Living with arrhythmogenic right ventricular cardiomyopathy caused by a p.S358L disease-causing variant in *TMEM43*: Symptoms of anxiety, depression, and post-traumatic stress in non-carrier first-degree relatives of patients with an ICD

By

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A thesis submitted to the School of Graduate Studies in partial fulfillment of the requirement for the degree of Master of Science in Medicine (Clinical Epidemiology)

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October 2020

St. John's, Newfoundland and Labrador

Abstract

This pilot study investigated the mental health impact of implantable cardioverter defibrillator (ICD) therapy on families in Newfoundland and Labrador that are affected by arrhythmogenic right ventricular cardiomyopathy caused by a p.S358L mutation in transmembrane protein 43 (*TMEM43*).

The sample for this study was individuals born at an *a priori* 50% risk of having the *TMEM43* mutation but tested negative and had a first-degree relative with an ICD. A total of 25 participants completed three psychometric scales that assessed symptoms of depression, anxiety, and post-traumatic stress disorder (PTSD).

Our sample scored significantly lower on depression, anxiety, and PTSD than ICD patients but significantly higher on anxiety than the general population. A significant relationship was observed between symptoms of anxiety and the duration of time since their relative had an ICD implanted. As the time since implant increased, anxiety significantly decreased.

These preliminary findings suggest that testing negative for the *TMEM43* mutation raises anxiety above general population norms; however, within the family context, they have fewer potential mental health sequalea. Studies of this kind can inform healthcare professionals and health system decision makers regarding the provision of mental health services to high risk individuals and their families.

General Summary

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart disease which causes sudden cardiac death due to abnormal heart rhythms caused by a p.S358L mutation in the *TMEM43* gene in Newfoundland and Labrador (NL) families. Effective treatment is an implantable cardioverter defibrillator (ICD) in the upper left chest which delivers electric shocks to restore heart rhythm. We explored the mental health impact of the ICD on family members.

Twenty-five individuals born at 50% risk of having the mutation but tested negative and had a first-degree relative with an ICD completed three surveys measuring symptoms of depression, anxiety, and post-traumatic stress disorder (PTSD).

The results showed that first-degree relatives who tested negative for the *TMEM43* mutation had more anxiety than the general population, although fewer mental health consequences than affected relatives with an ICD, and their spouses. These findings may help inform provision of mental health services to this population.

Acknowledgments

I would like to acknowledge and thank those who assisted the completion of this thesis. I am sincerely appreciative of your help:

To the families affected by arrhythmogenic right ventricular cardiomyopathy in Newfoundland and Labrador, thank you for your willingness to participate in this study, your insight, and continued support for ongoing research.

To my co-supervisors, Dr. Holly Etchegary and Dr. Kathy Hodgkinson, thank you for providing me with support, guidance, and expertise throughout the research process.

To my committee member, Dr. Daryl Pullman, and my two co-investigators, Mary Walsh and Dr. Magda Orzylowski, thank you for your valuable input throughout the study.

To Dr. Sean Connors, Dr. Fred Paulin, and the genetics nurses at the cardiac clinic in the Health Sciences Centre, thank you for aiding in participant recruitment.

To Translational and Personalized Medicine Initiative (TPMI)/NL Support, thank you for the monetary support.

To my family and partner, thank you for your unwavering support and encouragement.

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List of Abbreviations

ARVC	Arrhythmogenic right ventricular cardiomyopathy
ATP	Antitachycardia pacing
BRCA1	*BRCA1* DNA repair associated
BRCA2	*BRCA2* DNA repair associated
DCM	Dilated cardiomyopathy
HCM	Hypertrophic cardiomyopathy
HD	Huntington's Disease
ICD	Implantable cardioverter defibrillator
NL	Newfoundland and Labrador
PCL-C	PTSD Checklist for Civilians
PHQ-9	Patient Health Questionnaire-9
PTSD	Post-Traumatic Stress Disorder
SADS	Sudden Arrhythmias Death Syndrome
SAS	Zung Self-Rating Anxiety Scale
SCD	Sudden cardiac death
TMEM43	Transmembrane protein 43
VF	Ventricular fibrillation
VT	Ventricular tachycardia

CHAPTER 1

Introduction

Inherited cardiomyopathies are genetic diseases of the heart muscle. They are a major cause of heart disease and are comprised of genetically heterogeneous disorders (Watkins et al., 2011). Inherited cardiomyopathies are classified into clinical categories based on phenotype such as hypertrophic, dilated, restrictive, and arrhythmogenic right ventricular cardiomyopathy (ARVC) (Watkins et al., 2011). Each clinical category consists of multiple causative disease genes and mutations (Watkins et al., 2011). For instance, there are currently 15 disease genes reported that cause ARVC mainly due to mutations in cardiac desmosomal genes (Vimalanathan et al., 2018). These mutations impair the function of desmosomes which attach cardiomyocytes to each other (Marcus et al., 2013). This results in detachment of cardiomyocytes creating scarring in the myocardium which leads to a build-up of fatty deposits and scar tissue over time (Millar & Sharma, 2014). The ventricle wall often becomes thin making it difficult for the heart to pump blood properly, increasing the risk of arrhythmias (Millar & Sharma, 2014). Although ARVC has been called a 'disease of the desmosome', mutations in non-desmosomal genes cause ARVC as well (Vimalanathan et al., 2018). The focus of this thesis is a missense mutation (p.S358L) in a non-desmosomal gene, transmembrane protein 43 (*TMEM43*), causing ARVC. The *TMEM43* p.S358L mutation was identified by an interdisciplinary research team in Newfoundland and Labrador (NL) who discovered 15 unrelated families in NL affected by this subtype of ARVC (Merner et al., 2008).

Prior to 1996, the original term used was arrhythmogenic right ventricular dysplasia (ARVD) (Fontaine & Prost-Squarcioni, 2004). The term ARVD was coined in 1977 when six patients experienced sustained ventricular tachycardia (VT) and showed signs of heart disease that were resistant to antiarrhythmic drugs (Fontaine et al., 1977). A report of 24 cases of ARVD was the first to note a familial occurrence and revealed a clinical profile of the condition that typically included young or middle-aged males who presented with palpitations, tachycardia, or syncope (Marcus et al., 1982). Multiple studies quickly emerged suggesting a strong association between a genetic origin and ARVD (Ibsen et al., 1985; Laurent et al., 1987; Nava et al., 1985; Nava et al., 1988; Rakovec et al., 1986; Ruder et al., 1985). Further research determined that ARVC was generally inherited with an autosomal dominant mode of inheritance and characterised by fibro fatty replacement of the myocardium and VT which lead to heart failure and sudden cardiac death (SCD) (Fontaine et al., 1998). There are multiple genetic subtypes of ARVC with varying pathogenicity, penetrance, and expressivity creating a difficult diagnostic process (Hodgkinson et al., 2016; Protonarios et al., 2001). Physical symptoms range from no symptoms to chest pain, ventricular arrhythmias, biventricular heart failure, and SCD (Fontaine et al., 1998). Diagnosis can occur at any age; however, it is usually at a young age which necessitates adjusting to lifestyle changes such as avoiding competitive sports and activities, lifelong medical checkups, and living with a fear of SCD (Ingles et al., 2013).

Treatment options for ARVC focus on controlling arrhythmias by using pharmacological therapy and/or an implantable cardioverter defibrillator (ICD) or in

extreme cases, a heart transplant. Prophylactic ICD therapy is widely used for the prevention of SCD in patients with ARVC. Prophylactic ICD therapy significantly increased life expectancy by up to 30 years in males in the NL population with ARVC, caused by the *TMEM43* p.S358L mutation (Hodgkinson et al., 2016). While ICD therapy has a considerable impact on lowering mortality risk, there are significant psychological burdens to consider as it is associated with elevated anxiety scores and post-traumatic stress symptoms (Ingles et al., 2013). Although rare, ARVC patients with an ICD can experience adverse events such as inappropriate shocks, infection, and lead displacement and malfunction (Schinkel, 2013). Patients express psychological difficulties adapting to lifestyle changes and can experience a loss of control once ICD therapy is introduced (Dickerson et al., 2000). Typical daily experiences that now require additional thought include clothing choices, driving, vacation destination, and physical/sporting activities (Dickerson et al., 2000; Etchegary et al., 2017).

The psychological impacts of ICD therapy are also experienced by family members of ICD patients. Family members describe feelings of stress, anxiety, fear, anger, depression, hopelessness, and guilt (Dunbar et al., 2012). There is a lack of research in the literature pertaining to the psychological impact of ICD therapy on family members of ARVC patients. Specifically, there is a paucity of research on family members who have tested negative for the disease-causing genetic mutation. The majority of research that exists regarding the psychological impact of ICD therapy investigates patients who are living with an ICD. However, research concerning the psychological impact on non-carriers of other hereditary conditions, such as inherited

cancers and Huntington's disease, may mimic the psychological impact experienced by non-carriers of ARVC as both conditions follow an autosomal dominant pattern. This means that an individual only has to inherit the disease gene from one parent to be affected. There is qualitative evidence showing that individuals who test negative for an inherited cancer can experience survivor guilt that can exceed the relief they feel from receiving a negative test result (d'Agincourt-Canning, 2006).

Qualitative research on families affected by the *TMEM43* p.S358L mutation of ARVC showed that family members who tested negative also experienced psychological distress including fear and survivor guilt (Etchegary et al., 2017). Although this particular subtype has been extensively researched, there is no quantitative research on the psychological impact of ICD therapy (Etchegary et al., 2015; Etchegary et al., 2017; Hodgkinson et al., 2005; Hodgkinson et al., 2009; Hodgkinson et al., 2013; Hodgkinson et al., 2016; Merner et al., 2008). Based on findings from other autosomal dominant conditions and the limited qualitative research on the population affected by the *TMEM43* p.S358L subtype, it is important to explore the psychological well-being of individuals who are at an *a priori* 50% risk of inheriting this lethal subtype. The purpose of this study is to provide descriptive, quantitative data to further measure the psychological impact of ICD therapy in the NL population of patients being treated with an ICD for ARVC (*TMEM43* mutation) and their families. Psychological consequences will be assessed by measuring symptoms of anxiety, depression, and post-traumatic stress disorder (PTSD) in non-affected family members using validated scales. In particular, the Patient Health Questionnaire-9 (PHQ-9), Zung Self Rating Anxiety Scale (SAS), and

PTSD Checklist for Civilians (PCL-C). This study will raise awareness of the extent of the mental health impacts of ICD therapy not only in ICD patients, but their families as well. By definition, genetic disorders are family disorders. However, care and service provision understandably and typically are focused on the affected individuals with little attention paid to unaffected family members. Ultimately, one goal of this project is to provide preliminary data that might help to improve the mental health services available to families affected by ARVC by integrating psychiatric services within the cardiac genetics clinic to promote positive psychiatric outcomes.

Background and Rationale

A particularly lethal subtype of ARVC is caused by a missense mutation (p.S358L) in the *TMEM43* gene which changes the amino acid serine to the amino acid leucine (Christensen et al., 2011; Merner et al., 2008). This causes a fully penetrant form of ARVC, meaning the gene is expressed in all individuals who inherit the mutation for this subtype (Merner et al., 2008). The *TMEM43* p.S358L mutation was identified in 2008 when a local NL interdisciplinary research team discovered that 15 unrelated families in NL shared a disease-associated haplotype on chromosome 3 (Merner et al., 2008). These families form a founder population for the *TMEM43* p.S358L subtype of ARVC (Merner et al., 2008). In 2015, the incidence rate of ARVC in NL was estimated to be between 1/500 and 1/1000 (Etchegary et al., 2015). To date, 27 large families have been ascertained with the largest family covering 10 generations including 1,200 individuals on the expanded family tree.

This subtype of ARVC is sex-influenced and mostly affects young males. The relative risk of dying is significantly (6.8 times) higher for affected males compared to affected females (Merner et al., 2008). The median age for males to develop a disease phenotype is 32 years with full penetrance occurring by 63 years; in females, the median age to develop a disease phenotype is 44 years with full penetrance occurring by 76 years (Merner et al., 2008). What makes this form of ARVC particularly complex is the first symptom of having the disease is often SCD highlighting the importance of identifying at risk families, thereby providing effective management and early, appropriate therapy. The median age of death due to SCD is 40 years in untreated males and 67 years in untreated females (Hodgkinson et al., 2013). The youngest event of SCD in the *TMEM43* p.S358L population was a 19-year-old male (Hodgkinson et al., 2016). The magnitude of SCD and the absence of early symptomatology necessitated a focus on identifying families at risk in the province and their clinical management.

ICD Therapy

An ICD is a device that is placed in the upper left chest to monitor heart rhythm. If a sustained ventricular arrhythmia is detected, the ICD discharges an electrical shock to abort VT/ventricular fibrillation (VF) (Gregoratos et al., 2002). This returns the heart back to sinus rhythm. If the abnormal heart rhythm detected is a life-threatening arrhythmia, the ICD discharge would be considered an appropriate shock. However, there are instances where patients receive inappropriate shocks which means the ICD misinterprets a non-life-threatening heart rhythm as life-threatening and discharges an unnecessary electrical shock (Borne et al., 2013).

The first ICD was implanted in a human in 1980 (Mirowski et al., 1980). The ICDs were large, heavy, and placed in the abdomen (van Welsenes et al., 2010). Implantation of the ICD required open heart surgery due to the lead system where two electrode leads passed from the heart through the diaphragm and into the pulse generator located in the abdomen (Mirowski et al., 1980; van Welsenes et al., 2010). The device was designed to solely detect and terminate VF; however, it was unable to detect unstable VTs which could degenerate into VF (van Welsenes et al., 2010). In addition, a separate pacemaker was required for bradycardia pacing as the ICD was not programmable (Cannom & Prystowsky, 2004). ICD therapy was not widely accepted and the procedure was associated with a high rate of complications (van Welsenes et al., 2010). Second-generation devices introduced transvenous leads in 1988 which eliminated open heart surgery for ICD implantation (Cannom & Prystowsky, 2004). This device had bradycardia pacing which meant a separate pacemaker was not needed (Cannom & Prystowsky, 2004; van Welsenes et al., 2010). Third-generation devices introduced antitachycardia pacing (ATP) in the early 1990s (Cannom & Prystowsky, 2004; van Welsenes et al., 2010). The benefit of ATP is it reduces painful shocks by providing low energy pulses to terminate VT as opposed to a high energy shock (Bardy et al., 1992; Leitch et al., 1991).

ICD therapy was relatively new in the early 1990s with limited scientific data on ICD use as therapy for VT (Breithardt et al., 1994). Additional treatment modalities included antiarrhythmic drugs and cardiac ablation (Breithardt et al., 1994). Antiarrhythmic drugs were shown to have minimal effectiveness when compared to

placebo (Echt et al., 1991). Randomized control trials showed that ICD therapy is superior to antiarrhythmic drugs for increasing survival (Buxton et al., 1999; Connolly et al., 2000; Echt et al., 1991; Moss et al., 1996; The Antiarrhythmics Versus Implantable Defibrillators Investigators, 1997). ICD therapy significantly reduced overall mortality whereas, antiarrhythmic drugs had no observable effect on survival benefit (Moss et al., 1996). As a result, ICD therapy was considered the treatment of choice for VT (Gregoratos et al., 2002).

SCD in patients with ARVC is often due to tachyarrhythmias; however, there was limited research regarding the effectiveness of ICD therapy for patients with ARVC (Link et al., 1997; Peters & Reil, 1995). Therefore, studies retrospectively explored the efficacy of utilizing an ICD as treatment for ARVC (Corrado et al., 2003; Link et al., 1997; Roguin et al., 2004; Tavernier et al., 2001; Wichter et al., 2004). These studies concluded that ICD therapy is feasible, safe, and well tolerated in patients with ARVC (Link et al., 1997; Roguin et al., 2004; Tavernier et al., 2001). Results showed that ICD therapy effectively terminates life-threatening arrhythmias and suggests an improvement in long-term prognosis (Corrado et al., 2003; Wichter et al., 2004).

Mortality after ICD implantation was assessed in the NL population for high-risk patients from 11 families affected by the *TMEM43* p.S358L mutation of ARVC (Hodgkinson et al., 2005). ICD therapy demonstrated a significant increase in survival among males when compared to a control group matched for high-risk status, age, sex, and family (Hodgkinson et al., 2005). The five-year mortality rate for males after ICD implantation was significantly different than the control group (0% compared to 28%)

showing significantly reduced mortality in high-risk males with an ICD (Hodgkinson et al., 2005). A follow-up study emphasized the long-term effectiveness of ICD therapy among the population with this subtype (Hodgkinson et al., 2016). A substantial and significant survival benefit was shown among men and a smaller, yet significant, benefit among females for both primary and secondary prophylaxis (Hodgkinson et al., 2016). The importance of this study is it showed the ICD was successful for primary prophylaxis among this population despite an International Task Force guideline for the treatment of ARVC that did not recommend ICD implantation for primary prophylaxis (Corrado et al., 2015; Hodgkinson et al., 2016). According to these guidelines, patients in the NL population would not have met the criteria to receive an ICD. ICD therapy is currently the only effective treatment for preventing SCD in patients who test positive for the *TMEM43* p.S358L mutation. Early implementation of ICD therapy is important and can be lifesaving prior to clinical evidence of the presence of the disease (Hodgkinson et al., 2016).

Psychological Impact of ICD Therapy

Patients describe ICD shocks as an 'earthquake', 'being hit by a truck', and being 'kicked by a mule' (Ahmad et al., 1998). These discharges have the force to throw individuals off their feet unless the arrhythmia has already rendered them unconscious. Inappropriate shocks are painful, psychologically distressing, and potentially arrhythmogenic (van Rees et al., 2011). Although adverse events such as inappropriate discharges, infection, and repeated procedures are rare, the psychological ramifications of

ICD therapy should be acknowledged when considering this treatment (Hodgkinson et al., 2016; James et al., 2012; Schinkel et al., 2013).

There is minimal research focused on mental health impacts in families affected by inherited cardiomyopathies. What does exist has largely explored psychological burdens experienced by mutation carriers. In addition, there is no quantitative research regarding the psychological impact of ICD therapy for families affected by the *TMEM43* p.S358L mutation. Despite the survival benefit associated with ICD therapy, recent qualitative evidence from a NL population has shown these families experience psychological burdens. Empirical evidence of significant mental health impacts was revealed through interviews with patients and their families recounting stressful events related to living with ARVC and ICD therapy (Etchegary et al., 2015). This demonstrated the need for further research regarding the psychological well-being of these families and, in particular, the need to consider non-affected family members. Local qualitative research, in conjunction with clinical observations and conversations with families, subsequently led to this quantitative, pilot exploration of the mental health impacts of living with the *TMEM43* p.S358L subtype of ARVC.

Purpose and Objectives

This project is part of a larger, three-arm study with an overall purpose of measuring the psychological impact of ICD therapy on patients affected by ARVC and their family members. The goal of this arm of the study is to describe symptoms of anxiety, depression, and PTSD in unaffected first-degree relatives of patients with an ICD who were born at an *a priori* 50% risk of having the disease but tested negative. Other

arms of the study will focus on mutation carriers with an ICD and their unaffected spouses. It is hypothesized that unaffected first-degree relatives will score higher than the general population and lower than ICD patients and spouses of ICD patients on scales that assess symptoms of depression, anxiety, and PTSD.

The objectives of the current study are to:

1. Determine the prevalence of anxiety, depression, and post-traumatic stress symptoms in unaffected first-degree relatives of ICD patients
2. Determine whether the severity of the psychiatric symptoms correlates with the severity of disease (as measured by the type and number of discharges from the ICD and other cardiac morbidities in these individuals' first-degree relatives who tested positive and have an ICD). This information is collected and maintained in the large dataset under the cardiomyopathy project HREB 00-176
3. Compare the prevalence of psychiatric symptoms in different family groups (ICD patients, unaffected first-degree relatives, and spouses of ICD patients)
4. Compare the prevalence of psychiatric symptoms with the general population levels
5. Ultimately, obtain data which could inform the provision and type of health care in this patient cohort regarding their mental health

CHAPTER 2

Review of Literature

The purpose of this literature review is to explore the current research regarding the psychological impact of ICD therapy for hereditary cardiac conditions. The focus of this chapter is to examine the psychological impact of ICD therapy on non-carriers of ARVC. The first section explores the decision to participate in genetic testing and the psychological impact of ICD therapy on ICD patients and family members. Specifically, family members that are non-carriers of the inherited disease. Due to the lack of research pertaining to the psychological impact of ICD therapy on non-carriers of hereditary cardiac conditions, the second section examines the psychological burden of non-carriers in the autosomal dominant diseases Huntington's disease (HD) and *BRCA1* or *BRCA2* DNA repair associated (*BRCA1*/*BRCA2*). The third section discusses the limited research available regarding the psychological impact of unaffected first-degree relatives of patients with an ICD as therapy for the *TMEM43* mutation of ARVC.

Genetic Testing

A sample of individuals in NL who had genetic testing for ARVC and their spouses participated in a qualitative study regarding the decision to get tested (Manuel & Brunger, 2014). The results showed the decision was influenced by availability and relevant predictive genetic testing, numerous deaths within the family, physical signs and symptoms of disease, gender, sense of relational responsibility or moral obligation to other family members, and family support (Manuel & Brunger et al., 2014). Another qualitative study regarding genetic testing decisions among 15 families affected by

ARVC in NL revealed the majority of participants described genetic testing as a genetic responsibility to rule out risk for other family members (Etchegary et al., 2015). Two unaffected females provided their views on the decision to participate in genetic testing:

> *"And what really bothers me is that I have relatives and I find myself saying to them, 'have you had your testing done?' And they're, 'no I don't want to know.' And I think, 'you have two teenage boys. What is your problem?'" (Etchegary et al. 2015).*
>
> *"With regards to myself, I didn't care whether or not I had the gene . . . My concern was for my children, just to make sure they were healthy and they weren't going to have to deal with something further down the road" (Etchegary et al., 2015).*

Psychological Impact of ICD Therapy

ICD Patients

There is a large body of literature regarding the psychological impact of ICD therapy. Multiple reviews have shown considerable evidence of psychological distress among ICD patients (Sears et al., 2002; Thomas et al., 2001; Thomas et al., 2006). Anxiety and depression are common psychological ramifications experienced by cardiac patients with an ICD (Dunbar et al., 2012; Thomas et al., 2006). A systematic review concluded that self-reported rates of anxiety and depressive disorders were present in 8 to 63% and 5 to 41% of ICD patients, respectively (Magyar-Russell et al., 2011). Anxiety prior to ICD implantation and ICD concerns predicted PTSD at six months post ICD

implantation (Versteeg et al., 2011). Another study indicated that 13% of ICD patients reported symptoms of PTSD one year after ICD implantation (Kapa et al., 2010).

Research shows that anticipating or receiving ICD shocks contributed to psychological consequences such as anxiety, depression, PTSD, and a decrease in quality of life (James et al., 2012; Thomas et al., 2006; Von Kanel et al., 2011). A review reported that patients who received ICD shocks experienced more symptoms of anxiety and depression and had a poorer quality of life than patients who did not receive ICD shocks (Thomas et al., 2006). In addition, experiencing at least five ICD shocks was associated with increased post-traumatic stress at a five-and-a-half-year follow-up (Von Kanel et al., 2011).

The limited research on the psychosocial implications of ICD therapy among the population in NL affected by the *TMEM43* p.S358L mutation focuses largely on carriers and has revealed the complexity of adjusting to risk, carrier status, and living with an ICD (Manuel & Brunger, 2014, 2015, 2016). Participants experienced anxiety pre and post-ICD shock and associated a shock as an indicator of being at an increased risk of death (Manuel & Brunger, 2016). Attempting to predict when an ICD shock will occur, the anticipation of a shock, and modifications to their lifestyle to try to prevent a shock from occurring contributed to psychological stress (Manuel & Brunger, 2016).

Family Members

Research regarding the psychological impact of ICD therapy focuses on ICD patients and their spouses. The limited research that exists regarding family members suggests that psychological distress of ICD therapy occurs within a family context

(Dunbar et al., 2012). A comprehensive review indicated that family members of ICD patients express feelings of overprotectiveness, stress, anxiety, fear, depression, and guilt after ICD implantation or a cardiac event (Dunbar et al., 2012). The uncertainty of ICD shocks, appropriate or inappropriate, and a lack of control over the occurrence without a warning created a level of helplessness among family members (Eckert & Jones, 2002).

The majority of the literature utilizes the term 'family member' to group parents, siblings, and children together when describing the impact ICD implantation has on these individuals. This makes it difficult to differentiate whether one relation is impacted more than another. There is a gap in the literature specifically focusing on the psychological impact of hereditary cardiac conditions on unaffected relatives who are born at an *a priori* 50% risk of having the disease. These individuals are in a unique position as they feel relief of testing negative while having siblings, sometimes many, who test positive.

Psychological Impact on Non-Carriers of Autosomal Dominant Diseases

Survivor Guilt

Living within a family affected by an autosomal dominant disease causes various levels of distress (Gargiulo et al., 2009). Being identified as a non-carrier showed a failure to experience relief, emotional numbness, and difficulty in coping with effects of test results on the family as a whole (Huggins et al., 1992; Tibben et al., 1992). A common psychological burden shown among non-carriers of HD and *BRCA1/2* is survivor guilt (Gargiulo et al., 2009; Hayden & Bombard, 2005; Huggins et al., 1992; Lynch et al., 1997; McAllister et al., 2007; Sobel & Cowan 2003; Tibben et al., 1992; Wagner et al., 2000; Williams et al., 2000; Winnberg, 2018). In other words, the burden

of being healthy and feeling guilty about celebrating a negative result while some family members test positive (Crozier et al., 2015).

It is suggested that siblings who test negative for cardiomyopathies may experience survivor guilt (Aatre & Day, 2011). As previously noted, it is possible that psychological burdens experienced by non-carriers of HD and inherited cancer mutations are comparable to non-carriers of the *TMEM43* p.S358L mutation of ARVC as they are all inherited by an autosomal dominant mode of inheritance. This comparison is relevant to this thesis due to the lack of research on the psychological impact of non-carriers of cardiomyopathies.

Non-carriers of HD expressed feeling ashamed to be the lucky sibling to receive a negative result (Winnberg et al., 2018). Feeling guilty for escaping HD may result in heightened care for affected family members, hindering the development of their personality and talent, or sacrificing pleasure and happiness (Evers-Kiebooms & Decruyenaere, 1998). Adverse impacts such as strained relationships, sadness, or clinical depression resulted from feelings of guilt toward the affected sibling (Winnberg et al., 2018).

An increase in overall depression scores for non-carriers of *BRCA1/2* from baseline to six weeks after receiving a negative mutation result was suggested to be a reflection of survivor guilt (Wagner et al., 2000). A non-carrier described that the relief of receiving a negative mutation result was overshadowed by family members testing positive (d'Agincourt-Canning et al., 2006). Another non-carrier explained that feelings of guilt

were due to escaping the disease for which other family members tested positive (Lynch et al., 1997).

Anxiety and Depression

A review reported that 10-20% of non-carriers of HD experienced psychological burdens after genetic test results (Duisterhof et al., 2001). However, multiple studies have shown a decrease in depression at one week and up to 5 years after genetic testing (Almqvist et al., 2003; Broadstock et al., 2000; Decruyenaere et al., 1996; Decruyenaere et al., 2003; Huggins et al., 1992; Tibben et al., 1997; Wiggins et al., 1992). A review reported that non-carriers experienced the most distress at six months post-test results (Duisterhof et al., 2001). Within one year, they appeared to be less distressed than they were prior to the test (Duisterhof et al., 2001). A longitudinal study showed that mean distress scores for non-carriers were within normal range five years after receiving a negative test result (Decruyenaere et al., 2003).

Studies have shown that individuals who receive a negative *BRCA1/2* test result have decreased depression and anxiety (Croyle et al., 1997; Lerman et al., 1996)
A statistically significant decrease was reported in anxiety, 7-10 days, and in depression, four months, after receiving a negative test result (Meiser et al., 2002). One study found there was no difference in symptoms of anxiety and depression from pre to post-test (Schwartz et al., 2002). However, a five-year follow-up study reported that non-carriers showed a significant increase in anxiety and depression from one to five years after receiving the genetic test result (van Oostrom et al., 2003). Another study reported that non-carriers who had a sister who is a mutation carrier had higher levels of post-test

depression than non-carriers who did not have a mutation positive sister (Lodder et al., 2001).

Psychological Impact of Unaffected ARVC Family Members in NL

A qualitative study provided preliminary evidence of the psychological impact of being in a family affected by ARVC and testing negative (Etchegary et al., 2017). Interviews with unaffected family members born at an *a priori* 50% risk of having the *TMEM43* p.S358L mutation of ARVC exposed psychological burdens despite receiving a negative result (Etchegary et al., 2017). Various negative emotions such as fear, anxiety, lingering doubts, and survivor guilt were reported by unaffected family members (Etchegary et al., 2015; Etchegary et al., 2017). An unaffected male revealed that receiving a negative result did not eliminate stress due to having family members living with an ICD and family members who were not yet tested (Etchegary et al., 2017). Survivor guilt was described by two unaffected females who expressed feeling guilty and unhappy for receiving a second chance when their sibling did not (Etchegary et al., 2017). An unaffected male stated it affected every part of his life and described feeling ongoing anxiety even after receiving a negative test result (Etchegary et al., 2015). Experiencing a family member receiving an ICD shock was recounted by an unaffected female:

> *"I was in the next bedroom and I hear the big bang, your body just flies. Here was Dad on the floor and Mom on the other side of the floor. The two of them popped out of the bed. You know, I witnessed a lot of scary things at an early age."* (Etchegary et al., 2017).

Ultimately, the survival benefit of ICD therapy was understood by ICD patients, spouses of ICD patients, and unaffected first-degree relatives (Etchegary et al., 2017). An unaffected female conveyed her gratitude for ICD therapy:

> *"The research has done so much . . . it has given people an opportunity . . . it has saved two of my relatives at least twice."* (Etchegary et al., 2017).

Discussion of Literature

The quantitative studies discussed in the literature review used validated scales to measure outcomes such as distress, anxiety, depression, or PTSD. Qualitative research designs used semi-structured and structured interviews which revealed psychological distress such as fear and survivor guilt among unaffected-first degree relatives. There is minimal research in the literature regarding the psychological impact on non-carriers of cardiomyopathies, particularly those affected by the *TMEM43* p.S358L subtype of ARVC. The studies that do exist focus on patients who test positive for cardiomyopathies such as hypertrophic cardiomyopathy (HCM). It is important to note that family members are affected by cardiomyopathies as well. There is a gap in the literature pertaining to the psychological well-being of individuals who are born at an *a priori* 50% risk of having ARVC but test negative. In terms of the *TMEM43* p.S358L mutation of ARVC, the qualitative evidence showed that individuals who tested negative experienced psychological burdens (Etchegary et al., 2017). However, it is not known how prevalent the problem is and research with a larger sample of unaffected family members would be useful. The initial qualitative research revealed the necessity of obtaining quantitative

evidence regarding the psychological well-being of individuals who tested negative for the lethal *TMEM43* p.S358L subtype of ARVC.

CHAPTER 3

Methodology

This retrospective cohort study is part of a previous long-standing project (HREB 00-176) regarding SCD in families affected by the *TMEM43* p.S358L mutation of ARVC in NL. This pilot study builds on recent qualitative research conducted by Etchegary et al. (2017) which raised awareness of the psychological burdens experienced by affected families. There are three separate, yet interrelated, arms of the current study led by three Masters students. The aim was to identify mental health outcomes in carriers of the disease-causing mutation with an ICD, unaffected first-degree relatives of patients with an ICD who are at an *a priori* 50% risk of having the mutation, and spouses of carriers with an ICD. This particular arm of the study focused on the mental health impact of ARVC in unaffected first-degree relatives of patients with an ICD who, at birth, have a 50% risk of carrying the mutation (HREB 2017.071).

Patient-Oriented Research

The project was informed by patient-identified priorities for research on ARVC in NL. Patients agreed to join the interdisciplinary team as patient partners to explore the mental health impacts of ARVC on affected families. A patient engagement lunch was held in September 2017 to ensure the research was relevant to them and their priorities were met in hopes of improving mental health outcomes in families affected by ARVC. During the engagement lunch, a summary of the proposed research was presented and patient partners were asked to comment on the key aims and objectives of the study as well as the instruments used. Seven patients and family members (from two different

families) reviewed the scales to determine whether the questions were accurate or if there were any questions they felt were missing. They collectively agreed the questions were suitable and that investigating mental health surrounding ARVC was important. They provided insight to their perspective and unique experiences in living with an ICD and living with family members who have an ICD, the access or opportunities available to them in terms of psychiatric care, and if required, ways to improve these services and quality of care. This provided the research team with a different perspective and allowed patients and their families to feel they had contributed.

Population and Sample

The population of interest to this study was families affected by the *TMEM43* p.S358L mutation of ARVC in NL. There are currently 27 affected families who have been genetically tested and followed by the clinical cardiac genetic team in NL. The three sample cohorts of this study were ICD patients (n=53), unaffected first-degree relatives of ICD patients (n=25), and spouses of ICD patients (n=26). The sample for this arm of the study was unaffected first-degree relatives of patients with an ICD (n=25). Individuals were eligible to participate if they were born at an *a priori* 50% risk of having the disease but tested negative and were a first-degree relative (i.e., sibling/child) of an affected patient with an ICD. Detailed clinical and family history information is maintained for families who participated in the long-standing ARVC program of research. Those who were tested during the original cardiomyopathy research are part of the pre-existing, de-identified dataset as they were patients before receiving a negative genetic result. A negative genetic result means they are discharged from follow-up at the cardiac

genetic clinic and from being treated with an ICD. An example of a pedigree of an ARVC family in NL with ICD patients, spouses, and unaffected siblings is shown in Figure 1. This pedigree was created by Dr. Kathy Hodgkinson and is used with her permission. It has not been published elsewhere. In pedigree diagrams, a female is represented by a circle and a male is represented by a square. Line I of the sample pedigree in Figure 1 shows two spouses, an affected male and unaffected female who are deceased. Their seven deceased children (four females and three males) are shown in line II. Of the seven children, one male was affected with an unaffected female spouse. Their children are shown in line III.

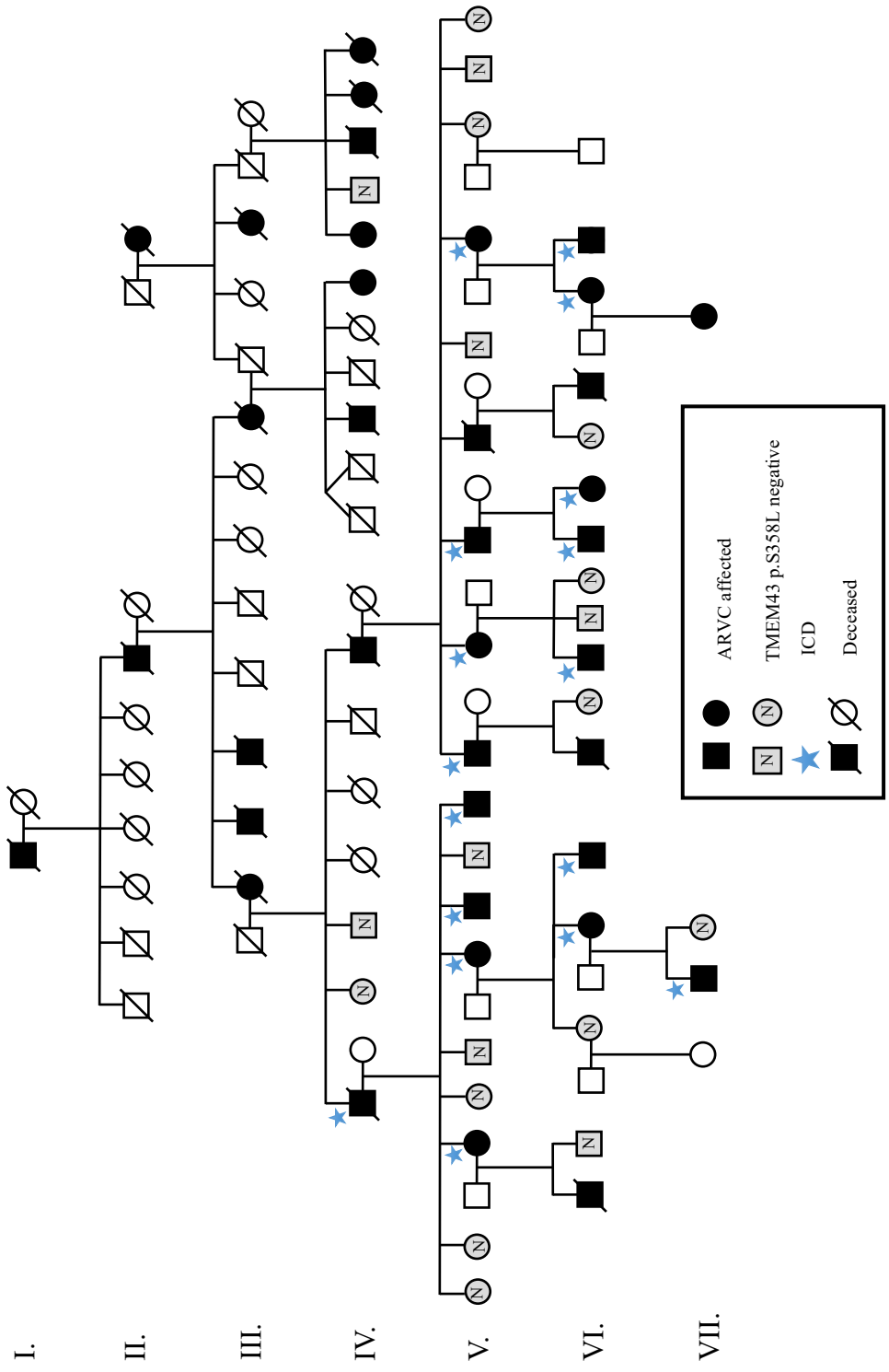

Figure 1: Pedigree of a family affected by the *TMEM43* p.S358L subtype of ARVC

Recruitment was limited to the finite number of individuals who were born at an *a priori* 50% risk of having the *TMEM43* p.S358L mutation but tested negative. They also had to have a first-degree relative who tested positive for *TMEM43* p.S358L mutation and is being treated with an ICD. The unaffected first-degree relatives are no longer patients and do not follow up at the cardiac clinic; therefore, these individuals had to be contacted by telephone. The first eight families that were discovered to be affected by this mutation were included in this study. The first eight families were chosen as the group of interest as they are not coping with a new diagnosis and have been known to the research team longer than more recently diagnosed families. They have participated in previous research and were thought to be a good sample for this preliminary research regarding psychological burdens of ICD therapy.

The total number of individuals potentially eligible for participation from the first eight families diagnosed with ARVC was 148. There were 69 unaffected first-degree relatives contacted after exclusions were made. The reasons for these exclusions can be found in Figure 2. Twenty-seven of the 69 individuals were excluded due to reasons such as telephone number not in service, no answer after repeated contact attempts, and wrong telephone number. Since these individuals are no longer patients, their telephone numbers are not updated. Thirty-four participants received a mail out package, nine participants were provided the scales by hand, and two participants received the scales through the ICD clinic. Three of the nine participants who were hand given the scales were not part of the first eight families. These participants attended the International Sudden Arrhythmias Death Syndrome (SADS) Conference in Toronto, Ontario in

September 2017 and were given the scales by chance. We ended with a total of 25 participants, giving a response rate of 55.5% (25/45).

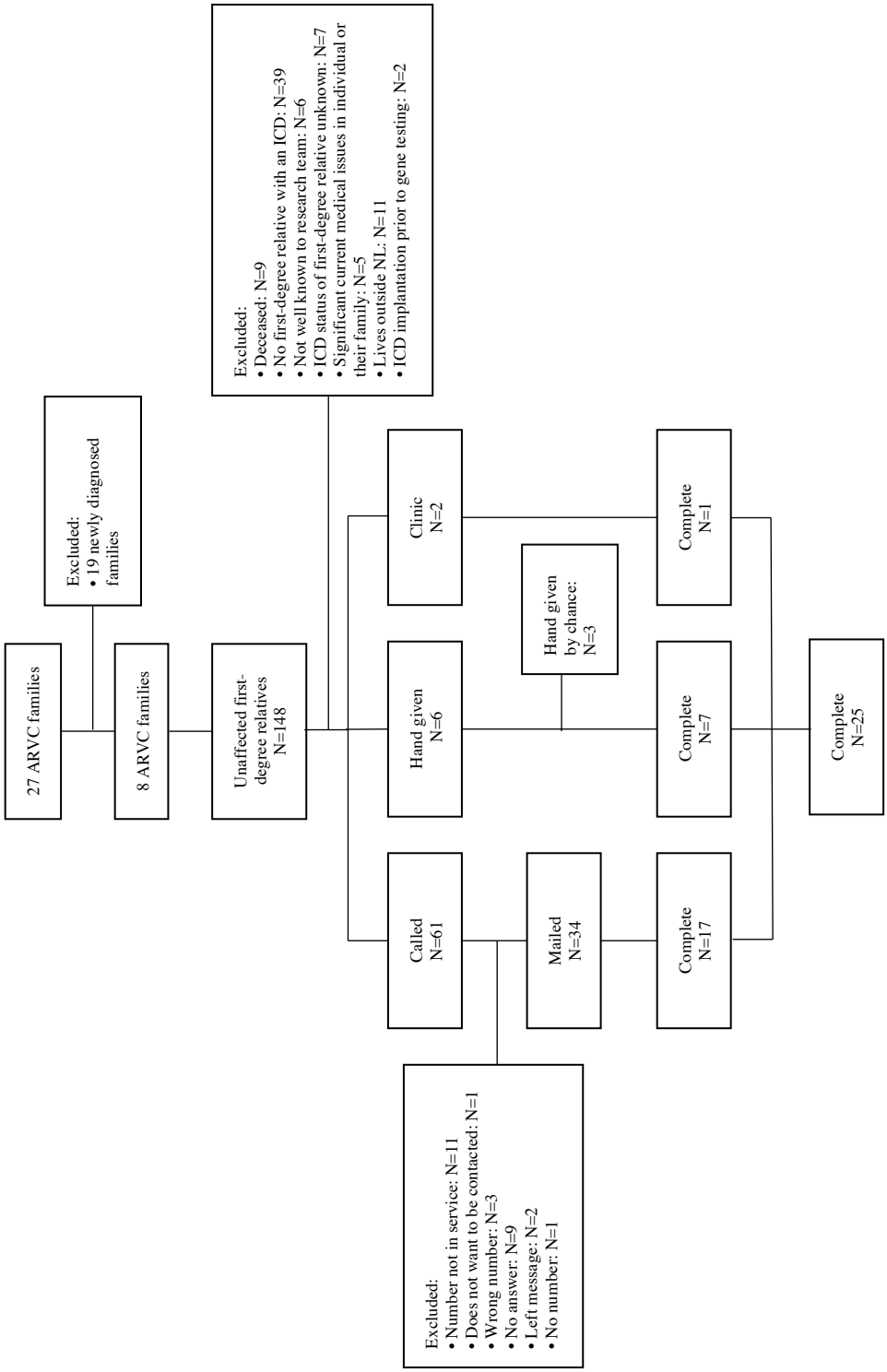

Figure 2: Recruitment Flow Chart

Procedure

The unaffected first-degree relatives were contacted by Dr. Hodgkinson by telephone using a telephone script (see Appendix B). Unaffected first-degree relatives that were part of the long-standing cardiomyopathy research project have a relationship with Dr. Hodgkinson due to prior clinical contact. The telephone call consisted of a brief description of the project followed by asking permission to receive a mail out package. Each package consisted of a cover letter that described the study, a support information sheet with contact information of professionals if support was needed, and three psychometric scales. It was explained that three short, validated scales were chosen to assess symptoms of anxiety, depression, and post-traumatic stress, taking a total of 10-15 minutes to complete. If permission was granted, Dr. Hodgkinson asked for their mailing address to ensure the most up to date address was used. Individuals were notified that email addresses of three members of the research team and telephone numbers for help lines were provided in the package if participants had questions or concerns. Data collection commenced in September 2017; however, mail out scales were completed between June 2018 and October 2018. Reminder mail outs were not sent to participants.

The main form of data collection was through mail out due to the nature of the questions included in the three scales. Individuals may find it difficult being asked personal questions regarding their mental health over the telephone which could have resulted in altered responses or no response. In addition, some individuals may find it easier having a physical copy of the scales when answering the questions. However, participants were able to fill out the scales by telephone during the initial phone call with

Dr. Hodgkinson if they preferred this method. Other forms of recruitment occurred through the cardiac genetic clinic at the Health Sciences Centre, the patient engagement lunch, and at the SADS conference in September 2017. Seventeen participants who were contacted by telephone returned their completed scales through mail. Two unaffected first-degree relatives were recruited at the cardiac genetic clinic when their affected relative attended their bi-annual ICD check-up. The scale package was sent home with the affected patient with an envelope and paid postage stamp; one of these scales was returned. Participants were hand given the scales through the patient engagement lunch and the SADS conference. Three participants were recruited at the patient engagement lunch, one participant was hand given the scales by Dr. Hodgkinson, and three participants completed the scales at the SADS conference by chance. The participants at the SADS conference were approached by Dr. Hodgkinson at the conference who obtained permission for two of the co-PIs (the author and one other student who were at the conference) to provide them with more information regarding the research project. Figure 2 provides a detailed sequence of the recruitment process.

Psychometric Scales

The three scales measure depression, anxiety, and post-traumatic stress symptoms on a self-report basis. The scales were chosen primarily because they were (a) validated, (b) accessible, (c) short, and (d) had free access. An advantage of the scales is the brevity and subsequently limited time required for completion. In addition, the scoring is not complex, meaning no special training is required to administer or score the scale. If a participant scored higher than the cut off suggested on all three scales, Dr. Orzylowski

(co-PI and Psychiatry Resident) was contacted who then contacted the participant (with the permission of the participant).

Patient Health Questionnaire-9

The PHQ-9 is a self-administered measure to screen for depression severity and is not used as a diagnostic tool (Kroenke et al., 2001). The scale has excellent reliability, test-retest reliability, and validity (Kroenke et al., 2010). It consists of nine items which are derived from the full PHQ and is half the length of most scales that measure depression (Kroenke et al., 2001). Specific items include 'little interest or pleasure in doing things' and 'feeling bad about yourself, or that you are a failure, or have let yourself of your family down'. Responses to each item indicate how the individual has felt over the last two weeks. The severity measure ranges from 0-27 with each individual item ranging from 0 (not at all) to 3 (nearly every day). An additional question at the end of the scale acts as a functional health assessment which asks, '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?'. Scoring thresholds of 0-4, 5-9, 10-14, 15-19, and 20-27 represent normal range, minimal depressive symptoms, major depression (mild severity), major depression (moderate severity), and major depression (severe severity) that may necessitate treatment with antidepressants and psychotherapy, respectively (Kroenke et al., 2001). Major depressive disorder is suggested if five of the nine responses are 'more than half of the days' which is a minimum score of 10 (Kroenke et al., 2001).

The Zung Self Rating Anxiety Scale

The SAS is a self-report screening tool used to assess the presence and severity of anxiety symptoms and is not used as a diagnostic tool (Zung, 1971). It is a 20-item scale that is based on affective and somatic symptoms (Zung, 1971). The scale has been shown to have good reliability, validity, and consistency (Dunstan et al., 2017; Zung, 1971). Responses to each item indicate how the individual has felt during the past week. Fifteen items reflect a negative experience such as 'I feel more nervous and anxious than usual' and 'I feel like I'm falling apart and going to pieces'. Five items reflect a positive experience such as 'I feel that everything is alright and nothing bad will happen' and 'I can breathe in and out easily'. The items are worded symptomatically positive and negative, meaning individuals are less likely to detect a trend in the answers (Zung, 1971). Response options for each item consist of none or a little of the time, some of the time, good part of the time, or most or all of the time. The raw total score ranges from 20-80 which is then converted to the anxiety index (Zung, 1971). The clinical interpretation of the anxiety index is within normal range for a score below 45, mild to moderate anxiety for a score of 45-59, moderate to severe anxiety for a score of 60-74, and severe anxiety for a score of 75 and greater (Dunstan & Scott, 2018). The recommended cut-off score to indicate the presence of anxiety is an indexed score of 45 (Dunstan & Scott, 2018).

The PTSD Checklist for Civilians

The PCL-C is a 17-item, self-report scale that assesses symptoms of PTSD (Weathers et al., 1994). It was derived from the PCL-Military version and is not used as a

diagnostic tool (Conybeare et al., 2012). There is support for the psychometric properties including internal consistency, test-retest reliability, and validity (Conybeare et al., 2012; Ruggiero et al., 2003). Items are measured on a 5-point scale with 1 indicating not at all and 5 indicating extremely. Responses to each item indicate how the individual has felt in the past month. Scale items include 'feeling emotionally numb or being unable to have loving feelings for those close to you' and 'avoid activities or situations because they remind you of a stressful experience in the past'. The total score ranges from 17-85 with a cut-off score of 50 as a good predictor of the presence of PTSD (Weathers et al., 1993).

Ethical Considerations

Participant privacy and confidentiality were carefully considered at each step of the research process. Initial contact was made by Dr. Hodgkinson as she has had previous contact with the individuals eligible to participate and was in their circle of care. Those who agreed to receive the scales through mail out provided their mailing address which was kept in a locked office at Memorial University. Members of the research team created mailing labels and mailed each study package. The study package contained a consent form providing a description of the study, a support information sheet, and three psychometric scales. Consent was obtained if individuals mailed completed scales to the return address. The support information sheet included telephone numbers of two helplines and two psychiatrists in the province as there was a risk that participants would become emotionally upset by participating in this study. The contact information of Dr. Hodgkinson, Dr. Etchegary, and the PI of this arm of the study was also included in the consent form if individuals had questions or concerns.

Once the scales were received, they were kept in a locked office with the participant's ID number as the sole form of identification. Each participant has been genetically tested for the *TMEM43* p.S358L mutation and therefore already has a specific ID number identified with their name. Only select members of the research team have access to files that link ID numbers with names and the data collected for those who were involved in the original cardiomyopathy research project. These files are password protected and kept in a locked office.

Data Analysis

Data were entered into IBM SPSS Statistics for Mac version 25 for analysis and Statistical Analysis System version 9.4 was used for a portion of the analysis. Analysis consisted of descriptive statistics for participants in all three groups. Overall mean scores were generated for each scale to determine the prevalence of anxiety, depression, and PTSD among the unaffected first-degree relatives. Pearson's bivariate correlation was used to explore the relationship between each scale for the unaffected first-degree relatives with the severity of disease of the ICD patient. A one sample test of proportion was conducted to compare the proportion of unaffected first-degree relatives who met the clinical cut-off score for each scale with the proportion of the general population who experience depression, anxiety, and PTSD in their lifetime. In addition, a one-way analysis of variance was used to compare the mean scores of the unaffected first-degree relatives with the ICD patients and spouses of ICD patients for the three scales.

CHAPTER 4

Results

Study findings are presented with a focus on the unaffected first-degree relatives as they are the group of interest in this arm of the study. The results are presented in three sections. The first section provides a description of a patient engagement consultation designed to inform study design and choice of measures. The second section summarizes the descriptive statistics for the participants in all three arms of the study with a comprehensive analysis of the findings for the unaffected first-degree relatives. The third section presents inferential analyses, in particular, comparing the mean scores of the unaffected first-degree relatives on each psychometric scale with ICD patients and spouses of ICD patients. In addition, the proportion of unaffected-first degree relatives who met the clinical cut-off score for each scale was compared to the proportion of the general population who experience depression, anxiety, and PTSD in their lifetime.

Patient-Oriented Research

The patient engagement meeting highlighted the lack of information provided to families at the time of diagnosis and ICD implantation, specifically concerning what to expect with ICD therapy. There were two families represented at the meeting who participated in one of the three arms of the study. Family 1 was represented by an affected patient whose child died of SCD; Family 2 was represented by an individual whose carrier status is unknown, two affected children with an ICD, two unaffected children, and a spouse of an ICD patient. The individual whose carrier status is unknown did not participate in the study.

A pre-study patient engagement lunch was held in September 2017 where the following quotations were obtained from two unaffected siblings when asked how it affected them:

Unaffected sibling 1 – *"I was away and couldn't be there (crying). It's so hard."*

Unaffected sibling 2 – *"Well first, it's the worry that you have it. I had five babies at the time. The first was relief for my babies. Then relief for me. Then the guilt starts."*

The family members present collectively raised the concern of the lack of education provided to patients and their families regarding ICDs post-surgery. Unaffected siblings confirmed that families are released with little idea of what to expect which causes unnecessary anxiety and worry.

Unaffected sibling 2 – *"We need to educate patients, yes. My brother and sister (both carriers) had to educate everyone else, their work, their children, their friends. That takes a toll on you too. They are living with this illness and disease and then they are ones who are going out and educating others."*

The patient engagement meeting raised the concern of the lack of information provided to patients and their families regarding ICDs and confirmed concern that ICD therapy can, and does, raise mental health impacts for the entire family.

Descriptive Profile of Participants

A total of 104 individuals participated in the larger study: 53 ICD patients, 25 unaffected first-degree relatives, and 26 spouses of ICD patients. Tables 1a and 1b summarize the descriptive statistics for each arm of the study. The minimum age of the

participants was 18 and the maximum age was 83. The mean age across the three groups was similar and the majority of the participants were female.

Table 1a: Number of males and females in each group

	N	%
ICD patients		
Male	19	35.8
Female	34	64.2
Unaffected first-degree relatives		
Male	7	28.0
Female	18	72.0
Spouses of ICD patients		
Male	13	50.0
Female	13	50.0

Table 1b: Minimum and maximum age at the time of scale completion in 2018

Participants	Minimum age	Maximum age	Mean age (SD*)
ICD patients	22	71	48.49 (13.81)
Unaffected first-degree relatives	18	83	46.04 (18.98)
Spouses of ICD patients	19	69	50.69 (13.53)

*SD: standard deviation

Unaffected First-Degree Relatives

The remainder of the analysis provides a comprehensive look at the prevalence of psychiatric symptoms among the unaffected first-degree relatives. The participants in this group have at least one first-degree relative with an ICD (i.e., a parent or sibling as their child cannot be affected). The majority of the participants had one or two first-degree relatives living with an ICD; however, one participant had four siblings each with an ICD. The patients in this study had their ICD implanted as early as 1996 and as late as 2010 with a mean of 15 years (SD = 3.47) since implant at the time the scales were completed in 2018. Although several ICD implantations were recent, these families were not new to the diagnosis of ARVC in their family history.

Prevalence of Psychiatric Symptoms

Each respondent's raw overall scores were entered in SPSS. The scores for SAS were indexed using the scoring sheet for the scale. Table 2 summarizes descriptive statistics for the minimum and maximum score, overall mean score, and range on the PHQ-9, SAS, and PCL-C scales. As previously noted, the three scales are utilized for screening purposes only and are not a diagnostic tool.

Seven of the 25 participants met the clinical cut off on at least one psychometric scale. Of these participants, six were female and one was male. All participants scored lower than the clinical cut off score on the PCL-C which assesses symptoms of PTSD. Three participants met the clinical cut off of scoring 10 or higher on the PHQ-9 which screens for depression severity (two participants scored 10). Seven participants met the clinical cut off of scoring higher than or equal to 45 on the SAS which assesses the presence and severity of anxiety symptoms (two participants scored 45). The maximum score on the PHQ-9 and SAS was 13 and 53, respectively. Three participants scored 53 on the SAS and one of these participants was the sole participant who scored 13 on the PHQ-9. This participant indicated the problems they checked off on the PHQ-9 made it somewhat difficult for them to do their work, take care of things at home, and get along with other people. There were three participants who met the clinical cut off on more than one scale. One participant scored 10 on the PHQ-9 and 51 on the SAS, a second participant scored 10 on the PHQ-9 and 53 on the SAS, and a third participant scored 13 on the PHQ-9 and 53 on the SAS. Since these participants did not meet the clinical cut off on all three scales, they were not contacted by Dr. Orzylowski.

The overall mean score for depression severity (PHQ-9) among this group was interpreted as minimal depressive symptoms. A score of 10 is considered major depressive disorder on the scoring sheet. The overall mean indexed score for anxiety symptoms (SAS) is lower than the indexed score that indicates the presence of anxiety which is a score of 45. The overall mean score for PTSD (PCL-C) is lower than 50 which is the score that suggests the presence of a significant level of symptom severity. Overall, the mean scores for depression, anxiety, and PTSD in this sample were within normal range.

Table 2: Descriptive statistics of the scores for unaffected first-degree relatives

Psychometric Scale	**Minimum score**	**Maximum score**	**Clinical cut off score**	**Overall mean score**	**Range of scores**	**Standard Deviation**
PHQ-9	0	13	10	4.24	13	3.92
SAS	25	53	45	39.84	28	7.72
PCL-C	17	48	50	27.12	31	8.47

PHQ-9: Patient Health Questionnaire-9; SAS: Zung Self-Rating Anxiety Scale; PCL-C: PTSD Checklist-Civilian Form

Item Level Analysis

Tables 3, 4, and 5 provide item-level descriptive statistics for each scale. There is a functional health assessment at the end of the PHQ-9 which asks how emotional difficulties impact work, things at home, or relationships with other people. Four participants did not complete this section. Of the 21 participants who responded, 17 selected 'not difficult at all', three selected 'somewhat difficult', and one selected 'very difficult'. To provide some context, two of the three participants that indicated 'somewhat difficult' have two affected siblings with an ICD and the other participant has a parent who is affected with an ICD. The participant who selected 'very difficult' is

male with two affected siblings who have ICDs. His score was interpreted as minimal depressive symptoms according to the scale's scoring sheet. In addition, one participant did not provide a response for one of the questions on the PHQ-9, a second participant did not provide a response for one of the questions on the PCL-C, and a third participant did not provide a response for four questions on the SAS. As a result, the questions with no response were omitted from scoring for these three participants.

Table 3: Item level descriptive statistics for PHQ-9

Item	**Mean**	**SD**	**Response Value Frequency**			
			0	**1**	**2**	**3**
Little interest or pleasure in doing things	0.52	0.714	15	7	3	0
Feeling down, depressed, or hopeless	0.28	0.542	19	5	1	0
Trouble falling/staying asleep, sleeping too much	1.00	0.957	10	6	8	1
Feeling tired or having little energy	0.88	0.927	10	10	3	2
Poor appetite or overeating	0.71	0.859	12	8	3	1
Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	0.24	0.523	20	4	1	0
Trouble concentrating on things, such as reading the newspaper or watching TV	0.40	0.707	18	4	3	0
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 more than usual	0.12	0.440	23	1	1	0
Thoughts that you would be better off dead or of hurting yourself in some way	0.12	0.440	23	1	1	0

Table 4: Item level descriptive statistics for SAS

Item	Mean	SD	Response Value Frequency			
			1	2	3	4
I feel more nervous and anxious than usual	1.24	0.523	20	4	1	0
I feel afraid for no reason at all	1.13	0.338	21	3	0	0
I get upset easily or feel panicky	1.20	0.500	21	3	1	0
I feel like I'm falling apart and going to pieces	1.16	0.374	21	4	0	0
I feel that everything is all right and nothing bad will happen	2.44	1.193	8	4	7	6
My arms and legs shake and tremble	1.08	0.282	22	2	0	0
I am bothered by headaches, neck and back pains	1.84	1.106	13	7	1	4
I feel weak and get tired easily	1.29	0.550	18	5	1	0
I feel calm and can sit still easily	2.72	1.308	7	4	3	11
I can feel my heart beating fast	1.28	0.542	19	5	1	0
I am bothered by dizzy spells	1.16	0.473	22	2	1	0
I have fainting spells or feel faint	1.00	0.000	25	0	0	0
I can breathe in and out easily	1.36	0.810	20	2	2	1
I get feelings of numbness and tingling in my fingers and toes	1.28	0.614	20	3	2	0
I am bothered by stomach aches or indigestion	1.54	0.977	17	3	2	2
I have to empty my bladder often	2.08	1.077	10	6	6	3
My hands are usually dry and warm	2.64	1.350	8	4	2	11
My face gets hot and blushes	1.52	0.872	17	4	3	1
I fall asleep easily and get a good night's rest	2.76	1.165	6	2	9	8
I have nightmares	1.24	0.436	19	6	0	0

Table 5: Item level descriptive statistics for PCL-C

Item	Mean	SD	Response Value Frequency				
			1	2	3	4	5
Repeated, disturbing memories, thoughts, or images of a stressful experience from the past?	1.84	1.106	13	7	1	4	0
Repeated, disturbing dreams of a stressful experience from the past?	1.24	0.436	19	6	0	0	0
Suddenly acting or feeling as if a stressful experience were happening again (as if you were reliving it)?	1.28	0.542	19	5	1	0	0
Feeling very upset when something reminded you of a stressful experience from the past?	1.64	0.757	13	8	4	0	0
Having physical reactions (e.g. heart pounding, trouble breathing, or sweating) when something reminded you of a stressful experience from the past?	1.60	0.707	13	9	3	0	0
Avoid thinking about or talking about a stressful experience from the past or avoid having feelings related to it?	1.84	1.068	12	8	3	1	1
Avoid activities or situations because they remind you of a stressful experience from the past?	1.52	0.770	16	5	4	0	0
Trouble remembering important parts of a stressful experience from the past	1.40	0.866	19	4	0	2	0
Loss of interest in things that you used to enjoy?	1.60	0.764	13	10	1	1	0
Feeling distant or cut off from other people?	1.42	0.584	15	8	1	0	0
Feeling emotionally numb or being unable to have loving feelings for those close to you?	1.36	0.757	19	4	1	1	0
Feeling as if your future will somehow be cut short?	1.44	0.870	19	2	3	1	0
Trouble falling or staying asleep?	2.24	1.165	9	6	5	5	0
Feeling irritable or having angry outbursts?	1.72	0.891	13	7	4	1	0
Having difficulty concentrating?	1.60	0.764	13	10	1	1	0
Being “super alert” or watchful on guard?	1.80	1.118	14	5	4	1	1

Being jumpy or easily startled?	1.64	0.860	14	7	3	1	0

Psychiatric Symptoms and Severity of Disease

Pearson's bivariate correlation was used to determine whether variables relevant to their family member's severity of disease were related to the psychological well-being of the unaffected first-degree relatives. The variables chosen from the long-standing dataset to represent severity of disease were: number of hospitalizations, heart transplant, number of first-degree relatives with an ICD, heart failure, absolute number of appropriate and inappropriate shocks, and year of defibrillator implant. There was no statistically significant correlation between these variables and symptoms of depression or PTSD among the unaffected first-degree relatives. However, the year of defibrillator implant was the only variable that had a statistically significant correlation (r=-.530, p=.006, two-tailed) with symptoms of anxiety. In addition, age and sex did not correlate with symptoms of depression, anxiety, or PTSD. A correlation matrix is presented to show the lack of relationship among symptoms of depression, anxiety, and PTSD and the clinical variables, sex, and age (see Table 6).

Table 6: Correlations for clinical variables and each scale for unaffected first-degree relatives

		PHQ-9 scale	**SAS scale**	**PCL-C scale**
Heart transplant	Pearson Correlation	.055	.269	.139
	Significance	.793	.194	.508
Number of hospitalizations to Jan. 2019	Pearson Correlation	-.068	-.098	.113
	Significance	.748	.641	.591
Number of first-degree relatives with an ICD	Pearson Correlation	.013	.034	.224
	Significance	.952	.871	.281

Absolute number of appropriate ICD shocks by Jan. 2019	Pearson Correlation	-.137	-.337	-.131
	Significance	.612	.201	.630
Absolute number of inappropriate ICD shocks by Jan. 2019	Pearson Correlation	-.132	-.021	.406
	Significance	.627	.940	.119
Heart failure	Pearson Correlation	-.295	-.224	-.119
	Significance	.153	.281	.570
Year of defibrillator implant	Pearson Correlation	-.283	-.530	-.136
	Significance	.171	.006	.517
Sex	Pearson Correlation	.062	.152	.202
	Significance	.768	.469	.332
Age	Pearson Correlation	.233	.155	.215
	Significance	.263	.460	.302

PHQ-9: Patient Health Questionnaire-9; SAS: Zung Self-Rating Anxiety Scale; PCL-C: PTSD Checklist-Civilian Form

General Population

A one sample test of proportion was used to compare the proportion of depression, anxiety, and PTSD among the unaffected first-degree relatives compared to the proportion among the general population (see Table 7). For the general population, 11.3% experience depression, 8.7% experience generalized anxiety, and 9.2% experience PTSD in their lifetime (Government of Canada, 2016; Pelletier et al., 2017; Van Ameringen et al., 2008). The results indicated the proportion of depression and PTSD in unaffected first-degree relatives was not significantly different than the proportion of the general population. However, the proportion of anxiety was significantly greater for unaffected-first degree relatives compare to the proportion among the general population.

Table 7: Proportion of depression, anxiety, and PTSD among unaffected first-degree relatives compared to the general population

	Category	Frequency	Proportion of unaffected first-degree relatives	Proportion of the general population who experience symptoms	Significance
Clinical cut off for depression is met (≥10)	Yes	3	0.120	0.113	0.912
	No	22	0.880		
Clinical cut off for anxiety is met (≥45)	Yes	7	0.280	0.087	<0.001
	No	18	0.720		
Clinical cut off for PTSD is met (≥50)	Yes	0	0.000	0.092	0.112
	No	25	1.000		

Comparison Across Three Arms of the Study

A one-way analysis of variance was conducted to compare the mean scores between unaffected first-degree relatives and two other groups (ICD patients and spouses of ICD patients) for depression, anxiety, and PTSD. The unaffected first-degree relatives scored significantly lower than ICD patients on the PHQ-9 (depression symptoms), SAS (anxiety symptoms), and PCL-C (PTSD symptoms) scales (see Table 8a). There was no significant difference between unaffected first-degree relatives and spouses of ICD patients on the PHQ-9 (depression symptoms) or SAS (anxiety symptoms) scales. However, unaffected first-degree relatives scored significantly lower than spouses of ICD patients on the PCL-C (PTSD symptoms) scale (see Table 8b).

Table 8a: Comparison of the mean scores of unaffected-first degree relatives and ICD patients

	Mean score for unaffected first-degree relatives	**Mean score for ICD patients**	**F**	**Significance**
PHQ-9	4.24	7.43	5.558	0.021
SAS	39.84	45.96	8.214	0.005
PCL-C	27.12	33.55	4.832	0.031

PHQ-9: Patient Health Questionnaire-9; SAS: Zung Self-Rating Anxiety Scale; PCL-C: PTSD Checklist-Civilian Form

Table 8b: Comparison of the mean scores of unaffected first-degree relatives and spouses of ICD patients

	Mean score for unaffected first-degree relatives	**Mean score for spouses of ICD patients**	**F**	**Significance**
PHQ-9	4.24	4.96	0.288	0.594
SAS	39.84	42.65	0.389	0.244
PCL-C	27.12	35.77	6.445	0.014

PHQ-9: Patient Health Questionnaire-9; SAS: Zung Self-Rating Anxiety Scale; PCL-C: PTSD Checklist-Civilian Form

Summary

Overall, study findings showed the mean scores for depression, anxiety, and PTSD among the unaffected first-degree relatives were within normal range. The unaffected first-degree relatives scored significantly lower than ICD patients on all three scales and significantly lower than spouses of ICD patients on symptoms of PTSD. There was no significant difference between unaffected first-degree relatives and spouses of ICD patients on symptoms of depression or anxiety. The year of defibrillator implant was one of the variables used to represent their family member's severity of disease. It was the sole variable that had a statistically significant correlation with symptoms of anxiety among unaffected first-degree relatives. The proportion of anxiety was significantly

greater for unaffected-first degree relatives compared to the proportion among the general population.

CHAPTER 5

Discussion

This study explored the mental health impacts of living with ARVC. We found that unaffected first-degree relatives scored significantly lower than ICD patients on all three scales, significantly lower than spouses of ICD patients on PTSD, and significantly higher than the general population on anxiety. This chapter is a discussion of the analysis assessing depression, anxiety and PTSD symptoms in unaffected first-degree relatives of ICD patients. This includes a discussion of the patient engagement session, the results from the unaffected first-degree relatives compared to ICD patients and spouses of ICD patients, the proportion of symptoms compared to the general population, and the psychological distress shown among carriers and non-carriers of other autosomal dominant diseases.

Interpretation of Scores

The scores on all three scales did not show a presence of symptoms of depression, anxiety, or PTSD for the unaffected first-degree relatives. The mean score for each scale was below the clinical cut off. However, it is noteworthy that seven of the 25 participants met the clinical cut off on at least one psychometric scale. It shows these individuals can also be experiencing increased psychological symptoms although they tested negative for the disease.

Pearson's bivariate correlation showed there was no significant relationship between the severity of disease of ICD patients and symptoms of depression or PTSD among unaffected first-degree relatives. There was a significant relationship between the

year of defibrillator implant and symptoms of anxiety. The longer an ICD patient has had their ICD, symptoms of anxiety among unaffected first-degree relatives significantly decreased. This suggests that over time, they have become less anxious as they adapt and cope with having a first-degree relative with an ICD. When comparing the unaffected first-degree relatives to the other two groups, they scored significantly lower than ICD patients on symptoms of depression, anxiety, and PTSD and significantly lower than spouses of ICD patients on symptoms of PTSD. These results were expected as unaffected first-degree relatives do not have an ICD and their offspring are no longer at risk of inheriting the disease. Adult unaffected first-degree relatives typically do not live in the same household as ICD patients and their spouses; therefore, they would likely not be present if and/or when their relative experiences adverse events such as an ICD shock. Experiencing ICD shocks has been previously associated with increased PTSD and contributes to anxiety and depression (Dunbar et al., 2012; James et al., 2012; Thomas et al., 2006; Von Kanel et al., 2011).

The proportion of depression, anxiety, and PTSD among the general population was obtained to compare the proportion of these symptoms among unaffected first-degree relatives. This comparison shows the proportion of depression and PTSD experienced by unaffected first-degree relatives is not significantly different than the proportion experienced by the general population. However, the proportion of anxiety among unaffected first-degree relatives was significantly higher than the proportion among the general population. Although the scores on the anxiety scale did not display a substantial presence of symptoms, the significant difference compared to the general population is

important to note as psychological distress of ICD therapy occurs within a family context (Dunbar et al., 2012). The patient engagement lunch revealed instances of survivor guilt which research has shown is common for non-carriers of autosomal dominant diseases (Aatre & Day, 2011; d'Agincourt-Canning et al., 2006; Etchegary et al., 2017; Gargiulo et al., 2009; Hayden & Bombard, 2005; Huggins et al., 1992; Lynch et al., 1997; McAllister et al., 2007; Sobel & Cowan 2003; Tibben et al., 1992; Wagner et al., 2000; Williams et al., 2000; Winnberg, 2018).

Patient-Oriented Research

An overarching consensus emerged that families require further information regarding ICD therapy and, particularly, its impact on mental and emotional well-being. An unaffected sibling from Family 2 confirmed that patients are released with minimal knowledge of what to expect which causes unnecessary anxiety and worry. Information such as what a shock will look and feel like, whether anything precipitates a shock, and whether others touching a patient during a shock will also be affected were noted as important areas for discussion. An unaffected sibling emphasized the importance of education by adding that their affected siblings had to educate everyone in their lives including coworkers, children, and friends. Thus, not only do carriers have to live with the disease, they have the added burden of explaining symptoms and consequences to others. The unaffected siblings confirmed that being unaffected in terms of carrying the deadly mutation did not mean they were unaffected. As previously noted, one of the unaffected siblings cried as they described feeling an initial relief for their children first, then themselves, followed by guilt.

The experiences of these siblings confirmed the potential impact of ICD therapy on unaffected family members. There was inconsistency on whether and when mental health support was offered to families. While both families did not emphasize a need for psychological support at the time of diagnosis, all members were adamant that it should be part of a holistic approach to ARVC management as it would likely be needed at a later time. Overall, it was observed that ARVC can, and does, impact the mental health of all family members and mental health support should be available to families if and when needed. Their perspective contributed a patient lens to this research and confirmed the importance of considering mental health impacts due to ARVC in addition to obvious clinical foci.

Carriers Compared to Non-Carriers

There is a general consensus that non-carriers experience less psychological distress than carriers of inherited diseases (Croyle et al., 1997; Horowitz et al., 2001; Lerman et al., 1996; Lickleder er et al., 2008; Lodder et al., 2001; Schwartz et al., 2002; Wynn et al., 2018). The psychological impact of genetic testing for cardiomyopathies has not been well studied. A recent comparison of carriers and non-carriers of mutations for two cardiomyopathies, HCM and dilated cardiomyopathy (DCM), yielded similar results to the current study (Wynn et al., 2018). Carriers scored significantly higher on measures of intrusive thoughts, avoidance behaviours, and distress compared to those with negative genetic test results (Wynn et al., 2018). They were also more likely to make life changes including having a biological child which was reported most frequently (Wynn et al., 2018). There is a lack of research comparing the psychological well-being of carriers

with an ICD and non-carriers of cardiomyopathies, specifically ARVC. As previously mentioned, most research comparing carriers and non-carriers focused on HD and *BRCA1/2* as these are autosomal dominant disorders. These findings may be relevant to the psychological impact experienced by carriers and non-carriers of ARVC.

A systematic review including genetic testing for both HD and hereditary breast and ovarian cancer found a decrease in distress over time for both carriers and non-carriers with non-carriers showing a greater and faster decrease (Broadstock et al., 2000). Other studies regarding HD showed that non-carriers described less general distress, depression, hopelessness, and a greater well-being compared to carriers at one week post genetic testing (Tibben et al., 1994; Wiggins et al., 1992). At one year, these differences between carriers and non-carriers no longer existed (Tibben et al., 1994; Wiggins et al., 1992). A review on HD reported that in the first weeks after genetic testing, psychological distress increased in carriers whereas, non-carriers experienced relief (Duisterhof et al., 2001). The relief demonstrated by non-carriers subsided and they experienced most psychological distress at six months after testing and carriers returned to baseline within one year (Duisterhof et al., 2001). Two studies concerning HD found significantly higher levels of distress and depression in carriers compared to non-carriers; however, this was solely for carriers who were symptomatic (Horowitz et al., 2001; Lickleder et al., 2008). There was no significant difference between non-carriers and asymptomatic carriers (Horowitz et al., 2001; Lickleder et al., 2008).

A one-to-two-week follow-up after B*RCA1* gene mutation testing showed that general distress decreased for both carriers and non-carriers during this time frame;

however, carriers were more distressed than non-carriers at the follow-up (Croyle et al., 1997). A study that completed a follow-up at one month after *BRCA1* testing revealed a significant decrease in symptoms of depression for non-carriers compared to carriers (Lerman et al., 1996). At a six-month follow-up, carriers of *BRCA1/2* experienced higher levels of distress compared to non-carriers (Schwartz et al., 2002). An assessment of mean distress levels prior to *BRCA1/2* genetic testing was similar for both carriers and non-carriers; however, the difference in anxiety and depression from pre-to-post-test was significantly different between the two groups (Lodder et al., 2001). Post-test assessments occurred one to three weeks after receiving test results which showed that anxiety and depression decreased for non-carriers, whereas carriers showed a slight increase (Lodder et al., 2001).

The unaffected first-degree relatives in the current study scored significantly lower for symptoms of depression, anxiety, and PTSD compared to ICD patients. These results are comparable to previous research in HD and *BRCA1/2* populations that revealed non-carriers experienced less psychological consequences after genetic testing. However, the majority of HD and *BRCA1/2* research discussed thus far focused on analyzing the short-term psychological impact, typically up to 12 months, of receiving genetic test results. Participants in the current study have had a first-degree relative with an ICD for a mean of 15 years. Although the mutation in the *TMEM43* gene was discovered in 2008, the research team used a genetic haplotype to identify those at 99% risk (Hodgkinson et al., 2005). The longest follow-up studies regarding psychological impacts of HD and *BRCA1/2* are three and five years. A three-year follow-up study examined the impact of

genetic testing for HD which revealed no difference between carriers and non-carriers at three years post genetic testing (Tibben et al., 1997). Two follow-up studies conducted five years after predictive testing for HD revealed significant improvement in quality of life and mean distress scores within normal range for non-carriers (Almqvist, 2003; Decruyenaere et al., 2003). There was a significant decrease in mean anxiety and depression for both carriers and non-carriers; however, mean distress levels of non-carriers did not differ from carriers (Decruyenaere et al., 2003). Meanwhile, a follow-up study five years after genetic testing for *BRCA1/2* indicated there was a significant increase in anxiety and depression among both carriers and non-carriers (van Oostrom et al., 2003). In addition, multiple distress measures revealed there was no difference between carriers and non-carriers (van Oostrom et al., 2003).

These longitudinal studies all found that carriers and non-carriers did not differ in psychological distress over time which is noteworthy based on the results of the current study (Almqvist, 2003; Decruyenaere et al., 2003; Tibben et al., 1997; van Oostrom et al., 2003). The contradictory results of the current study in finding significantly higher scores in depression, anxiety, and PTSD among carriers compared to non-carriers may reflect the differences in the diseases such as treatment and burden of disease. Interestingly, results in a study including other cardiomyopathies (HCM and DCM) supported the findings of the current study showing greater psychological distress in carriers compared to non-carriers more than one year after genetic testing (Wynn et al., 2018). This study found that a greater length of time after receiving genetic testing results (average of 17 months) was associated with greater distress and uncertainty (Wynn et al., 2018).

Diseases such as HD and *BRCA1/2* lack the presence of an ICD and the risk of SCD which creates additional burdens that can impact the psychological well-being of families affected by ARVC. Despite an average of 15 years of having a first-degree relative with an ICD, unaffected first-degree relatives who participated in this study showed significantly higher symptoms of anxiety compared to the general population. Although they scored significantly lower than carriers on all three psychological scales, it appears that longitudinal studies with larger samples are necessary to determine the extent of the psychological ramifications for non-carriers over time.

Study Implications

This pilot project provides empirical evidence that concur with previous qualitative research in this population. The patient engagement session demonstrated psychological distress (i.e., guilt) among unaffected first-degree relatives. The quantitative analysis showed the psychological burden appears to be more evident in ICD patients and their spouses compared to unaffected first-degree relatives. The proportion of depression and PTSD among unaffected first-degree relatives is comparable to the proportion among the general population; however, the proportion of anxiety is significantly greater for unaffected first-degree relatives. This shows that while unaffected first-degree relatives may not require the same amount of psychological support as ICD patients and their spouses, they experience more anxiety than the general population. This suggests that they should not be forgotten as inherited diseases occurs within a family context (Dunbar et al., 2012).

Clinicians focus on carriers and clinical symptoms which understandably is the primary concern; however, a negative test result does not signify instant positive mental health. These family members may also need some form of support, whether it is being offered information about local support groups or online resources such as the SADS Foundation website (The Canadian SADS Foundation, 2020). The SADS foundation is a patient advocacy group that supports patients affected by inherited cardiac disorders and their families (The Canadian SADS Foundation, 2020). Their website provides resources for both patients and their families including general information, a community to connect with, current news, and a list of publications and helpful websites (The Canadian SADS Foundation, 2020). While families at the patient engagement meeting agreed mental health may not be the first service families think about as they are coping with genetic testing and ICD surgery, all endorsed a holistic approach to care for families affected by ARVC. Findings suggest families would appreciate an informational resource that can be accessed over time and when they deem necessary.

Future research may benefit from the results of this study by working with patients and their families to develop psychosocial and mental health services that utilize resources efficiently and cost effectively. This would aid the health care system to properly allocate mental health services to those patients and family members that require more resources, which is essential in the current climate of resource scarcity. Our results suggest mental health resources may need to be allocated to ICD patients and their spouses, whereas unaffected first-degree relatives could benefit from services that do not utilize a substantial amount of health care resources such as online support. By working

with families as a whole, a comprehensive understanding of what these families need will help create services that provide families with proper support and simultaneously conserve limited mental health resources.

Study Limitations and Strengths

The current study had several limitations and strengths that should be noted. This is a pilot study with a small sample size which decreases the statistical power and limits the generalizability of the data. For this reason, Pearson's bivariate correlation was used to analyze the relationship between symptoms of depression, anxiety, and PTSD and the most relevant variables to severity of disease as the recommended sample size for this test is greater than or equal to 25 (David, 1938). In addition, the significant difference in anxiety between unaffected first-degree relatives and the general population cannot be generalized to the population of interest due to the small sample size and eligible individuals who did not participate.

Three different participants did not provide a response for at least one question on one scale. The PHQ-9 and PCL-C each had one question with no response. The SAS had four questions with no response. Due to data collection by mail out, we were unable to verify that all questions received a response before collecting the scales. Consequently, the questions with no response were omitted from scoring for these three participants.

This sample may also be subject to selection bias. Participants in this arm of the study consisted of unaffected first-degree relatives from the first eight families affected by ARVC. Due to the recruitment process and time constraints, newly ascertained families were excluded. Dr. Hodgkinson was required to be the initial contact for ethics

purposes since the unaffected first-degree relatives are no longer patients and she is well known to the first eight families affected by ARVC.

The results may be an overrepresentation of the long-term mental health impact of ICD therapy. Newly diagnosed ARVC families may have responded differently than families that have adjusted to lifestyle changes. Although, even in these 'older' families, mental health impacts were noted during the patient engagement session and in anxiety scores. In addition, there were 27 unaffected first-degree relatives that were unable to be contacted due to an incorrect telephone number, telephone number not in service, or no telephone number despite taking steps to acquire the correct telephone number. Information regarding individuals who are no longer patients is far more difficult to update.

Some of the strengths of this study are the psychometric scales, response rate, and ascertainment of the population. The scales chosen for this study were validated and reliable scales. They were self-administered, short, and had free access. In addition, the scoring was not complex and did not require training. This study had a good response rate of 55.5% which may be attributed to the brevity of the psychometric scales and the ascertainment of this population. The families affected by ARVC in NL are identified in pedigrees. These pedigrees contain comprehensive knowledge regarding all family members, including those who do not have an ICD. A long-standing, de-identified ARVC dataset includes detailed clinical and family history information of those who were testing during the original cardiomyopathy research. This information is updated periodically by the genetics research team as required for various research studies. While

the long-standing ARVC dataset is a strength, dedicated resources for its maintenance would be highly valuable.

Conclusion

This pilot study measured the psychological impact of ICD therapy on unaffected first-degree relatives of patients with an ICD. This study builds on qualitative research conducted by Etchegary et al. (2017) and it is the first quantitative study to examine the psychological impact of ICD therapy on patients in NL with ARVC and their family members.

Preliminary findings of the mental health impact of ICD therapy was assessed using variables associated with ICD therapy including number of hospitalizations, heart transplant, number of first-degree relatives with an ICD, heart failure, absolute number of appropriate and inappropriate shocks, and year of defibrillator implant. The results indicated that having a first-degree relative with an ICD does not appear to significantly impact symptoms of depression or PTSD of those who tested negative for the *TMEM43* p.S358L mutation. However, the longer an ICD patient has had their ICD, symptoms of anxiety among unaffected first-degree relatives significantly decreased. Unaffected first-degree relatives experience significantly less symptoms of depression, anxiety, and PTSD compared to ICD patients, significantly less symptoms of PTSD compared to spouses of ICD patients, and significantly more symptoms of anxiety compared to the general population. In addition, the patient engagement session showed that unaffected first-degree relatives expressed experiencing psychological burdens. This aligns with the evidence obtained by the qualitative research on this population (Etchegary et al. 2017).

This study highlights the importance of assessing the psychological burdens of ARVC in the province. Future research with a larger sample size containing newly diagnosed families affected by ARVC in the province would provide a more comprehensive view of the psychological impact of ICD therapy among unaffected first-degree relatives.

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APPENDIX A

Ethical Approval

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

NEWFOUNDLAND AND LABRADOR
HREB
HEALTH RESEARCH ETHICS BOARD

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 B

Telephone Script

Telephone Script for Dr. Kathy Hodgkinson

- Dr. Hodgkinson knows the families of the unaffected siblings and has known them for several years. She will make initial contact with the unaffected siblings to inform them of the research study.

Hello, may I please speak to (insert name)?

When desired person is on the phone:

Hello [first name], this is Kathy calling, how are you? I am calling to let you know about a new research project we are starting that might be of interest to families with ARVC.

We want to ask about the psychological well-being of the brothers and sisters of patients with an ICD, like your [brother/sister] has. We will ask siblings to fill out three scales, this should take about 15 minutes or so.

There is certainly no requirement at all that you should take part. This study has nothing to do with the care you or your family receives from the cardiac clinic. But if you would like to know more about the study, would it be okay if a Masters' student, Natalie Butt, involved in the study gives you a call? She can give you more detail about the scales and would even fill out the scales with you over the phone if you decide you want to take part.

If refusal: Okay, no problem. Thank you for taking the time to speak with me.

If yes: Okay, is there a time that works best for you? I will give Natalie your telephone number and she will contact you. Thank you for taking the time to speak with me.

Telephone Script for Natalie Butt

Hello, my name is Natalie Butt and I am a Masters student at the Faculty of Medicine at Memorial University. May I please speak to (insert name)?

When the desired person is on the phone:

Hi (insert name), my name is Natalie Butt and I'm a Masters student with the Faculty of Medicine at Memorial University. I was speaking to Dr. Kathy Hodgkinson and she said you would like to hear a bit more about our latest research project about ARVC. Are you still interested in hearing about our study? If so, is this a good time for you?

If no: That's not a problem. Would you like to reschedule for a better time?
    If no: Okay, thank you for your time.
    If yes: Okay, what time would work best for you?

If yes: I want to start off by saying there is no requirement at all that you should participate. I will give you a bit of information about this study and feel free to stop me at any time if you have any questions or decide you do not want to participate.

My research project is concerned with the unaffected siblings in ARVC families. We know that having an ICD for ARVC (implantable cardioverter defibrillator for Arrhythmogenic Right Ventricular Cardiomyopathy) can have many impacts for the person with the ICD. But we wonder if there is any impact of living in a family with ARVC on their brothers and sisters who are not affected. Psychological impact such as depression, anxiety, and post-traumatic stress symptoms. Because your [brother or sister] has an ICD and you are unaffected, you are eligible to take part.

Taking part in this study involves filling out three scales, that should take about 15 minutes. You can fill these out on the phone with me, online or they can be mailed out to you with a return postage stamp.

If not interested in participating: Okay, thank you for taking the time to speak with me.

If interested in participating: Would you like to fill out the questionnaires now over the phone, at a later time convenient for you over the phone, online, in-person, or have them mailed to you?

If online is chosen: I will read out the website url (insert website url).

If in-person is chosen: When is a good time for you to come in and fill out the questionnaires?

If mail out is chosen: We will send you a package with the questionnaires and a paid

postage stamp. I will call you in a couple weeks if I haven't heard from you.

If telephone at a later time is chosen: When is a good time for me to call you back?

If current telephone conversation is chosen: If you are uncomfortable at any time or feel that after hearing the type of questions being asked that you don't want to continue with the rest of the questions, please let me know. You are not required to finish the questions once we start if you do not want to. Is that okay?
I would like to read out the consent for and obtain your verbal consent that you agree to take part in the study: You are invited to take part in a research study called Living with sudden cardiac death in the family: *Anxiety, depression, and post traumatic stress disorder (PTSD) in unaffected siblings of patients with an ICD as treatment for Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). The study involves filling out three scales that are included with this letter.*

You are being invited to take part in this study as a person who has been tested for ARVC. Researchers from Memorial University would like to study how ARVC diagnoses in your family has affected/impacted your mental health. Ultimately, we hope the data will change practice and improve the mental health services available to you and lead to more positive psychiatric outcomes.

Please note that there are no right or wrong answers; we are only interested in your opinions. Filling out the scales is voluntary and you are free to leave out any question you do not wish to answer. If you are not interested in taking part, please feel free to ignore the scale. Taking part in this scale will not affect any healthcare you or your family receives. There are no names attached to the scale, so no one will know your answers. Your name will never be reported in any papers or reports prepared from the scale. The data we collect for this study will be stored for at least 5 years. Should you wish to withdraw from the study at any time, any scale data you have provided will be removed from the data set and destroyed.

I will provide you with my email and my co-supervisors' emails in case you have any questions or concerns or would like more information: ndb132@mun.ca, holly.etchegary@med.mun.ca, khodgkinson@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 the Ethics Office 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.

If verbal consent is obtained, the questions from all three questionnaires will be read one by one to the participant.

Once the questions have been answered the participant will be thanked for their time and participation.

APPENDIX C

Cover Letter and Consent

March 2018

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 first-degree relatives 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 person who has been tested for the p.S358L mutation in the gene *TMEM43* causing ARVC **but who does not have the mutation**.

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.

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. The questionnaires will be coded and linked with data from a previous study on ARVC that you participated in (HREB 00-176 SCD Cardiomyopathy). The following information from the previous study will be used:

1. Genetic information (mutation positive/negative), number of family members with severe disease (e.g., sudden early death)
2. Demographics (age, sex)

Once the scales are returned, they will be de-identified and linked only by your identification number. Your name will never be reported in any papers or reports prepared from the research.

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

Filling out the three scales 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 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

Natalie Butt, M.Sc. Candidate Clinical Epidemiology, Faculty of Medicine
Memorial University of Newfoundland
Email: ndb132@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 Natalie Butt, on behalf of the research team.

APPENDIX D

Psychometric Scales and Scoring

Patient Health Questionnaire-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
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	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING *0* +_____ +_____ + _____

=Total Score: _____

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**
☐	☐	☐	☐

PHQ-9 Scoring

Major depressive disorder is suggested if:

- Of the 9 items, 5 or more are checked as at least 'more than half the days'
- Either item a. or b. is positive, that is, at least 'more than half the days'

Other depressive syndrome is suggested if:

- Of the 9 items, a., b. or c. is checked as at least 'more than half the days'
- Either item a. or b. is positive, that is, 'more than half the days'

Also, PHQ-9 scores can be used to plan and monitor treatment. To score the instrument, tally each response by the number value under the answer headings, (not at all=0, several days=1, more than half the days=2, and nearly every day=3). Add the numbers together to total the score on the bottom of the questionnaire. Interpret the score by using the guide listed below.

Guide for Interpreting PHQ-9 Scores

Score	Recommended Actions
0-4	Normal range or full remission. The score suggests the patient may not need depression treatment.
5-9	Minimal depressive symptoms. Support, educate, call if worse, return in 1 month.
10-14	Major depression, mild severity. Use clinical judgment about treatment, based on patient's duration of symptoms and functional impairment. Treat with antidepressant or psychotherapy.
15-19	Major depression, moderate severity. Warrants treatment for depression, using antidepressant, psychotherapy or a combination of treatment.
20 or higher	Major depression, severe severity. Warrants treatment with antidepressant and psychotherapy, especially if not improved on monotherapy; follow frequently

Functional Health Assessment

The instrument also includes a functional health assessment. This asks the patient how emotional difficulties or problems impact work, things at home, or relationships with other people. Patient responses can be one of four: Not difficult at all, Somehat difficult, Very difficult, Extremely difficult. The last two responses suggest that the patient's functionality is impaired. After treatment begins, functional status and number score can be measures to assess patient improvement

Zung Self-Rating Anxiety Scale (SAS)

For each item below, please place a check mark (✓)in the column which best describes how often you felt or behaved this way during the past several days.

Place check mark (✓) 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.				

SAS Scoring

This instrument is designed for screening purposes only and is not to be used as a diagnostic tool.

How to Use
Patients will circle 1 of the 4 numbers in response to the questions. The healthcare provider, nurse, or medical staff assistant then scores the completed questionnaire and interprets the score using the information found in the box at right.

How to Score

- Check that all statements have been answered
- Scoring values are printed next to the response
- Add up the Raw Total Score
- Convert the Raw Total to the Anxiety Index

Interpreting the Anxiety Index

Anxiety Index	Clinical Interpretation
Below 45	Within normal range
45 – 59	Minimal to moderate anxiety
60 – 74	Moderate to severe anxiety
75 and over	Severe anxiety

PTSD Checklist-Civilian Form (PCL-C)

*Instructions to patient: "Below is a list of problems and complaints that people sometimes have in response to stressful life experiences. Please read each one carefully, and then fill in the circle of the response to indicate how much you have been bothered by that problem **IN THE PAST MONTH**." Please fill in ONE option only for each question."*

	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?					
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?					

PCL-C Scoring

Total score is the sum of all 17 items.

A score of 50 suggests the presence of a significant level of symptom severity which should be further evaluated with a formal assessment.

APPENDIX E

Supporting Documents for Study Package

Support Information Sheet

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

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709-864-6605

Dr. Magda Orzylowski
Psychiatry Resident, Memorial University
mo3633@mun.ca
709-758-9028

Dr. Mandeep Grewal
Psychiatrist, Eastern Health
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709-777-8665