DNA which instructs the cell in its specific role. In some cases, this DNA is mutated, which can affect the cells ability to function and may lead to disease. Diseases caused by genetics can be hereditary, meaning inherited from a parent's DNA, or de novo, where a spontaneous mutation has occurred. The disease at the heart of this project is ARVC. ARVC is part of the larger group of heart diseases known as cardiomyopathies.

ARVC is a rare genetic disease estimated to affect one in every 1000-5000 people.16 Its cause is heterogeneous with over 13 associated genes and disease-causing variants within those genes identified to date.[17,18] The mechanism of this disease is not fully understood. It typically

follows an autosomal dominant inheritance pattern, where each child of an affected parent has a 50% chance of getting the gene variant. Whether the person with the variant develops the disease depends on the penetrance. Penetrance is the proportion of individuals with the genetic variant who exhibit traits of the disease.

Of those affected by ARVC, approximately half have variants in genes that encode for cardiac desmosomes. Desmosomes are intracellular junctions that provide adhesion between cells. It is hypothesized that the myocardial cells detach from one another due to the abnormal desmosomes; these damaged cells are then replaced by fibrofatty tissue.[16] As more of the myocardium is replaced by the tissue, the heart wall begins to stretch out, preventing the heat from effectively pumping blood. Similar to the genotype, the disease phenotype is highly variable. Symptomology can range from asymptomatic, to arrhythmias, to sudden cardiac death (SCD).[18] Symptomatic patients generally present with ventricular arrhythmias which can manifest as palpitations, presyncope, or syncope.

ARVC is a progressive disease and once symptoms appear, they will continue to worsen. Without treatment ARVC can lead to SCD or heart failure. Despite the progressive nature of the disease, the first symptom can sometimes be SCD. The variability of the disease is also observed by the influence of sex, with men being at a greater risk of fast ventricular tachycardia (VT).[16]

Diagnosis of ARVC can be challenging due to phenotypic variability. In 1994 an International Task Force created criteria for diagnosis that took structural, histological, electrocardiographic, arrhythmic, and familial features in to account to address the variability.[19] The criteria are divided into two categories, major and minor. A diagnosis of ARVC could be made if the patient had either two major criteria, or one major plus two minor criteria, or four minor criteria. These criteria were informed mainly by ARVC patients that were symptomatic or

suffered SCD, which means the criteria may lack sensitivity for asymptomatic or familial cases.[2020]

In 2002, a Hamid et al. found that 11% of probable ARVC diagnoses were being missed by the International Task Force criteria. Hence the criteria were broadened to be more inclusive of the asymptomatic to mild end of the disease spectrum.[21] A further study was done in 2010 to reflect advances in technology and knowledge of the disease.[20] Computer programs and 2D Magnetic Resonance Imaging (MRI) are able to give detailed readings and pictures of abnormalities of the heart and its function. This study led to a further, and most recent, amendment of the criteria which increased the diagnostic sensitivity without losing specificity.[20] See Appendix 1 for task force criteria.

Once a diagnosis is made, cascade screening is used to identify at risk family members. Cascade screening can be complex even when the original diagnosed patient, the proband, is willing to cooperate. Family histories are taken, pedigrees created, and family members near and far are contacted. Then there are appointments with doctors, nurses, and genetic counsellors. It is truly a family affair. This process can be further complicated by family dynamics.

1.2.1 TREATMENT

There is currently no cure for ARVC. However, both pharmacological and mechanical treatments are available to treat the disease and attempt to slow the progression. A pharmacological approach to slowing the heart rate and hopefully preventing arrhythmias is usually the first course of treatment. One of the drug classes used for this purpose are beta-adrenoceptor antagonists, more commonly known as beta blockers. Beta blockers work by slowing the heart rate and conduction through the atrioventricular node, which can suppress dysrhythmias.[22] In addition to their ability to reduce arrhythmias, beta blockers can have

negative side effects including dizziness, fatigue, trouble breathing, depression, weight gain, nightmares, cold hands and feet, and decreased sexual activity. The other type of drugs used to treat ARVC are antiarrhythmic drugs (class I and III).[16] Antiarrhythmic drugs work by altering membrane ion conductivity which affects cardiac action potential. Class I are sodium-channel blockers that reduce the rate of depolarization and class III are potassium-channel blockers that reduce the rate of repolarization. Both function to slow conduction between cardiac cells, which can suppress arrhythmias. Anti-arrhythmic drugs, however, come with an array of potential side effects including, dizziness, gastrointestinal problems, and changes in heartbeat.

If drugs alone are not enough to prevent arrhythmias, another method of treatment is an Implantable Cardioverter Defibrillator (ICD).[16] An ICD is a device that is implanted under the skin on the chest and lead wires are fed into the heart. The device is about the size of small box of matches and once implanted the outline can usually be seen under the skin. Its purpose is to detect abnormal heart rhythms and correct them. If an abnormal rhythm is detected, the device will attempt to pace the heart back to normal. If this does not work, it will deliver an electric shock to correct the sustained VT/ventricular fibrillation (VF) to return the heart to sinus rhythm and prevent sudden death.[23] The heart rate required to trigger the device is individualized to each patient. Some ICD patients can feel their heart racing and know a shock is coming, while others have no warning at all. The VT or VF may impact the heart's ability to perfuse blood to the point the patient does not receive enough oxygen to their brain and they may lose consciousness before the shock. When the device fires, the shock has considerable force, sometimes described as being kicked in the chest by a horse.

Patients with an ICD are followed up regularly by a cardiology team including a cardiologist and specialized nurses. At these appointments, the device history is reviewed for any

abnormal heart rhythms or shocks, either appropriate or inappropriate. The ICD device is battery powered and a replacement battery and accompanying surgery are needed approximately every ten years.

Possible complications from an ICD include both physical and psychological impacts. Physical complications include infection of the incision or along the device. Another is lead fracture, where the wire going from the device into the heart breaks and may require another surgery to correct.[24] The other major physical complication is the delivery of inappropriate shocks. Inappropriate shocks occur when the patient has a normal fast heart that is outside the prescribed threshold and the device interprets this as an abnormal rhythm or less often, when the device malfunctions and fires outside of the prescribed heart rate threshold.[25] Psychological complications include an increased risk of negative mental health impacts. A systematic review found a 20% prevalence rate for depressive and anxiety disorders in patients with an ICD and a separate study found a similar prevalence rate of PTSD.[26,27] Due to the risk of complications of the ICD treatment, it is reserved for patients at a high risk of SCD.[28]

ICD treatment can be indicated for primary or secondary prevention. Primary prevention is when the device is placed in a patient with no history of SCD or VT/VF and secondary prevention is when an ICD is placed after a patient has shown symptoms, such as sustained VT or an aborted SCD. Using an ICD for secondary prevention is more common and utilized for conditions such as ischemic heart disease and genetic cardiomyopathies.[29] Guidelines for ICDs as secondary prevention for ARVC are well established, with the latest being published in 2015.28 Primary prevention guidelines are less established and have usually been left to physician's discretion.

ICD placement is an invasive treatment requiring surgery, lifelong device dependence, and risk of complications; however, it is a lifesaving treatment. Studies estimate a 20-30% reduction in mortality in patients that received an ICD as treatment for ARVC.[30]

1.3 ARVC IN NEWFOUNDLAND AND LABRADOR (NL)

ARVC has been identified and studied across the globe with one of the most studied populations being here in NL.[31] NL was populated by a small number of European settlers and Indigenous peoples. The people were historically isolated by the remote geography of the province and this resulted in a founder population with reduced heterogeneity.[32] Newfoundlanders and Labradorians also have a strong connection to their families and their home. This connection means many people in the province can trace their lineage back for generations and across to distant cousins. This unique NL population has aided in the study of several monogenic diseases including a subtype of ARVC caused by a p.S358L variant in the Transmembrane Protein 43(*TMEM43*) gene.[33,34]

Until the late 1900's certain families across NL suffered from a mysterious condition where the men in the family would often drop dead at a young age without any prior warning. In the late 1970's, a diagnosis of ARVC was made in one of these families.[35] Over the next few decades, extensive research was conducted on the families with ARVC and a history of SCD from which families were ascertained and pedigrees mapped. This research also led to the creation of a database of all individuals born at *a priori* 50% risk for ARVC. Due to the autosomal dominant mode of transmission, all children of an affected parent are at 50% risk of inheriting the disease-causing variant.

Genetic study of the individuals in this database led to the 2008 discovery of the causative gene for this particular type of ARVC as a p.S368L variant in *TMEM43*.34 This

variant is thought to have originated in Europe from a single founder approximately 1400 years ago.[36] The *TMEM43* gene encodes for a highly conserved 400 amino acid protein that contains a transactivation domain, four transmembrane domains, and sites for phosphorylation, O-glycosylation and sumoylation.[37,34] The variant p.S358L indicates that in the protein codon sequence a serine has been replaced by a lysine. See Figure 1.1 for illustration of *TMEM43* protein with p.S358L mutation.

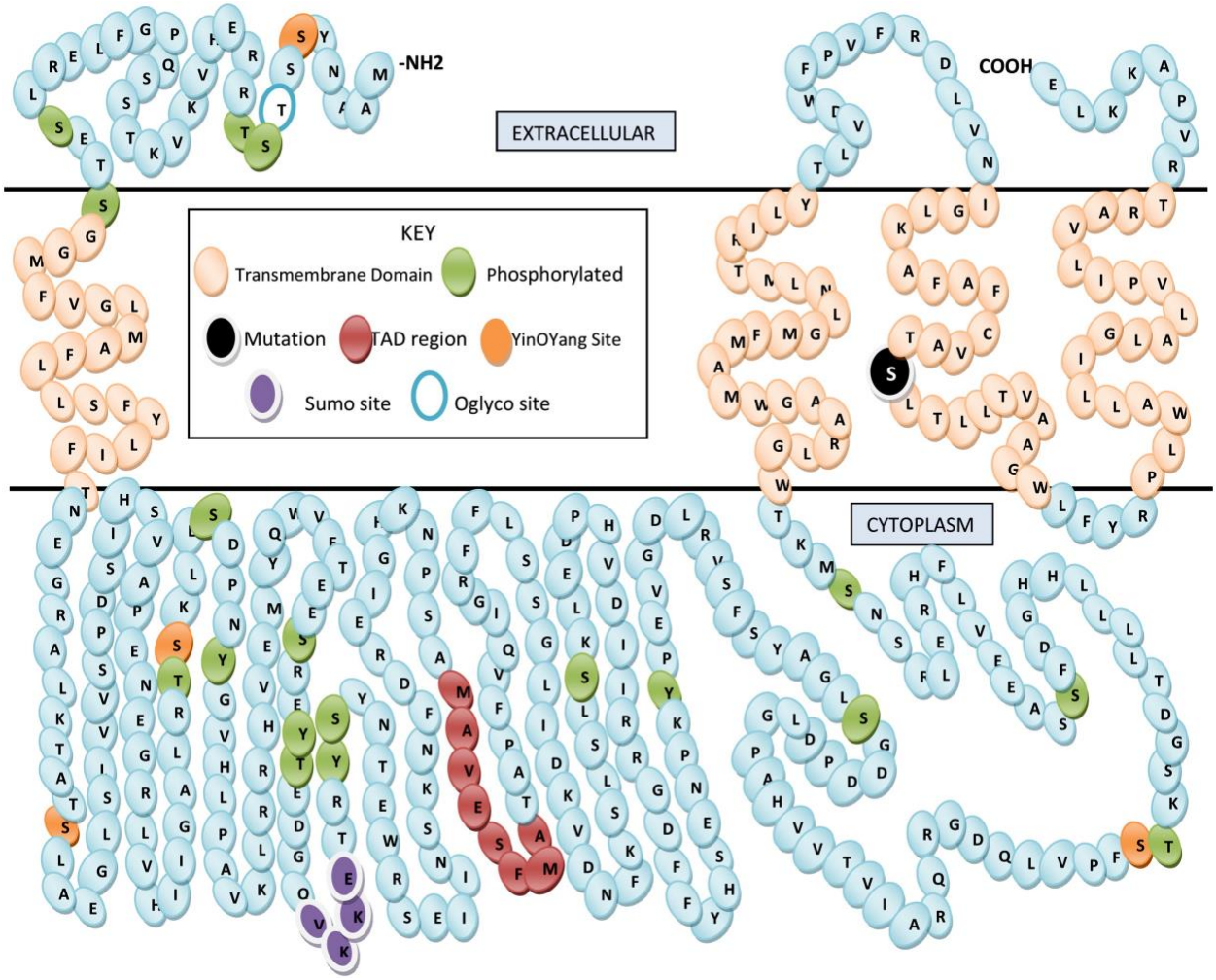

Figure 1.1 Predicted Topography of the TMEM43 Protein Used with Permission[1]

[1] Reprinted from, American Journal of Human Genetics, 82/4, Merner ND, Hodgkinson KA, Haywood AFM, et al., Arrhythmogenic Right Ventricular Cardiomyopathy Type 5 Is a Fully Penetrant, Lethal Arrhythmic Disorder Caused by a Missense Mutation in the TMEM43 Gene, 809-821, 2008, with permission from Elsevier

To date 27 families with the p.S358L variant have been identified in Newfoundland, the largest of which spans ten generations and is comprised of over 1500 members. Unlike other forms of ARVC, the p.S358L variant is fully penetrant and everyone with the variant will at some point in their lives show evidence of having the disease.[34] Although all affected will have some sign they have the disease, this disease has a high degree of variability of expression.[33]

ARVC caused by the p.S358L variant in the *TMEM43* gene is a particularly lethal subtype where SCD is often the first symptom. Manifestation of the disease is sex influenced favouring females. Left untreated, the median age of death for males is 40 and females 67.[33] A study on the *TMEM43* population in 2016 compared the survival curves of ARVC patients treated with ICDs and controls. The study showed that appropriate firings of the ICD for sustained VF/VT were considered an aborted death where the patient would have died if left untreated.[38] These results, coupled with the first symptom often being SCD, suggested an ICD for primary prevention was indicated. Individuals found to have the *TMEM43* p.S358L variant are recommended for prophylactic ICD implantation post puberty for males and ≥30 years for females. However, some females may be given an ICD earlier if they have clear clinical signs, or if the female patient is psychologically compromised by not having an ICD.[38] This treatment course means ARVC families may have many members with ICDs. Often these individuals are being implanted young and hence are living with the device for the majority of their lives.

In Newfoundland all ICD treatment and management takes place at the cardiac clinic within the Health Science Centre hospital in St. John's. ICD patients attend the cardiac clinic twice a year where they meet with specialized nurses, doctors, and technicians who monitor the functionality of the device. It is important to note there is currently no systematic provision of mental health care for ICD patients or their families.

1.4 Disease Impact on Unaffected Partners

As previously discussed, ICD treatment is life altering and comes with serious risk of complications. Most individuals with an ICD do not experience the disease or subsequent ICD treatment in isolation. The majority have families and partners who, while unaffected genetically by the disease, are affected in other ways. A study by Etchegary and the SCD team in 2017 looked at the psychological impact of having an ICD on both variant positive and negative members in the *TMEM43* families.[39] A range of impacts were discovered affecting emotional and psychological health, family dynamics, intimate relationships, and recreational activities. The results showed negative mental health effects not only in the variant positive ICD recipients, but also in the variant negative relatives and spouses. This qualitative data, along with anecdotes from clinicians and *TMEM43* families, highlighted the need for further research and quantitative data on the mental health sequale of this population.

To address this gap in the literature, a three-armed survey study was planned. Across all three arms, quantitative measurement of psychological impacts, specifically anxiety, depression, and PTSD within the TMEM43 population was undertaken. The study population included three cohorts, variant positive ICD patients, their variant negative partners, and negative first-degree relatives. The focus of this thesis is the variant negative partners.

CHAPTER 2. LITERATURE REVIEW

A search of the literature was performed using PubMed, The Cochrane Library and Memorial University of Newfoundland (MUN) library. MeSH terms "Implantable cardioverter defibrillator" and "spouse" were used in PubMed and returned 23 results, seven of which were relevant to this study. A separate search using MeSH terms "Implantable cardioverter defibrillator" and "partner" yielded 267 results, eight that were relevant to this study of which five did not overlap with the previous search. Additional searches were performed using MeSH terms "Implantable cardioverter defibrillator" and "spouse" with "anxiety", "depression" and "PTSD" which yielded no new results. This process was repeated for MeSH terms "Implantable cardioverter defibrillator" and "partner" with "anxiety", "depression" and "PTSD" also yielded no new results. A search of The Cochrane Library yielded no results. A search of the MUN library using all above searches and terms yielded one new result. A final search using MeSH terms "arrhythmogenic right ventricular cardiomyopathy" and combinations of "partner", "spouse", "anxiety", "depression", and "PTSD" yielded no new results.

2.1 PARTNERS OF ICD PATIENTS AND DEPRESSION AND ANXIETY

Dougherty et al. (1995) explored the psychological reactions and family adjustment in ICD patients and their partners.[40] The ICD patients had received this treatment post cardiac arrest from cardiac fibrillation. The cohort was divided between ICD patients who received shocks and their partners, and those who received no shocks. This was a longitudinal study following 15 ICD patients and 15 partners with data collection at hospital discharge, six-months, and one-year. Psychological reactions, including anxiety and depression were measured using the Profile of

Mood States Questionnaire (POMS) and the State-Trait Anxiety Inventory(STAI). Anxiety levels of the partners was found to be higher than that of the ICD patients. Of the partners, those with partners who had shocks, had higher levels of anxiety than those of partners who had no shocks. Despite the small sample, results clearly demonstrated negative mental health impacts of ICD therapy on partners.

In 2004, Pedersen et al. described the prevalence of anxiety and depression symptoms in ICD patients and their partners and explored the role of personality factors and social support as determinants of distress.[41] This was a cross sectional study of 182 ICD patients and 144 partners in the Netherlands. The authors did not indicate the reason for the patient receiving an ICD. Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). Results revealed that symptoms of anxiety were significantly more prevalent in partners (42%) than ICD patients (31%) and depressive symptoms were equally prevalent between the groups (28%-29%). Male partners had significantly more anxiety symptoms than female partners, with no difference in depression symptoms between sexes. Partners using psychotropic medication had a higher prevalence of anxiety and depression symptoms than partners using no medication. The study also found that partners with Type D personality were more likely to suffer from symptoms of anxiety and depression. Type D personality, *distressed personality,* is one where individuals experience negative affectivity and social inhibition.[42]

A study by Sowell at al (2007) in Florida, USA looked at anxiety and marital adjustment in patients with an ICD and their partners.43 This cross-sectional study consisted of 40 patients with ICDs as treatment for ischemic cardiomyopathies and 22 partners. Data collection happened at clinic appointments using the following scales: Multidimensional Fear of Death Scale

(MFODS) for death anxiety, Florida Shock Anxiety Survey (FSAS) for shock anxiety, Revised STAI for general anxiety, and Dyadic Adjustment Scale (DAS) for marital adjustment and quality. The results found no difference between ICD patients and partners for death or general anxiety, but partners had significantly higher shock anxiety.

In 2009, Pedersen et al. published another study examining the prevalence of anxiety and depression symptoms on ICD patients and their partners in the Netherlands.[44] This longitudinal study had 392 participants total, 196 ICD patients and 196 spouses; again, it was not noted why ICD implantation was indicated. Patients and partners were given the HADS scale pre and six months post implantation. They were also assessed for Type D personality. The results showed significantly higher prevalence of anxiety symptoms in partners as compared to patients both pre- and post-implantation. Anxiety symptoms in both groups had a significant reduction at post implantation compared to pre. They also found no difference in partner's anxiety symptoms when stratified by sex. No statistically significant differences were found for depression symptoms between patients and partners. Higher levels of anxiety and depression symptoms in partners were associated with the ICD patient receiving shocks when the ICD was for secondary, not primary prevention.

Also in 2009, Dougherty et al. reported on partners' mental and physical health after ICD implantation in their spouses as treatment for sudden cardiac arrest.[45] This prospective, longitudinal study collected data from partners at hospital discharge, one-, three-, six-, and 12-months post implantation. 100 partners were recruited from across the Pacific Northwest and completed the Short Form Health Survey (SF-12PCS) for physical health, STAI for state anxiety, and Centre for Epidemiologic Studies Depression (CES-D) for depressive symptomology. The study found that partners' physical health scores declined significantly from discharge to both

three- and 12-months. Anxiety levels in partners at hospital discharge were high (39.21±12.81) where a score of 40 indicates severe anxiety and level remained elevated, though significantly reduced, at 12-month follow up (35.6±12.47). Levels of depression in partners was not found to be elevated at any of the measurement points, but did reduce significantly from the baseline at each point.

A study from the United Kingdom (UK) was published by Redhead in 2010 examining psychopathology in patients with ICDs as secondary prevention post infarction and their spouses.[46] This cross-sectional study recruited participants from hospitals and had 100 ICD patients, 41 spouses, 284 cardiac control cases, and 89 spouse control cases. Anxiety and depression were measured using HADS and quality of life measured using the Medical Outcomes Study Short-Form 36 (MOF SF-36). Results found high levels of anxiety (47%) and depression (14%) in ICD spouses compared to the rate of anxiety (4%) and depression (1.2%) in the UK general population.

In 2011 a systematic review was published by Palacios-Ceña et al. on qualitative research examining patients', partners', and family members' experiences with an ICD.[47] This review covered research from 1999-2009 and included 22 papers. Findings on partner experience included changes in life view where partners searched for deeper meaning of the experience. Various studies showed that immediately following implantation, patients and partners experienced a period of physical, psychological and emotional adaptation with normal cognitive function returning after six months. Sexual intimacy was a concern among patients and partners focusing on worrying if sexual activity would trigger arrhythmias and if the intimate relationship would return to normal.

Van Den Broek at al published a study in 2013 looking at anxiety and depression in ICD patients and their partners.[48] This was a longitudinal study where 343 patients and partners were recruited from hospitals where data collection happened at implantation and two-, 12-, and 18-months post-surgery. Type D Scale (DS14) was used to measure Type D personality, STAI to measure state anxiety and the Beck Depression Inventory (BDI) for depressive symptoms. The study found partners had significantly higher levels of anxiety than patients at implantation but no significant differences at follow up points. Partners had significantly lower levels of depression at all measurement points except at two-months post implantation. Partners' and patients' anxiety and depression levels were significantly positively correlated at all measurement points. Partner anxiety and depression was associated with partner Type D personality.

A 2015 study by Brouwers et al. examined the Health Status and psychological distress of partners of patients with a Left Ventricular Assist Device (LVAD) compared to partners of patients with an ICD.[49] This was an observational study of 33 partners of LVAD patients and 414 partners of ICD patients from hospitals in the Netherlands and Canada. Data collection happened one-day prior to implantation and three- and six-months post-surgery. Health status was measured using SF-12, anxiety and depression measured by HADS, and type D personality using DS14.They found the prevalence of anxiety among partners of ICD patients to be highest pre-implantation (43%) that declined over time to be the lowest (31%) at six-month follow up. The prevalence of depression in partners (21-22%) was stable throughout baseline and follow up points.

Dougherty et al. (2016) that compared patient and partner quality of life and physical health outcomes after ICD treatment.[50] Patients received an ICD as secondary prevention

following SCA or serious VA. Forty-two ICD patients and 42 partners participated in the longitudinal study where data was collected at ICD implantation, then one-, three-, six-, and 12-months post-surgery. Mental health was assessed using Short Form Health Survey for mental health (SF-12 MCS), depression with CES-D, and state anxiety using STAI. The study found at baseline 48% of partners had elevated anxiety scores and 29% had elevated depression scores. There were no significant changes to scores across the measurement periods. Partners had significantly higher anxiety than patients, but there was no difference for depression.

A 2018 study from the Netherlands by Rottman et al. looked at psychological distress in ICD patients and their partners.[51] This longitudinal study included 286 ICD patients and their partners and followed them from one-day pre implant and ten-day, three-, six-, and 12-months post-surgery. Two thirds of patients had ICDs as primary prevention. The HADS was used to measure symptoms of anxiety and depression. The study found partners had significantly more anxiety than patients and no significant differences were found for depression. Both anxiety and depression scores in partners improved significantly over time. Having a partner who received ICD shocks was significantly associated with less improvement over time for symptoms of both anxiety and depression.

From the scant literature available about the mental health of partners of patients with ICDs, certain trends are notable. Symptoms of anxiety in partners tends to be higher than ICD patients, particularly immediately prior to and following implantation. Depression symptoms do not differ significantly between partners and ICD patients regardless of time from implantation. Where prevalence is measured, significant levels of anxiety and depression are found in 42-47% and 14-28% of partners respectively. Additionally, being a partner of an ICD patient who has received shocks is associated with higher levels of anxiety. While some research found that

partners with Type D personality profile had higher levels of anxiety than those without this profile, in the main, partners generally had higher levels of anxiety than their partners with an ICD

2.2 Partners of ICD Patients and PTSD

A noticeable gap in the literature is in the study of partner post-traumatic stress. There are currently no available studies exploring the prevalence of PTSD symptoms in partners of ICD patients.

2.3 Partners of ICD Patients with ARVC

Only one study was found that explored the mental health of partners of ICD patients as treatment for ARVC. This study by Etchegary et al. out of Newfoundland, Canada was a qualitative interview study that included nine patients with an ICD as treatment for ARVC caused by a *TMEM43* p.S358l variant, eight variant negative family members, and four spouses.[39] Data analysis revealed four major themes. The first was acceptance and gratitude, where spouses acknowledged the lifesaving effect of the ICD. The second was grudging acceptance where despite the known benefits, acceptance of the ICD was somewhat grudging and took time. Third was the psychological impact which was further divided into emotional and psychological wellbeing, functioning of the broader family unit, and relationships. In this theme, spouses acknowledged feelings of anxiety, depression, fear, guilt, and challenges with interpersonal relationships. The final theme was practical concerns, where spouses' lives were tangibly and practically affected by the ICD patients' loss of a licence and availability of medical

care in the province (limiting recreational activities such as travel). This small pilot study revealed a host of negative mental health impacts on both ICD patients, but also their spouses.

2.4 Prevalence of Anxiety, Depression, and PTSD in General Population

Data on the prevalence of mental health issues was not available for the Newfoundland Population. The next closest comparable population is that of Canada. The most common anxiety disorder, generalized anxiety disorder has a 12-month and lifetime prevalence of 2.6% and 8.7% respectively.[52] The 12-month and lifetime prevalence of major depressive disorder is 11.3% and 4.7% respectively.[53] The one-month (current) and lifetime prevalence of PTSD is 9.2% and 2.4% respectively.[54]

2.5 Summary

In summary there is a paucity of literature available on the mental health impacts on partners of ICD patients and even less on ARCV populations specifically. What is available shows that ICD patients are not carrying the burden alone; the impact of this treatment is also felt by partners who have significant mental health concerns. It is clear that more research is necessary in this population to better understand the mental health sequale of partners.

CHAPTER 3. METHODS

This study occurred over two phases. Initially, a patient engagement meeting was held, which included a small number of ICD patients, their partners, and negative relatives. This meeting allowed the team and affected families to discuss the project and ensure the project's focus aligned with patient priorities. Information from this meeting informed the creation of the study protocol. Phase two of the project included a cross sectional survey study measuring anxiety, depression and post-traumatic stress in partners of ICD patients affected by ARCV.

3.1 PURPOSE OF STUDY

The purpose of this study is to provide initial data on mental health sequale in partners of individuals with an ICD as treatment for ARVC caused by a *TMEM43* p.S358L variant and more broadly contribute to a better care experience for these families; to help raise awareness of mental health issues in these families, to provide information for health system decision makers and providers who work with these families that ultimately leads to an inclusion of mental health care for these families.

3.1.1 RESEARCH QUESTION

What is the prevalence of symptoms of anxiety, depression, and post-traumatic stress disorder in adult partners of ICD patients as treatment for ARVC caused by a *TMEM43* p.S358L variant? How do these prevalences compare with the ICD patients, their negative relatives, and national statistics?

3.1.2 Objectives

1. Determine the prevalence of anxiety, depression, and posttraumatic stress symptoms in the partners of ICD patients.
2. Determine whether the severity of psychiatric symptoms correlate with severity of disease in their partner and/or their family.
3. Compare the prevalence of psychiatric symptoms in partners of ICD patients with general population levels.
4. Compare the prevalence of psychiatric symptoms between the different family groups (ICD recipients, unaffected family members, and partners of ICD recipients).
5. Obtain data that might inform the provision and type of health care in this patient cohort regarding their mental health.

3.2 STUDY POPULATION

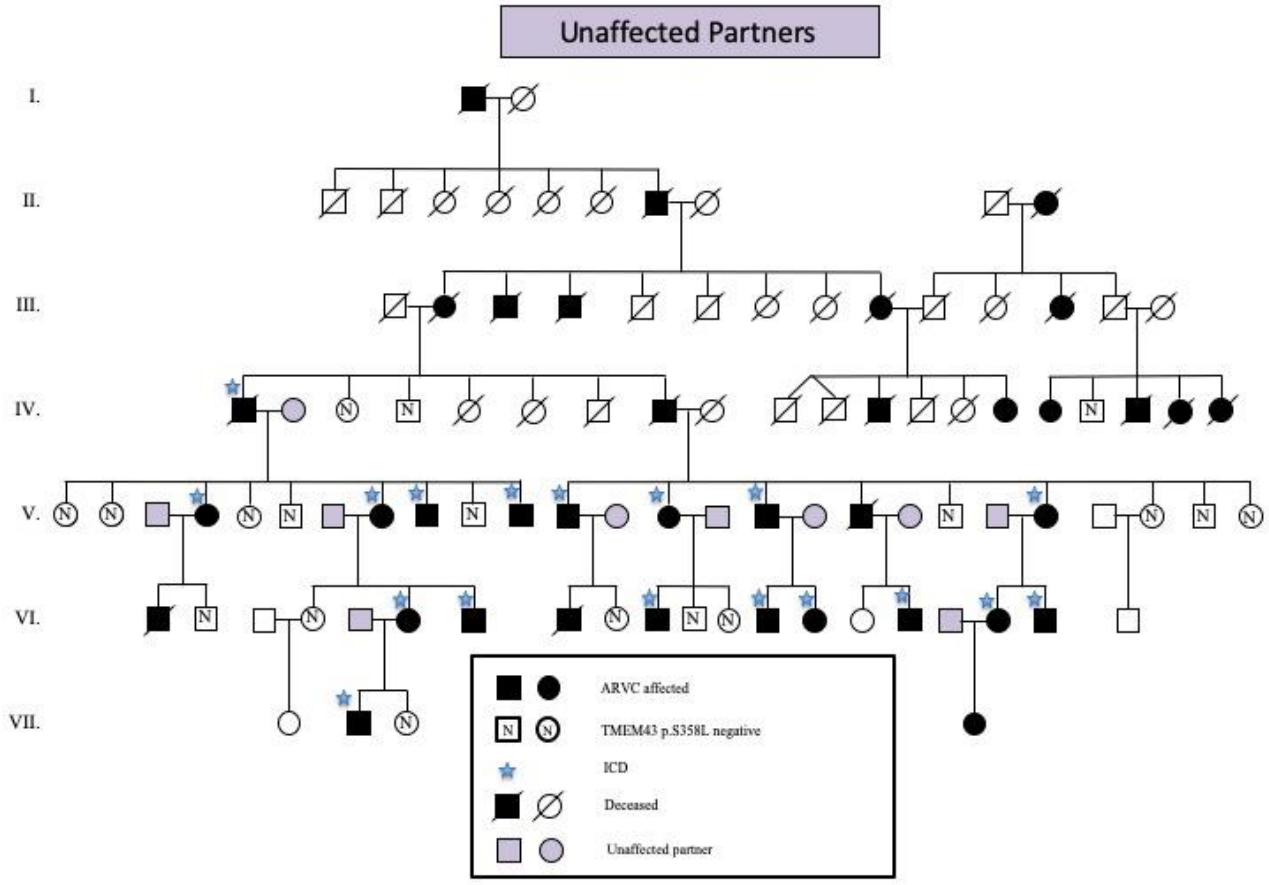

Figure 3.1 Sample Pedigree of the *TMEM43* p.S358L Population with Unaffected Partners Highlighted[2]

Of the twenty seven families with the p.S358L variant in the *TMEM43* gene in NL, the first 15 are the best ascertained, have a long standing relationship with the genetics/cardiac team at MUN, and have previously consented to be part of ongoing genetic studies (Health Research Ethics Board(HREB); study #:00-176). To attain manageable participant numbers for this pilot study, the first 8 of the 15 families were primarily ascertained for a study invitation. The expansive dataset (HREB; 00-176) and pedigrees were accessed with permission from the data

[2] Used with permission From Dr. Kathleen Hodgkinson.

custodian Dr. Hodgkinson and the project was approved by the HREB (study #: 2017-071). See Figure 3.1 for sample pedigree highlighting unaffected partners. From searching this data, 106 ICD patients, 148 variant negative first-degree relatives, and 59 partners were identified. The responsibility for accessing, collecting and analysing each group formed the basis of three different M.Sc. projects headed by three different students. ICD patients were studied by Dr. Magda Orzylowski, partners of ICD patients by Ms. Mary Walsh (the author of this thesis), and negative first-degree relatives by Ms. Natalie Butt.

3.3 MEASURES

From the literature review it was clear there was no standard of evaluating the mental health of partners of ICD patients. While the majority of studies did measure anxiety and depression, the methods were varied. Some focused on anxiety and depression within the hospital setting, and others measured types of anxiety, including shock anxiety separately. Additionally, there were no studies to reference that examined PTSD symptoms in partners. Within the larger field of cardiac research there are many mental health scales utilized. For anxiety and depression some examples are: HADS, SF-12MCS, and BDI.[55,56,57,58] For PTSD: Post Traumatic Diagnostic Scale (PTDS) and PTSD Checklist Specific (PCL-S).[59,60]

The purpose of this study was to gather quantitative data on the prevalence of symptoms of anxiety, depression, and PTSD. The scales chosen needed to be brief and easy to understand since they would be self-rated. They also needed to be validated and reliable within cardiac populations. While a diagnosis of anxiety, depression, or PTSD would not be possible without the involvement of a qualified mental health professional, the research team wanted scales that could screen for these conditions and reliably identify symptoms of these disorders.

Ultimately the instruments chosen were the Zung Self Rating Anxiety Scale (SAS), the Patient Health Questionnaire-9(PHQ-9), and the PTSD Checklist for Civilians (PCL-C) all three of which are validated and used widely across multiple health populaitons.[61,62,63]

3.3.1 Anxiety

The SAS is a 20-item self-rated measure of anxiety symptoms with a four-point response scale: one-a little of the time, two-some of the time, three-good part of the time, and four-most of the time. The scale focuses on the respondent's physical manifestations of and feelings of anxiety. The possible range of scores is 20-80. This score is then converted to an anxiety index with scores ranging from 25-100. This index score corresponds with severity of anxiety symptoms: <45 points = normal range, 45-59 points = minimal to moderate anxiety, 60-74 points = marked to severe anxiety, and ≥75 points = most extreme anxiety.[61] This scale has been validated as a screening tool for anxiety and has been shown to be a significant predictor of an anxiety diagnosis.[64] A cut off threshold of 45 and above was chosen for this study. Participants scoring above this threshold were considered to be positive for anxiety. See Appendix 2 for a copy of the SAS.

3.3.2 Depression

The PHQ-9 is a nine item self-rated measure of depression symptoms with a four-point response scale: zero-not at all, one-several days, two-more than half the days, three-nearly every day. The questionnaire focuses on the respondent's energy levels and ability to function in everyday life. The possible range of scores is zero to 27. This score corresponds with the level of depression severity: zero to four = minimal, five to nine = mild, 10-14 = moderate, 15-19 = moderately severe, 20-27 = severe. This scale is a reliable and valid measure of depression

severity.[62] A score of ≥ten has a 78% sensitivity and 96% specificity for any depression diagnosis.[65] A score of ten or greater was chosen as the cut-off threshold for this study and participants above this threshold were considered positive for depression. See Appendix 3 for a copy of the PHQ-9.

3.3.3 PTSD

The PCL-C is a 17-item self-rated measure of PTSD symptoms with a five-point response scale: one-not at all, two-a little bit, three-moderately, four-quite a bit, and five-extremely. The checklist focuses on the respondent's ability to cope with everyday life and physiological disturbances. There are three versions of this scale, a military, a specific and a civilian. The civilian version was used in this study. This scale is a valid and reliable measure of PTSD symptoms.[63] The interpretation and scoring of this scale was not as straightforward as the two previous scales. When choosing a threshold cut-off, the target setting and population had to be considered as per the National Centre for PTSD. The rate of PTSD within this specific population was not known. Prevalence estimates of PTSD in patients with ICDs as treatment for ARVC vary from 21-31%.[66,67,68,69] Clinical experience of the research team, coupled with pilot qualitative data and discussion during the patient engagement session, suggested the prevalence could likely be just as high within the partner population.[39] Therefore, a cut-off point of 36 and above was chosen, which corresponds to a PTSD prevalence 16-39. Participants scoring 36 and above were considered PTSD positive. A score of 44 or above was chosen to a high score for PTSD. See Appendix 4 for a copy of the PCL-C.

3.4 Recruitment

3.4.1 Patient Meeting

Members of two families affected by ARVC were contacted by a clinical professional in their circle of genetics care (Dr. Hodgkinson) and invited to attend the patient engagement session. The families contacted were chosen through purposeful sampling: they have a long-standing relationship with the research team and a long history with the disease. Experiences within families also varied in terms of numbers of affected family members, SCD in the family, family dynamics and relationships, and numbers of at-risk relatives. Collectively, participants in the patient engagement session represented varied experiences with ARVC and ICD therapy.

3.4.2 Quantitative

Study packages were created that contained a cover letter/consent form, the three scales, and contact information for mental health and study support. These packages were linked to the participant by their research number from the longstanding previous research project (HREB 00-176). This allowed the packages to be de-identified and could only be connected to the original participant through the dataset from the long standing SCD cardiac research group. This research number does not exist anywhere else in the patient record. Copies of the cover letter/consent form and support contact information can be accessed in Appendices 5 and 6 respectively. The packages were delivered in the following ways:

1. ICD patients are seen every six to twelve months at the cardiac clinic for follow up on their condition and device. They may be accompanied by their partner. At the appointment, a member of their health care team asked each ICD patient (and partner if present) if they were willing to speak to a member of the research team. If agreeable, the project was then explained by a team member. If the ICD patient (and partner) consented to participate, they were given the option of completing the

questionnaires in a private room or taking them home and returning by mail. This method of recruitment began in September of 2017 and ceased in September of 2018.

2. Partners of ICD patients who had not been successfully contacted through the clinic were contacted by Dr. Hodgkinson by phone. For those with 'out of date' phone numbers or without a number listed, best efforts were made to obtain this information via the systems already in place for the research. For those that consented following a telephone contact, a package was mailed out, containing a postage paid return envelope. This method of recruitment began in April 2018 and ceased in October 2018.
3. Partners of ICD patients who were not part of the first eight families identified for study invitations sometimes had chance encounters with the research team. This was often due to centralized medical services and the close-knit ARVC community in NL. During these encounters, if the partner was interested, the research project was discussed, and a study package sent by post if requested. This method of recruitment was utilized from September 2017 to October 2018.

3.4.3. INCLUSION/EXCLUSION CRITERIA

The inclusion criteria included being a partner of an ICD patient, over the age of 18 and able to complete the surveys. Of the 59 spouses, three did not reside in the province and were excluded. Seventeen of the remaining 56 were contacted by the research team through the cardiac clinic during their partner's ICD appointment. Of the remaining 39, four were deceased, contact information was not available for four, 11 did not have a connection to the research team, and a clinical decision was made not to contact another two due to concerns about causing distress, as the team were aware of major family issues at the time of this research. This left 15

partners that were contacted by phone. See Figure 4.1 for detailed flowchart of study population, recruitment and inclusion/exclusion.

3.5 Data Collection

3.5.1 Patient Engagement Meeting Qualitative

During the patient engagement meeting, a largely unstructured, fluid discussion took place. The research project was explained to the group. The group was then given the opportunity to critique the study. This conversation naturally led to the group discussing their experiences of living with ARVC in the family, and in particular, their experiences with mental health challenges and care provision. Information gathered from this meeting was used to both inform the study protocol and included in the results section of this thesis as it pertains to the impact of living with an ICD on the family unit.

3.5.2 Quantitative

Study packages were returned by participants either in person or through the mail. Retuned packages contained the completed scales. Although qualitative data was not a focus for this project, a small amount was collected from open comments on returned surveys. Although there was no prompt or question asking for additional information on the packages, some respondents chose to include their thoughts. There was not enough data via this method for a full coding analysis and creation of a framework; however, it is included in this thesis as it adds to the understanding of how families experience this disease and treatment.

From the database used to identify participants (HREB 00-176), clinical and demographic data was available for ICD patients. This data was used to explore whether partners' scores on

the questionnaires were related to disease severity in the ICD patient and the family. From the 1900+ variables in the dataset, the research team focused on nine that were thought to be the most relevant to this study. Both the literature and the clinical experience of the team suggested variables were likely to be related to the partner's mental health. They are as follows.

- Age
- Sex
- Number of Hospitalizations of Partner with ICD
- Age at which the ICD was implanted in partner
- Number of appropriate shocks experienced by partner with an ICD
- Number of inappropriate shocks experienced by partner with an ICD
- Did the partner with the ICD go on to have a heart transplant
- Did the partner with an ICD have a 1st Degree relative with either SCD/Heart Transplant/Accident(possible SCD)/Other at time of presentation
- Time from ICD implant

From the larger dataset, a smaller de-identified dataset with the above defined variables was created and used for the purposes of analysis.

3.6 Data Storage

The data collected became part of the large previously existing dataset (HREB 00-176) Physical copies of retuned surveys were filed in a locked cabinet behind a locked door in Dr. Hodgkinson's file room. Survey scores were entered digitally into the dataset which is kept on a password protected computer behind a locked door in Dr. Hodgkinson's office.

3.7 ETHICS

3.7.1 ETHICS APPROVAL

This study was approved by the HREB under Application for General Research at MUN under reference number HREB#20171983. Full board approval was granted on July 14, 2017. (Appendix 7)

3.7.2 ETHICAL CONSIDERATIONS

Ethical considerations were given to each step of this project. When this study was being planned, there were concerns that this population may be over studied. As noted, many of these families have been part of research studies since the 1980's. This disease is also life altering and families may have suffered distress and tragedy. Upon consultation with those who have worked closest with the families, it was decided that with appropriate risk mitigation, the potential benefits of this study outweighed the potential harm. Further, the patient engagement planning session revealed family members' support of a project focused on mental health in ARVC.

Strategies to mitigate risk included not contacting potential participants that were likely under duress. If the research team was aware of recent family tragedy, if the individual was at risk of self-harm, or any similar circumstance, the individual was not approached to be a part of the study. For those who were approached to participate, a clear cover letter was created that ensured individuals knew participation in the study was voluntary and would not impact their health care. Additionally, the research team identified that thinking about one's mental health, particularly in the context of this disease may be distressing. Included the study packages were mental health supports for both acute and chronic needs. Finally, the research team recognized the possibility of individuals scoring high (or in other words, the potential indicator of severe mental health symptoms) on one or more of the scales. If a participant scored within the highest

category on any of the scales, they were contacted by Dr. Hodgkinson and after consenting, were contacted by Dr. Orzylowski, a psychiatrist or, Drs. Paulin or Connors, their cardiologists, to discuss their concerns further. Guidance and referrals for mental health services were given as appropriate.

3.8 Statistical Analyses

All quantitative data were analyzed using SPSS v.25 for Mac. A significance level of $p<0.05$ was used for all statistical analyses. Participant responses on each scale were scored as per the scoring guidelines outlined under "Measures". Additionally, participants who scored within the above outlined thresholds on the scale were marked positive for that mental health outcome. This gave each participant a score and a categorization of yes or no for anxiety, depression, and PTSD.

3.8.1 Descriptive analyses

Descriptive statistics and frequencies were used to determine the demographics of respondents, survey response rates and mental health scale data.

3.8.2 Univariate Analyses

Associations between scale scores and continuous clinical and demographic data were analyzed using correlations. Continuous variables were: Age, PHQ-9 score of partner with ICD, SAS score of partner with ICD, PCL-C score of partner with ICD, number of hospitalizations of partner with ICD, age at which the partner was implanted with the ICD, number of appropriate shocks experienced by partner with ICD, number of inappropriate shocks experienced by partner with ICD, time from ICD implantation. Normality for each variable was assessed using a Shapiro-Wilk test which test. Variables were analysed using Pearson Correlation coefficient or the non – parametric Spearman correlation coefficient.

Relationships between scale scores and categorical variables were also explored. Categorical variables were sex (1=male, 2=female), Did the partner with an ICD go on to have a heart transplant (1=yes, 2=no), and did the partner with an ICD have a first degree relative with either SCD/Heart Transplant/Accident (possible SCD)/Other at time of presentation (1=yes, 2=no). Shapiro-Wilk was again used to test for normality. Normally distributed variables were analysed using a t-test and non-normal were analysed using the non-parametric equivalent, Mann-Whitney U.

3.8.3 Comparing between groups in the total study population

Differences in scale score were examined across the three groups: partners, ICD patients, and negative relatives. Normality was assessed using Shapiro-Wilk. Variables were assessed using Analysis of Variance (ANOVA) or the non-parametric equivalent Kruskall-Wallis. If a significant difference was found, a Dunn-Bonferroni post hoc test was used to determine where the significance originated.

3.8.4 Comparing Partners of ICD recipients and the General Population

Prevalence of anxiety, depression and PTSD were analysed in partners as compared to the general population. The prevalence for partners was determined from those who scored above the threshold on a scale and were considered positive for that condition. Prevalence in the general population was available from Statistics Canada and literature. To provide greater strength, the higher 'lifetime prevalence', of a condition was used rather than a 12-month prevalence. A binomial test was chosen rather than a chi squared test because some expected frequencies for all three questionnaires was less than five.

CHAPTER 4. RESULTS

4.1 PATIENT ENGAGEMENT MEETING

Two ARVC families were represented in the patient engagement session. From the first family, an ICD patient attended. From the second, two ICD patients, one assumed carrier without an ICD, one partner, and two negative siblings attended, representing a range of lived experience with ARVC. Also present were members of the research team: Dr. Holly Etchegary, Dr. Kathy Hodgkinson, Ms. Natalie Butt, and Ms. Mary Walsh.

During the patient engagement meeting, conversations covered the disease itself, diagnosis, supports (or lack thereof), family dynamics and mental health challenges associated with ARVC specifically. The ICD patient from the first family recounted feeling good about the diagnosis mainly because it explained previously unexplained deaths in the family. The family was offered a psychologist appointment at the time of diagnosis but declined. Later in the course of disease, however, the family was experiencing major mental health concerns, including suicidal ideation, but at that time did not know where to turn for support. This experience highlighted that mental health support may be required post-diagnosis.

Family two felt they were inadequately prepared for the physical and mental toll of the ICD treatment and noted they were not offered psychological support at all, unlike family one. An ICD patient from family two remarked that the only information they received was a tiny booklet and his partner (female, 50) responded, “We were trying to figure out if we should be worried, asking questions, but we just didn’t know.” An ICD patient from family two expressed that they didn’t feel the need for mental health supports at the time of diagnosis, they felt the needed more information about the disease itself and treatment. The ICD patient from family one

(female, 64) responded, “You may not need that kind of support at the beginning, but you could, later down the road. I had no idea what was coming.” The patient engagement session confirmed family members’ support of research focused on the mental health challenges associated with living with a disease like ARVC. They also supported a systematic approach to the provision of mental health care and resources.

Overall, there were a few key themes from this meeting. First was the need to address the lack of information about the disease and treatment itself provided at time of diagnosis and ICD surgery. Second was the need for mental health supports both at time of diagnosis and at follow up intervals. The third was overwhelming confirmation that ARVC and ICD treatment impacts the entire family, including partners, not just the ICD patients themselves.

4.2 STUDY POPULATION

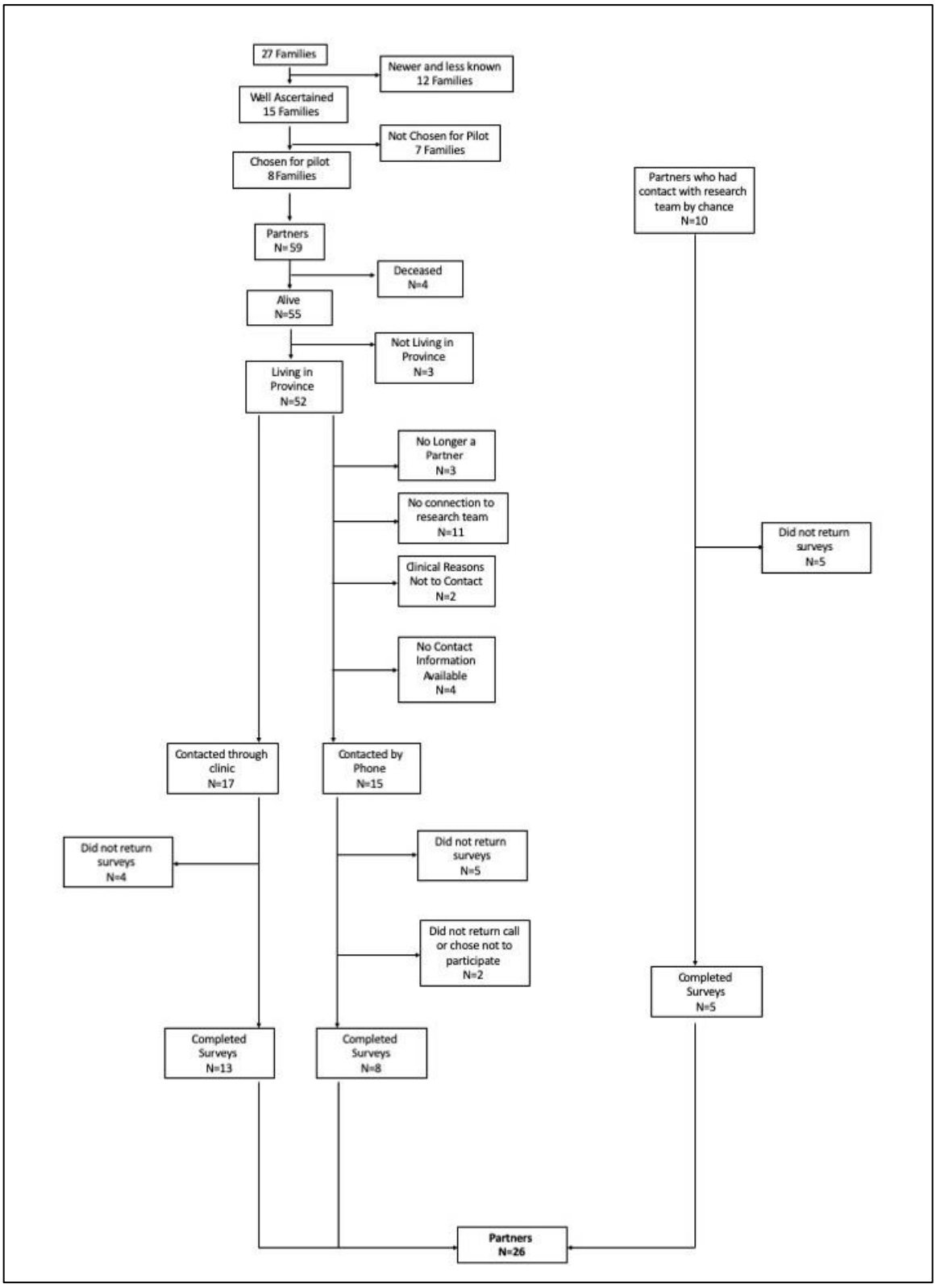

Figure 4.1 Flowchart of Participant Recruitment

For the larger study, 313 individuals were identified as potential participants: 103 ICD patients, 148 negative relatives, and 59 partners. See Figure 4.1 for a detailed recruitment flowchart of partners. See Appendix 8 for recruitment flowchart of larger project including ICD recipients and negative relatives. The focus of the current project and subsequent analyses will be the partners. Of the 59 potential participants, four were deceased and three were not living in the province, which left a possible 52. However, contact was made with some partners living outside the province. Of those living in the province, three were no longer a partner of a patient with and ICD, 11 had no connection to the research team, two were not contacted due to clinical decisions made by the research team, and contact information was not available for four. From the remaining 32, 17 were contact through the ICD clinic when they attended with their partner. Four chose not to return the surveys, which left 13 surveys completed through the clinic. The 15 who did not attend the clinics were contacted by phone; two chose not to participate or return the phone call and five requested a survey but did not return it. This left eight surveys completed by phone contact and returned by mail. The final mode of recruitment was by chance. There were ten partners from families outside of the first eight families that had contact with the research team; five of them did not return surveys, leaving five partners contacted by chance who completed the surveys. In total, 26 partners completed surveys and comprise the study sample.

4.3 Descriptive Profile of the Participant Partners of ICD recipients

Table 4.1: Participant Demographics

Age	Range	19-69
	Mean(SD)	51(13)
Gender	Males	12
	Females	14

The average age of partners was 51 years old and ranged from 19 to 69. There was an almost equal number of males (46%) and females (54%). Table 4.1 summarizes the participant demographics.

Table 4.2: Participant Response Rates by Method of Contact

Method of Contact	Number of Surveys Given	Number of Surveys Retuned	Response Rate (%)
Cardiac Clinic	17	13	76
Phone	15	9	60
By Chance	10	5	50
Total	42	26	62

Table 4.2 outlines the response rates of participants by method of contact. The best response rate was from partners seen at the clinic when attending with their partner, the ICD patients (76%), followed by those contacted through the phone and subsequently mailed a package (60%); the lowest rate was found in those contacted by chance who later received a mailed package (50%). The overall response rate for all participants was 62%.

4.4 Descriptive Profile of Questionnaire Responses

Table 4.3: Questionnaire Responses Scored

Questionnaire	N	Mean(SD)	Minimum	Maximum	Clinical Significance		Highest Category	
					Threshold	Number above threshold (%)	Threshold	Number above threshold (%)
SAS	26	40 (9.8)	25	60	45	9 (35%)	75	1(4%)
PCL-C-	26	37 (14)	17	63	36	17(65%)	44	9(35%)
PHQ-9	26	4.9 (5.3)	0	20	10	3(12%)	20	2(8%)

Table 4.3 describes the range of scores and presents the mean for each of the three mental health measures. All participants (n=26) completed all three questionnaires. The average SAS ranged from 25 to 60 with a mean of 40 (SD=9.8). The mean of the PCL-C questionnaire was 37

(SD=14), with scores ranging from 17 to 63. The scores on the PHQ-9 questionnaire ranged from zero to 20 and had a mean of 4.9 (SD=5.3). Of the study sample (n=26), the number of participants above the threshold for anxiety, PTSD, and depression were nine, 17, and three, respectively. The number of participants that scored in the highest category for anxiety, depression and PTSD were one, nine, and two, respectively.

4.5 Analyses of Questionnaire Scores, Clinical and Demographic Data

Relationships between the questionnaire scores and continuous clinical and demographic data were first explored using correlational analysis. Normally distributed variables were analysed using Pearson Correlation Coefficient and reported using *r*. These were: SAS score, PCL-C score, age, PHQ-9 score of partner, SAS score of partner, PCL-C score of partner, Age at which the ICD was implanted in partner. Variables that were non-normally distributed were analysed using the non-parametric Spearman's correlation coefficient and reported using r_S. These variables were: PHQ-9 score, number of hospitalizations of partner with ICD, number of appropriate shocks experienced by partner with an ICD, number of inappropriate shocks experienced by partner with an ICD, time from implant. Table 4.4 summarizes the correlational analysis.

Table 4.4: Correlations for Questionnaire Scores

	Scale			Missing (%)
Variable	**PHQ-9**	**PCL-C**	**SAS**	
PHQ-9 Score		$r_S(24)=0.469$, $p=0.016$*	$r_S(24)=0.632$, $p=0.001$*	0
PCL-C Score	$r_S(24)=0.469$, $p=0.016$*		$r(24)=0.546$, $p=0.004$*	0
SAS Score	$r_S(24)=0.632$, $p=0.001$*	$r(24)=0.546$, $p=0.004$*		0
Age	$r_S(24)=-0.102$, $p=0.619$	$r(24)=-0.161$, $p=0.433$	$r(24)=-0.151$, $p=0.462$	0
PHQ-9 Score of Partner with ICD	$r_S(24)=0.355$, $p=0.089$	$r(24)=0.114$, $p=0.596$	$r(24)=0.160$, $p=0.456$	2(7.8)
PCL-C Score of Partner with ICD	$r_S(24)=0.332$, $p=0.113$	$r(24)=0.593$, $p=0.002$*	$r(24)=0.374$, $p=0.071$	2(7.8)
SAS Score of Partner with ICD	$r_S(24)=0.335$, $p=0.110$	$r(24)=0.268$, $p=0.205$	$r(24)=0.086$, $p=0.689$	2(7.8)
Number of Hospitalizations of Partner with ICD	$r_S(24)=235$, $p=0.247$	$r_S(24)=0.407$, $p=0.039$*	$r_S(24)=0.189$, $p=0.356$	0
Age at which the ICD was implanted in partner	$r_S(24)=-0.085$, $p=0.681$	$r(24)=-0.272$, $p=0.179$	$r(24)=0.236$, $p=0.247$	0
Number of appropriate shocks experienced by partner with an ICD	$r_S(24)=0.518$, $p=0.011$*	$r_S(24)=0.564$, $p=0.005$*	$r_S(24)=0.366$, $p=0.086$	3(11.5)
Number of inappropriate shocks experienced by partner with an ICD	$r_S(24)=0.207$, $p=0.343$	$r_S(24)=0.179$, $p=0.413$	$r_S(24)=0130$, $p=0.555$	3(11.5)
Time from ICD implant	$r_S(24)=0.095$, $p=0.643$	$r_S(24)=0.246$, $p=0.226$	$r_S(24)=0.003$, $p=0.989$	0

*correlation is significant at the p=0.05 level (2-tailed)

The PHQ-9 score was significantly correlated with the other two scores, PCL-C score ($r_S(24)=0.469$, $p=0.016$)) and SAS score ($r_S(24)=0.632$, $p=0.001$). It was also significantly correlated with the number of appropriate shocks experienced by the partner with an ICD ($r_S(24)=0.518$, $p=0.011$).

As noted, the PCL-C score was significantly correlated with both the anxiety and depression scales. There were also significant positive correlations with the PCL-C score of the partner with an ICD ($r(24)=0.593$, $p=0.002$), number of hospitalizations of the partner with an

ICD ($r_S(24)=0.407$, $p=0.039$), and the number of appropriate shocks experienced by the partner with an ICD ($r_S(24)=0.564$, $p=0.005$).

The SAS, as noted above, had significant correlations with the PHQ-9 and PCL-C. There were no other significant correlations.

Relationships between categorical clinical and demographic data and questionnaire scores were also explored. These variables were: sex, did the partner with an ICD go on to have a heart transplant, and did the partner with an ICD have a first degree relative with SCD at time of presentation. The questionnaire scores were assessed for normality again using Shapiro-Wilk test. The PHQ-9 scores were distributed normally for all variables but sex. The PCL-C scores were distributed normally for all the variables. The SAS scores were distributed normally only for the variable, did the partner with an ICD go on to have a heart transplant. Normally distributed data was analysed using a t-test and reported using *t*. Non-normally distributed data was analysed using the non-parametric Mann-Whitney-U test and reported using the p-value.

Table 4.5: Analysis for Categorical Variables and Questionnaire Scores

	Scale			**Missing (%)**
Variable	**PHQ-9**	**PCL-C**	**SAS**	
Sex	$p=0.212$	$t(24)=-2.012$, $p=0.056$	$p=0.118$	0
Did the partner with an ICD go on to have a heart transplant	$t(24)=1.998$, $p=0.057$	$t(24)=3.497$, $p=0.002$*	$t(24)=1.681$, $p=0.106$	0
Did the partner with an ICD have a 1st Degree relative with either SCD/Heart Transplant/Accident(possible SCD)/Other at time of presentation	$t(24)=-1.871$, $p=0.074$	$t(24)=-2.029$, $p=0.54$	$p=0.390$	0

*significant at the p=0.05 level

Table 4.5 summarizes the analysis of categorical variables and questionnaire scores. There were no significant relationships with any of the categorical variables and either the PHQ-

9 or the SAS. There was a significant relationship, however, between the PCL-C and whether the partner with an ICD went on to have heart transplant.

4.6 Analyses comparing questionnaire scores among Partners, ICD Patients, and Negative Relatives

Table 4.6 summarizes the mean scores of the three questionnaires for the study groups: participants of this study, their partners with ICDs, and the partner's negative relatives.

Table 4.6: Summary of Scores for Partners, Negative Relatives, and ICD Patients

		PHQ-9	SAS	PCL-C
Partner	Mean Score (SD)	4.9 (5.3)	40 (9.7)	37 (14)
Negative relatives	Mean Score (SD)	4.6 (3.8)	37 (9.6)	27 (8.5)
ICD Patient	Mean Score (SD)	7.3 (6.4)	44 (12)	33 (13)

The three score distributions (PHQ-9, SAS, PCL-C) for each group (Partner, ICD patient, negative relative) were checked for normality using the Shapiro-Wilk test. Scores were not normally distributed, and a Kruskal-Wallis test was used to compare medians. Table 4.7 summarizes the results from the test.

Table 4.7: Summary of Kruskall-Wallis Test Between Groups for Scores

	PHQ-9	SAS	PCL-C
p-value	0.145	0.038*	0.037*

* significant at the p=0.05 level

The Krukal-Wallis test revealed no significant differences among the three groups in the PHQ-9 Scores. There were significant differences among the groups in both SAS scores and PCL-C scores. Post hoc Dunn-Bonferroni analysis in the SAS scores revealed a significant difference (p=0.038) between the ICD patients (x=44(12)) and Negative relatives (x=37(9.7)), such that ICD patients scored higher on the anxiety measure. The post hoc Dunn-Bonferroni for

the PCL-C score revealed a significant difference (p=0.035) between partners and negative relatives, such that partners of patients with an ICD scored higher on the posttraumatic stress measure.

4.7 Analyses comparing prevalence of Anxiety, Depression, and PTSD of partners and the general population.

Binomial tests were used to compare the proportion of participants who met the questionnaires' threshold for depression, anxiety, and PTSD with general population rates in Canada (Table 4.8). The proportion of the study sample meeting the threshold for clinically significant depression did not differ from general population rates. The prevalence of anxiety in partners (34.6%) was significantly (p<0.001) higher than that of the general population (8.7%). The prevalence of PTSD in partners (65.3%) was also significantly (p<0.001) higher than that of the general population (9.2%)

Table 4.8 : Summary of Binomial Test for Comparison with General Populations

	Category	N	Observed Proportion	Test Proportion	P-value
Do they meet the threshold for Depression(score≥10)	No	23	0.885	0.887	0.576
	Yes	3	0.115		
Do they meet the threshold for Anxiety (score≥45)	No	17	0.654	0.913	<0.001
	Yes	9	0.346		
Do they meet the threshold for PTSD(score≥36)	No	9	0.346	0.903	<0.001
	Yes	17	0.654		

4.8 Open-ended comments

Two respondents provided open comments about their experiences with ARVC and ICDs in the family. These correspond with scale data and help illustrate the burden of ARVC on partners.

> *"I remember prior to her being diagnosed with ARVC there would be times when she was just sitting at home watching TV and her heart would start to race 120-130 BPM and higher and she wasn't doing anything strenuous. After several bouts of this and a number of trips for her doctor and ever so many tests and it was confirmed that she does indeed have ARVC – the learning process begins. Well the first lesson is there is no cure, ok so how do you treat it? Again, google became my best friend.*" -Male, 52

This partner went on to describe several lifestyle adjustments he and his partner have made - from being aware of ambient temperature due to circulation issues, to preparing for ICD shocks:

> *"From here, there has been more adjustments and changes to [ICD patient]'s lifestyle and habits all because of ARVC, some small some not so small and it's a constant learning process of what she can and cannot do. To many of us, one of the small changes would be welcome, but with the many small ones and some large lifestyle changes it can be overwhelming and a constant challenge to live with ARVC."*

Another respondent described similar impacts:

> *"First was to explain my fear –Sword of Damocles. Constant threat of an event or change in the heart condition of my family. I push these thoughts away. Seeing the defibrillator go off numerous times and the fear and emotional stress on your partner is extremely hard. But you have to be strong for the other family members."* -Male, 69

While qualitative data was not a focus of this project, these comments help illustrate the impact on partners of living with partner with an ICD as treatment in the *TMEM43* population.

CHAPTER 5. DISCUSSION

This study is the first quantitative study of the mental health sequale in partners of patients with ICDs in the *TMEM43* p.S358L population.

The response rates for the surveys were on par with existing literature. A systematic review of the responses of surgery patients found in-person surveys yield a response rate of 76% which was the exact rate of our surveys completed in the cardiac clinic.[70] The study also found responses by mail to be 65% where our response by mail ranged from 50%-60%.

The mean score for anxiety (40) fell within the normal range (<45), while the mean score for depression (4.9) was borderline between minimal (0-4) and mild (5-9). The mean PTSD score (37) fell above the threshold determined to indicate PTSD positive (36). For each of the mental health surveys, there is subset of partners who scored above the threshold for clinically significant symptoms. For anxiety, clinically significant symptoms were found in 35% of partners which is less than the rate of 42-48% found in the literature.[41,46,50] Similarly the rate of depression (12%) was on the lower end of the rates of 14-29% from the literature. There were no studies of PTSD in partners to compare with this study's rate of 65%. Within this subset of participants scoring above the threshold for clinical significance, there was a smaller but important portion of partners that scored within the highest category for anxiety (4%), depression (8%), and PTSD (35%). This study population had lower rates of anxiety and depression than the general partners of ICD patients, which may be due to the multigenerational nature of the disease. Many of the families have been dealing with the effects for years and may have developed protective coping mechanisms. However, there is a very high rate of PTSD that indicates the mental health challenges of this population manifest as PTSD symptoms rather than anxiety and depression. When considering the lethality of the disease and the that an appropriate

shock is considered an aborted SCD, it stands to reason that witnessing an ICD patient receive a shock could be a traumatic event. These findings, despite being from a small pilot study, demonstrate the uniqueness of mental health experiences of partners in the *TMEM43* p.S358L families and highlight the necessity to fill the existing gap in the literature for this population.

There were two missing values in the three scale scores of partners with ICDs and three missing in the number of appropriate and inappropriate shocks of the partner with an ICD. The missing values for are due to two reasons. The first is not all respondent's partners chose to participate so there were two partners for whom there are no questionnaire scores. However, clinical and demographic data for these ICD patients could be extracted from the database for which they had previously given consent. The second is geographical constraints. Some ICD patients were treated outside of NL, which meant their medical histories were not readily available.

Scores for anxiety, depression, and PTSD were all positively significantly correlated with one another, which is unsurprising since all three scales measure some aspect of mental health. Thus, if a participant scored high on either score, they were likely to score high on the other two. Anxiety scores were only significantly correlated to one variable: number of appropriate shocks experienced by the ICD patient. This corresponds with the literature of partners of ICD patients with shocks having higher rates of anxiety than those who have not experienced shocks.[50] Interestingly, no significant association was found between anxiety scores and 'number of inappropriate shocks experienced by the partner with the ICD'. This may suggest that the anxiety comes from a knowledge of the appropriate shock being an aborted death, rather than the shock itself. Of the two studies from the literature that looked at sex, neither found differences in rates of depression and one found females had higher levels of anxiety.[41,44] This study found no

differences between scores of anxiety or depression when stratified according to sex. When anxiety and depression were measured at different points of time in the literature, it was generally found that symptoms of both decreased over time.[44,49,51] The current study was cross sectional and did not measure change in mental health scores over time. The variable of 'time from implant' gives some indication of how long a partner has been living with an ICD patient, but is not a true measure of an individual's mental health at two points in time. This variable was not significantly related to either anxiety, depression, or PTSD and did not indicate any change in symptoms over time as found in the literature.

Partners' PTSD scores were significantly associated with many variables and there is no literature with which to compare these novel findings. The PTSD score of partners was significantly positively related to the 'PCL-C score of partner with ICD', 'number of hospitalizations of partner with the ICD', 'number of appropriate shocks experienced by the partner with the ICD', and 'did the partner with an ICD go on to have a heart transplant'. It is likely all these variables are related and may even be confounding; however, without enough statistical power for linear regression this cannot be confirmed. Certainly, the findings appear to have face validity. When an ICD patient experiences a shock from their device, their partner may be present. With an increasing number of shocks, the likelihood that a partner will witness the event increases. Additionally, the ICD patient may lose consciousness during the event, while the partner observes. Also, with an increasing number of shocks, the disease severity is likely worse which would be related to the ICD patient needing a transplant. This is similar to the finding to the study on partners of epilepsy patients where higher levels of PTSD in the partners was associated with severity of the seizure.[9] While the study did not define severity it is likely to include loss of consciousness. This study, while small, indicates significant PTSD symptoms

within the partner population and subsequently the need for mental health interventions. With the paucity of literature currently available on partners' experiences with PTSD, further research is needed. Future studies that explore the risk factors associated with PTSD could help identify at risk individuals and inform intervention models.

In comparing the three groups from the larger study, partners, ICD patients, and negative relatives, significant differences in survey scores were found for anxiety and PTSD but not depression. Further analysis of the anxiety scores revealed the significance was due to the difference in ICD patients and negative relatives, meaning that the ICD patients had higher levels of anxiety. This is not consistent with the literature, where partners were found to have higher or equal levels of anxiety to the ICD patient.[40,41,42,44] The lethal and hereditary nature of the disease make it challenging to differentiate what effects are due to the ICD treatment and what effects are due to the disease itself. As previously discussed, the lower levels of anxiety in the partners could be due to developed coping mechanisms. However further research is necessary to determine whether these findings are artifact from the small sample size or would remain consistent in a larger study. Determining whether anxiety is an issue within this population is important to inform patient education and healthcare provision for the *TMEM43* p.S358L partners and their families.

The significance for the PTSD scores comes from the difference in scores for the partners and negative relatives. This is an interesting finding that partners are experiencing higher rates of PTSD than the ICD patients themselves. This may be because some patients lose consciousness before the shock and are therefore not remembering the actual event whereas their partner may be witnessing it. Findings point to the very real potential for partners of ICD patients to develop

PTSD and future research that confirms this finding will be critical to inform healthcare provision and policy regarding these family members.

Comparisons between the rates of mental health between partners and the general population revealed significant differences in anxiety and PTSD, but not depression. Partners' experiences of higher rate of anxiety and PTSD can likely be attributed being a part of a family living with a potentially fatal disease and everything that it encompasses. The treatment for the disease, while lifesaving, can carry physical and psychosocial burdens that are felt by the partner as well. Additionally, the disease is autosomal dominant and any biological children they and their partner conceive have a 50% chance of inheriting the disease. While this study cannot elucidate causation the findings indicate that the partners in the *TMEM43* p.S358L population have a unique mental health burden and support needs as compared to the general population.

While qualitative data was not the focus of the project, the small amount collected did correspond with the literature, as did the themes arising from the patient engagement session. The concept of ICD treatment having psychological implications for the entire family unit is found in other research.[39,40,47] In the literature, partners acknowledged feelings of anxiety, fear and guilt which were echoed by partners in this study. A topic that was not found in the literature but was noted at the patient engagement meeting and in open ended responses was the lack of information patients and their families received at the time of diagnosis and at ICD implantation. This finding is important and could help inform the creation of patient and partner-facing educational resources, as well as help clinicians provide anticipatory guidance to patients and their partners about the potential for mental health impacts and available local supports.

5.1 LIMITATIONS

This study had several limitations. First the sample size (n=26) is quite small, which limited the power for statistical analysis. However, this was a pilot study and did reveal significant mental health sequale within the *TMEM43* p.S358L population partners. Further studies with larger sample sizes can further investigate the extensive variables available in the *TMEM43* dataset. The next limitation was the dataset itself. It is not directly connected to medical records and is only updated when research projects occur. This meant that information may have been outdated and some phone numbers were no longer in service. As previously discussed, the *TMEM43* p.S358L population in NL is unique. The participants in the study all come from families affected by the same gene variant which creates a very homogenous sample that is not easily generalizable to other ARVC populations. Unfortunately, however, research using other ARVC and cardiac populations have also shown negative mental health outcomes in partners.

As most adult patients with ARVC due to a *TMEM43* p.S358L mutation receive an ICD as treatment it is difficult to differentiate the effects of the ICD and the disease itself. The finding of higher levels of PTSD symptoms being associated with appropriate shocks rather than inappropriate shocks suggests the PTSD may come from witnessing a traumatic event (aborted SCD) rather than the device function itself. Further studies to determine risk factors and elucidate the exact source of the mental health symptoms would be useful.

The cross-sectional design of this study means we cannot elucidate the partner's ICD as a cause for the findings. The measures used in this study were self-report measures, that are susceptible to respondent bias and do not equate to a physician's diagnosis of mental health conditions. Self-report measures were used because it was not feasible to have all participants

see a psychiatrist and best efforts were made to have the measures used comparable to other studies. Additionally, with any voluntary study there is the risk for respondent bias. It is possible that people with more severe mental health symptoms did not respond for fear of stigma and also possible that people with good mental health may have felt they are not impacted and did not respond. Respondent bias is likely to be present in the research teams' decision not to contact those who have suffered a recent family tragedy or were at risk of self-harm.

5.2 Conclusion

This pilot study examined the symptoms of anxiety, depression and post-traumatic stress in the partners of *TMEM43* p.S358L mutation positive individuals with ICD treatment. This was the first quantitative study of mental health symptoms in the Newfoundland ARVC population.

Findings in this study indicate that partners in this specific population have slightly lower rates of anxiety and depression than found in the literature for partners in the wider ICD treatment population. The rate of depression in partners was not significantly higher than the general population but the rate of anxiety was significantly higher. Rates of PTSD in the partners was higher than their partner with an ICD, their negative relatives and the general population. Significant associations were found between the survey scores for anxiety, depression, and PTSD. Number of appropriate shocks was also significantly associated with higher scores of depression and PTSD.

This study highlights that although the partners of the ICD recipients are not genetically burdened by the disease, their mental health is significantly affected. This suggests that partners' mental health should be considered, and appropriate supports given at the time of ICD treatment.

Future studies could explore risk factors and mental health interventions to determine the best way to support partners. Further studies of PTSD in partners of the wider ICD population would also be of interest.

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APPENDIX 1: DIAGNOSIS OF ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY/DYSPLASIA MODIFIED TASK FORCE CRITERIA

Table 1: Comparison of Original and Revised Task Force Criteria[3]

	Original Task Force Criteria	Revised Task Force Criteria
I. Global or regional dysfunction and structural alterations*		
Major		
		By 2D echo:
	• Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment	• Regional RV akinesia, dyskinesia, or aneurysm
		• *and* 1 of the following (end diastole):
		— PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2)
	• Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging)	— PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2)
	• Severe segmental dilatation of the RV	— *or* fractional area change ≤33%
		By MRI:
		• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
		• *and* 1 of the following:
		— Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female)
		— *or* RV ejection fraction ≤40%
		By RV angiography:
		• Regional RV akinesia, dyskinesia, or aneurysm
Minor		
		By 2D echo:
	• Mild global RV dilatation and/or ejection fraction reduction with normal LV	• Regional RV akinesia or dyskinesia
		• *and* 1 of the following (end diastole):
		— PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m^2)
	• Mild segmental dilatation of the RV	

[3] Reprinted from, Circulation, 121/13, Frank I. Marcus, William J. McKenna, Duane Sherrill, et al., Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia, 1533-1541, 2010, with permission from Wolters Kluwer Health, Inc.

Table 1: Continued

	Original Task Force Criteria	Revised Task Force Criteria
	• Regional RV hypokinesia	— PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m^2)
		— *or* fractional area change >33% to ≤40%
		By MRI:
		• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
		• *and* 1 of the following:
		— Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female)
		— *or* RV ejection fraction >40% to ≤45%
II. Tissue characterization of wall		
Major		
	• Fibrofatty replacement of myocardium on endomyocardial biopsy	• Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Minor		
		• Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization abnormalities		
Major		
		• Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms)
Minor		
	• Inverted T waves in right precordial leads (V_2 and V_3) (people age >12 years, in absence of right bundle-branch block)	• Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V_4, V_5, or V_6
		• Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete right bundle-branch block
IV. Depolarization/conduction abnormalities		
Major		
	• Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V_1 to V_3)	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)

	Original Task Force Criteria	Revised Task Force Criteria
Minor		
	• Late potentials (SAECG)	• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG
		• Filtered QRS duration (fQRS) ≥114 ms
		• Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms
		• Root-mean-square voltage of terminal 40 ms ≤20 μV
		• Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete right bundle-branch block
V. Arrhythmias		
Major		
		• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
Minor		
	• Left bundle-branch block-type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise)	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis
	• Frequent ventricular extrasystoles (>1000 per 24 hours) (Holter)	• >500 ventricular extrasystoles per 24 hours (Holter)
VI. Family history		
Major		
	• Familial disease confirmed at necropsy or surgery	• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria
		• ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative
		• Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation
Minor		
	• Family history of premature sudden death (<35 years of age) due to suspected ARVC/D	• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
	• Familial history (clinical diagnosis based on present criteria)	• Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative

Table 1: continued

	Original Task Force Criteria	Revised Task Force Criteria

		• ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative
PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead.		
Diagnostic terminology for original criteria: This diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups. Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories.		
*Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.		
†A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.		

APPENDIX 2: ZUNG SELF-RATING ANXIETY SCALE

Table 3: The Self-Rating Anxiety Scale(SAS)[4]

Place check mark (9) in correct column.	**A little of the time**	**Some of the time**	**Good part of the time**	**Most of the time**
1. I feel more nervous and anxious than usual.				
2. I feel afraid for no reason at all.				
3. I get upset easily or feel panicky.				
4. I feel like I'm falling apart and going to pieces.				
5. I feel that everything is all right and nothing bad will happen.				
6. My arms and legs shake and tremble.				
7. I am bothered by headaches neck and back pain.				
8. I feel weak and get tired easily.				
9. I feel calm and can sit still easily.				
10. I can feel my heart beating fast.				
11. I am bothered by dizzy spells.				
12. I have fainting spells or feel like it				
13. I can breathe in and out easily.				
14. I get feelings of numbness and tingling in my fingers & toes				
15. I am bothered by stomach aches or indigestion.				
16. I have to empty my bladder often				
17. My hands are usually dry and warm.				
18. My face gets hot and blushes				
19. I fall asleep easily and get a good night's rest.				
20. I have nightmares.				

[4] Adapted from Psychosomatics, 12/6, William W.K. Zung, A Rating Instrument for Anxiety Disorders, 371-379,1971, with permission from Elsevier

APPENDIX 3: PATIENT HEALTH QUESTIONNAIRE-9

Nine Symptom Checklist[5]

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things				
2. Feeling down, depressed, or hopeless				
3. Trouble falling or staying asleep or sleeping too much 4. Feeling tired or having little energy				
5. Poor appetite or overeating				
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down				
7. Trouble concentrating on things, such as reading the newspaper or watching television				
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual				
9. Thoughts that you would be better off dead or of hurting yourself in some way				

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

☐ Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult

[5] Adapted by permission from Springer Nature: Springer, Journal of General Internal Medicine, *The PHQ-9*, Dr. Kurt Kroenke MD et al., 2001

APPENDIX 4: PTSD CHECKLIST FOR CIVILIANS

Instruction to patient: Below is a list of problems and complaints that veterans sometimes have in response to stressful life experiences. Please read each one carefully, put an "X" in the box to indicate how much you have been bothered by that problem in the last month.[6]

Response	Not at all (1)	A little bit (2)	Moderately (3)	Quite a bit (4)	Extremely (5)
1. Repeated, disturbing memories, thoughts, or images of a stressful experience from the past?					
2. Repeated, disturbing dreams of a stressful experience from the past?					
3. Suddenly acting or feeling as if a stressful experience were happening again (as if you were reliving it)?					
4. Feeling very upset when something reminded you of a stressful experience from the past?					
5. Having physical reactions (e.g., heart pounding, trouble breathing, or sweating) when something reminded you of a stressful experience from the past?					
6. Avoid thinking about or talking about a stressful experience from the past or avoid having feelings related to it?					
7. Avoid activities or situations because they remind you of a stressful experience from the past?					
8.Trouble remembering important parts of a stressful experience from the past?					
9.Loss of interest in things that you used to enjoy?					
10. Feeling distant or cut off from other people?					
11. Feeling emotionally numb or being unable to have loving feelings for those close to you?					

[6] Weathers, Litz, Huska, & Keane, 1993, National Center for PTSD - Behavioral Science Division open source

Checklist continued

12. Feeling as if your future will somehow be cut short?					
13. Trouble falling or staying asleep?					
14. Feeling irritable or having angry outbursts?					
15. Having difficulty concentrating?					
16. Being “super alert” or watchful on guard?					
17. Feeling jumpy or easily startled?					

APPENDIX 5: COVER LETTER AND CONSENT

Date:

You are invited to take part in a research study called:

Living with a genetic form of arrhythmogenic right ventricular cardiomyopathy (ARVC) causing sudden cardiac death (SCD) in the family: anxiety, depression, and post traumatic stress disorder (PTSD) in (a) affected family members with an implantable cardioverter defibrillator (ICD), (b) unaffected siblings of those with an ICD born at a 50% risk of having the disease, but shown to be mutation negative and (c) spouses of affected family members with an ICD.

You are being invited to take part in this study as a **spouse** of a person with the p.S358L mutation in the gene known as TMEM43 causing ARVC.

We would like to know how the ARVC diagnosis in your family has affected/impacted your mental well being. We hope to find information that may improve mental health services available to families with ARVC.

We have three short questionnaires that ask you questions about how you feel.

Filling out these questionnaires is voluntary and you are free to leave out any question you do not wish to answer.

1. **You do not have to take part.**
2. **Taking part will not affect any healthcare you or your family receives.**
3. **There is no known benefit to participating in this study.**

There is a risk you may become emotionally upset by participating in this study. There is an information sheet in this package with supports you can contact if this occurs.

Once the surveys are returned they will be linked only by your identification number to the previous study. Your name will never be reported in any papers or reports prepared from the research.

The data we collect for this study will be stored for at least 5 years in Dr. Hodgkinson's office on a password protected computer behind locked doors.

Should you wish to withdraw from the study at any time please contact Dr. Hodgkinson and any data you have provided will be removed from the data set and destroyed.

Fillings out the three surveys should take approximately 15 minutes. Please return them in the postage-paid envelope provided. If you have any questions or concerns about the study or would like more information, please feel free to contact any of the following individuals:

Dr. Kathy Hodgkinson, Associate Professor, Faculty of Medicine
Phone: 709-864-6694; Email: khodgkin@mun.ca

Dr. Holly Etchegary, Assistant Professor, Faculty of Medicine
Phone: 709-864-6605; Email: holly.etchegary@med.mun.ca

Mary Walsh: M. Sc Candidate Clinical Epidemiology, Faculty of Medicine
Memorial University of Newfoundland
Email: mcw552@mun.ca

Or you can talk to someone who is not involved with the study at all, but can advise you on your rights as a participant in a research study. This person can be reached through:

Ethics Office at 709-777-6974
Email at info@hrea.ca

This study has been reviewed and given ethics approval by the Newfoundland and Labrador Health Research Ethics Board.

We thank you for taking the time to give us your thoughts and opinions.

Sincerely,

Kathy Hodgkinson, Holly Etchegary, and Mary Walsh, on behalf of the research team

APPENDIX 6: SUPPORT INFORMATION

Support Information

Useful numbers for individuals taking part in the research project.

Mental Health Crisis Line
24 hour crisis support
1-888-737-4668

CHANNEL Warm Line
Non-judgemental telephone peer support
Available 11am to 11pm
1-855-753-2560

Dr. Kathy Hodgkinson
Associate Professor, Clinical Epidemiology/Genetics
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APPENDIX 7: ETHICS APPROVAL

NEWFOUNDLAND AND LABRADOR
HREB
HEALTH RESEARCH ETHICS BOARD

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

July 14, 2017

Faculty of Medicine
Disciple of Medicine

Dear Dr. Orzylowski:

Researcher Portal File # 20171983
Reference # 2017.071

RE: "Living with a genetic form of arrhythmogenic right ventricular cardiomyopathy (ARVC) causing sudden cardiac death (SCD) in the family: anxiety, depression, and post traumatic stress disorder (PTSD) in (a) affected family members with an implantable cardioverter defibrillator (ICD), (b) unaffected siblings of those with an ICD born at a 50% risk of having the disease, but shown to be mutation negative and (c) spouses of affected family members with an ICD."

This will acknowledge receipt of your correspondence.

This correspondence has been reviewed by the Chair under the direction of the Health Research Ethics Board (HREB). ***Full board approval*** of this research study is granted for one year effective **May 11, 2017**.

This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approval from the Regional Health Authority (RHA) or other organization as appropriate. You can refer to the HREA website for further guidance on organizational approvals.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- Application, approved
- Cover letter and consent for spouses, approved
- ICD positive cover letter and consent, approved
- Negative Siblings letter and consent, approved
- Zung Self-Rating Anxiety Scale, approved
- Telephone script, approved
- Support information for patients, approved
- Initial contact telephone Script for the Negative Siblings, approved
- PTSD Checklist-Civilian Form (PCL-C), approved
- Patient Health Questionnaire – 9, approved

MARK THE DATE

This approval will lapse on May 11, 2018. It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date; you may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an Event form.

If you do not return the completed Ethics Renewal form prior to date of renewal:

- ***You will no longer have ethics approval***
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*
- *Lapse in ethics approval* ***may result in interruption or termination of funding***

You are solely responsible for providing a copy of this letter, along with your approved HREB application form; **to Research Grant and Contract Services** should your research depend on funding administered through that office.

Modifications of the protocol/consent are not permitted without prior approval from the HREB. **Implementing changes without HREB approval may result in your ethics approval being revoked, meaning your research must stop**. Request for modification to the protocol/consent must be outlined on an amendment form (available on the Researcher Portal website as an Event form) and submitted to the HREB for review.

The HREB operates according to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), the Health Research Ethics Authority Act (HREA Act) and applicable laws and regulations.

You are responsible for the ethical conduct of this research, notwithstanding the approval of the HREB.

We wish you every success with your study.

Sincerely,

Ms. Patricia Grainger (Chair, Non-Clinical Trials Health Research Ethics Board)
Dr. Joy Maddigan (Vice-Chair, Non-Clinical Trials Health Research Ethics Board)

CC: Dr. Holly Etchegary
Dr. Kathleen Hodgkinson

APPENDIX 8: FLOWCHART OF PARTICIPANT RECRUITMENT INCLUDING ICD PATIENTS, PARTNERS, AND NEGATIVE RELATIVES