THE DEVELOPMENT AND PRELIMINARY TESTING OF AN INSTRUMENT TO MEASURE THE PERCIEVED ECONOMIC BURDEN OF A SUBTYPE OF ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC) ON PATIENTS AND FAMILIES IN NEWFOUNDLAND

by

© Glenn Enright

A thesis submitted to the

School of Graduate Studies

in partial fulfillment of the requirements for the degree of

MSc (Medicine)

Faculty of Medicine

Memorial University of Newfoundland

May 2016

St. John's Newfoundland and Labrador

ABSTRACT

The goal of this thesis was to develop, construct, and validate the Perceived Economic Burden scale to quantitatively measure the burden associated with a subtype Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) in families from the island of Newfoundland. An original 76 item self-administered survey was designed using content from existing literature as well as themes from qualitative research conducted by our team and distributed to individuals of families known to be at risk for the disease. A response rate of 37.2% (*n* = 64*)* was achieved between December 2013 and May 2014. Tests for data quality, Likert scale assumptions and scale reliability were conducted and provided preliminary evidence of the psychometric properties of the final constructed perceived economic burden of ARVC scale comprising 62 items in five sections. Findings indicated that being an affected male was a significant predictor of increased perceived economic burden in the majority of economic burden measures. Affected males also reported an increased likelihood of going on disability and difficulty obtaining insurance. Affected females also had an increased perceived financial burden. Preliminary results suggest that a perceived economic burden exists within the ARVC population in Newfoundland.

ACKNOWLEDGEMENTS

I would like to extend my sincerest gratitude to all those who contributed to this work and also to those who have provided support and guidance to me over the past few years.

My first thoughts turn to the ARVC families for their contribution. They willingly opened up their lives and have committed to the success of the ongoing research that will influence generations to come.

The dedication and support of my supervisory committee has made the difference in my commitment to the work and to the ARVC families of Newfoundland and Labrador. Dr. Rick Audas welcomed me into the ARTC program and provided unfailing guidance to me during times of uncertainty and discouragement. Dr. Kathy Hodgkinson, thank you for your passion that inspired me to forge on and allowed me to see a true role model at work. To my other committee members, Dr. Holly Ethchegary and Dr. Daryl Pullman-Holly, thank you for your constant guidance and for responding to my million questions with patience, insight and expertise. Daryl, it was you who opened the doors for me to take on this experience and for that I am eternally grateful.

It always takes a team effort to bring a project to success and my support team at Memorial was beyond wonderful. I would particularly like to acknowledge Fiona Curtis, and Dr. Charlene Simmonds for their help with participant recruitment and Dr. Susan Stuckless for her work with the dataset. And for taking this journey with me, I would also like to thank both Alexandra States and Erin Baker.

One can never succeed without a backdrop of people who accomplish the administration duties. Thank you to those at the research and graduate studies office at Memorial and administrators of the ARTC program for answering my countless emails and phone calls. I would like to acknowledge the funding agency for this project, ACOA, Atlantic Innovation Fund and Memorial University for the ARTC program award in 2012.

There really are no words to thank my family, all of whom in some way contributed to my success, my mother Cathy and father Richard who never let me down no matter what I needed and to especially to my brother Brian and my sister Allison who counseled me on the ways of academia. I am very fond of you all and will always be grateful.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Arrhythmogenic Right Ventricular Cardiomyopathy [ARVC]

Canadian Health Act [CHA]

Canadian Life and Health Insurance Association [CLHIA]

Consumption and Savings [CS]

Financial Burden [FB]

Genetic Information Nondiscrimination Act [GINA]

Human Capital [HC]

Implantable Cardioverter Defibrillator [ICD]

Insurance [IN]

Labour Supply and Productivity [LSP]

Perceived Economic Burden [PEB]

Sudden Cardiac Death [SCD]

Transmembrane Protein 43 [*TMEM43*]

World Health Organization [WHO]

List of Appendices

Chapter 1: Introduction

Stories like that of Rick Ralph highlighted in Memorial University of Newfoundland's 'Dare To' campaign are not uncommon in the province of Newfoundland and Labrador, where a lethal genetic cardiac condition affects many families. The short video link provided in the footnote presents the story of Rick Ralph, an Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) patient for whom research like that conducted in this study has made a significant impact both for him, and his young family.[1] It is for families like the Ralphs that ongoing research continues in the hopes of making positive contributions to the holistic management of this life threatening disease. This study focuses on exploring the perceived economic burden of ARVC caused by a p.S358L mutation in *TMEM43*, to further understand its psychosocial effect on families, inform the provision of health services and contribute to the wider literature on the economic burden of genetic disease.

1.1 Problem Statement

ARVC has been affecting families since the 18th century when the Pope's physician Giovanni Maria Lancisi first documented it in his book *De Motu Cardis et Aneurysmatubus* (Romero, Mejia-Lopez, Manrique & Lucariello, 2013). Since then, significant research has been undertaken on ARVC that has resulted in an increased understanding of the cause, manifestation and treatment of the disease. ARVC is a genetically determined heritable heart disease causing irregular heart rhythms (arrhythmias), potential heart failure and sudden cardiac death (SCD).

[1] https://www.youtube.com/watch?v=bOwemOKYFIQ

On the island of Newfoundland, Canada, a particularly lethal subtype of ARVC is prevalent caused by a p.S358L gene mutation in *TMEM43* (Merner et al., 2008). A small but significant population of 25 families are known to be genetically at risk for the disease, comprising approximately 900 individuals past and present born at 50% risk of inheriting the genetic mutation (Hodgkinson et al., 2013). Advancements in genetic testing have hastened the identification, management and clinical monitoring of this population, along with the creation of a local ARVC registry used for both clinical and research purposes. Early identification of affected individuals allows for appropriate treatment decisions, often the implantation of a cardioverter-defibrillator (ICD) that shocks the heart in response to arrhythmias. Unlike more common cardiovascular diseases that manifest later in life, ARVC develops in young-mid adulthood and persists over a lifetime. Symptoms of the disease vary greatly between individuals and sexes, where men tend to develop more severe symptoms beginning at an earlier age. The most notable of symptoms is SCD, which most often occurs in seemingly young and otherwise healthy individuals.

An identified gap within existing psychosocial literature exists on the perceived economic burden of inherited illness, including the inherited cardiac condition of ARVC. This study is a contribution to a larger investigation into the genetics-related, ethical, environmental, economic, legal and social (GE3LS) aspects of ARVC. It focuses on providing descriptive measures at the microeconomic level, that is, the level of the household, family and individual (Ruger et al., 2006). To date, the majority of economic studies focus on the macroeconomic or societal level, which does not provide evidence on how individuals and families themselves perceive the economic burden of ARVC.

What is known, however, is that chronic disease can have a significant economic impact on individuals and their families. Reports also indicate that economic hardship in diseases such as cancer can contribute to a lower quality of life (Meneses et al., 2012). Furthermore, costs incurred by the acquisition of health goods and services as a consequence of disease can significantly impact the ability of individuals and their families to purchase and consume other goods and services (World Health Organization [WHO], 2009).

A possible lifetime of symptoms associated with ARVC and a risk for premature and possible sudden death can alter various economic outcomes of at risk individuals and families. For example, decisions pertaining to education, careers, and finances all have the potential to be affected by a risk for ARVC. Moreover, costs associated with the disease both directly and indirectly can result in financial burdens for families. Finally, the ability to acquire insurance to reduce the financial burdens that health costs place on families or to ensure financial security in the future may also be affected.

Even though many direct medical costs are covered by the publicly funded health care system in Canada, only 70% of direct medical costs are funded through provincial/territorial health insurance (Paris et al., 2010). Travel, accommodation, and medication costs are all costs exempt from the publicly funded health care system and as a result, are absorbed either by additional private medical insurance or by families themselves. The clinical management of ARVC patients in Newfoundland occurs at the Cardiac Genetics clinic at the Health Sciences Centre in St. John's (the tertiary referral centre for the Province of Newfoundland and Labrador) requiring many patients to travel from other parts of the province for their care. Additionally, some patients are required to

travel out of province for some aspects of care and incur costs for travel and accommodation, as well as lost time at work.

1.2 Research Question and Objectives

The purpose of this cross-sectional descriptive study was to develop, pilot and conduct preliminary evaluation of an instrument to measure the perceived economic burden associated with being born at risk of ARVC caused by a p.S358L mutation in *TMEM43*. It extended to explore the possible trends between ARVC and measures of economic burden identified in the literature from the perspective of the individual, household and family.

The study objectives were:

1. To develop and pilot a survey instrument using existing ARVC and other relevant literature to collect data on the perceived economic burden of ARVC.
2. To construct and provide preliminary validation of the Perceived Economic Burden (PEB) scale.
3. To conduct empirical analysis using the PEB scale to identify predictors of perceived economic burden of ARVC, particularly sex and clinical status.[2]

1.3 Rationale

Few health economic studies reported in the literature focus on the microeconomic environment since measuring an impact at the societal or macroeconomic level are considered of greater importance, particularly in high-income countries. Jeon et al. (2009) suggest that the economic consequences on patients and households are often

[2] Previous clinical studies indicate that sex and clinical status are significant factors in ARVC disease progression and severity (see: Hodgkinson et al., 2013; Merner et al., 2008). As a result, these indicators are afforded a specific focus in addition to other possible predictors as identified through the data analysis.

overlooked in high-income countries with publically funded health care systems, a possible explanation for the minimal number of microeconomic studies in countries such as Canada. Nevertheless, reports suggest that despite a publicly-funded health care system, health-related costs to families are increasing in Canada (Sanmartin et al., 2014). Increased costs for health-related expenses cause economic burden in chronic disease populations and often lead to households facing difficult decisions between care and basic living expenses (Jeon et al., 2009).

Research is lacking on the economic burden of ARVC, with only a single qualitative study conducted by Etchegary et al. (2015). The lack of literature extends to other inherited and non-inherited heart diseases, and many genetic conditions in general. As such a gap in the wider literature has been identified. This study represents the first quantitative investigation of its kind not only within Canada but also internationally. In the absence of knowledge concerning how ARVC affects the economic decisions of individuals and families, limits on the optimal holistic approach to care exist. An understanding of the experienced economic burden from disease on families is necessary to inform and guide optimal patient care and future policy development.

Findings from this study will provide an understanding of the effect that a risk for ARVC has on various economic measures of burden for individuals and families. This knowledge can aid clinicians in providing the most comprehensive, holistic management and guidance for ARVC patients. This knowledge may also inform policy decisions related to programs and services provided to ARVC patients and other similar populations facing economic burden as a result of disease. Finally, results can be used to inform

further research on the economic challenges faced by ARVC families and other heritable conditions.

This thesis presents a literature review that provides an overview of ARVC, background on the study population, and summarizes what is currently reflected in the literature concerning the measures of economic burden. The methodology used to address the study objectives is described in the context of the development and construct of a data collection survey instrument, the validation of the PEB scale, and both regression and chi-squared data analysis. Study results are presented and discussed as they reflect the findings in consideration of this population and existing literature. Finally, the conclusions of the study are presented including recommendations for future research on this population and relatable conditions.

This thesis comprises the economic component of the GE3LS research. All phases of this research were planned and executed by the author (Glenn Enright) with advice from the academic supervisory committee responsible for GE3LS. The supervisory members consist of a genetic counselor, a health economist, a clinical research scientist, and a medical ethicist. The committee is sometimes referred to as the research team in this thesis. At various stages of the research, advice and recommendations were sought out by a number of experts in their field, and are referenced in text.

Chapter 2: Background & Literature Review

2.0 Literature Review

A lack of research is evident in the literature pertaining to the economic burden experienced by ARVC patients and their families. The purpose of this research is to address this issue. Possible explanations for the absence of literature in this area are discussed in detail in the proceeding sections; however, they can be summarized briefly, and include (a) the relatively small ARVC population, (b) the research focus on the clinical management of the disease, and (c) the preference for economic studies at the societal or macroeconomic level. This literature review will reveal the lack of economic burden studies on ARVC patients and families, while discussing economic studies on related conditions, providing sufficient evidence and background information to rationalize the importance of conducting this study.

This literature review comprises two major sections. Firstly it addresses Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) presenting an overview of the biological, genetic, and medical understanding of the disease. Furthermore, ARVC as it occurs in the Newfoundland population, is also explained including disease characteristics of the specific genetic subtype of ARVC targeted in this study. It is essential to appreciate the various characteristics of this disease in order to understand how the disease can lead to a perceived economic burden for patients and their families.

The second section presents the measures of economic burden used in this study and explores how illness and disease (particularly a chronic disease such as ARVC) causes economic burden to patients and their families. A single qualitative study conducted by members of this research team exists that explores the economic burden of

ARVC, discussed in detail in section 2.2. To date, no quantitative studies exist on the economic burden of ARVC or other genetic cardiomyopathies. The relatively few microeconomic studies that exist in the wider literature on similar conditions to ARVC such as heart diseases and other genetic diseases as well as chronic illness and disease are reviewed in section 2.3. Finally, a brief summary of this chapter is included in section 2.4.

2.1 Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is classified as a genetically determined primary myocardial disease in which the heart muscle is structurally and functionally abnormal (Elliot & Mohiddin, 2012). Structurally, it is characterized by the progressive replacement of normal myocardial (heart muscle) tissue with fibrous and adipose (fat) tissues mostly within the right ventricle, although left ventricle tissue changes are also reported (Azaouagh et al., 2011; Campuzano et al., 2012; Romero et al., 2013). It is thought that fibro-fatty replacement of muscle interferes with the connections between the muscle cells disrupting the electronic signaling pathways responsible for heart contractions (Basso et al., 2009). Disruption of the electronic impulses leads to functional abnormalities in the form of irregular heartbeats, resulting in arrhythmias, heart failure and possible SCD (Basso et al., 2009; Cahill et al., 2013). Prognosis for patients is highly dependent on factors such as the genetic subtype of ARVC, the rate of disease progression, availability of treatment and follow-up and often sex, as males are often affected more severely than females.

ARVC is estimated to affect between 1 in 2000-5000 people within the general population, although some researchers suggest that difficulties with diagnosis may cause under representation and the true rate could be as high as 1 in 1000 (Corrado et al., 2000;

Murray, 2012; Sen-Chowdhry et al., 2010). This disease affects a relatively small proportion of the Canadian population, however, it is known that a significant ARVC population reside in or have genetic ties to specific families and communities in Newfoundland.

Specifically, one genetic subtype of ARVC commonly found in Newfoundland is caused by a p.S358L missense mutation in the *TMEM43* gene found on the ARVD5 region (locus) of chromosome 3 (Merner et al., 2008). While studies are ongoing to identify the extent and prevalence of the at-risk population in Newfoundland, the prevalence of ARVC caused by this genetic subtype remains unknown, although anecdotally is likely to be at least 1/1000 (Hodgkinson, Personal communication, 2014). Despite the unknown prevalence, to date, researchers and clinicians have identified twenty-five pedigrees with origins to Newfoundland known to carry the ARVC causing p.S358L mutation, comprising approximately 900 individuals[3].

2.1.1 Genetics and ARVC

ARVC is understood to be a genetic disease. Genes are the basic chemical unit of heredity and can be thought of as code sequences that carry information from one generation to the next. A change in the normal gene sequence that has obvious phenotypic (observable characteristic) effects is known as a mutation, whereas changes within gene sequences with no relevant phenotypic effects are known as polymorphisms. Gene mutations like those causing ARVC can be inherited from generation to generation usually resulting from one of two common inheritance patterns; (i), autosomal dominant (AD); and (ii) autosomal recessive (AR). In cases of AD inheritance, there is a 50%

[3] Dead or living. Since the early 1800's, identified born at 50% risk of having the *TMEM43* gene mutation.

chance a child will inherit a gene mutation and its associated characteristic, such as a disease or trait, from a parent who possesses the mutation. In cases of AR inheritance, the chance of inheriting a mutation remains 50%; however, the chance of developing the disease/trait is reduced to 25% as both parents must possess and pass on the gene mutation.

ARVC is most commonly associated with an AD inheritance pattern (Basso et al., 2009). Thus far, twelve subtypes of autosomal dominant ARVC have been identified named ARVD1 through ARVD12 respectively, based on the genetic location of the mutation (Romero et al., 2013). A single autosomal recessive AR subtype of ARVC exists and is referred to as Naxos Disease. Although many commonalities exist between ARVC types, differences in disease progression and severity of symptoms are observed between genetic subtypes (Romero et al., 2013).

Both family history and genetic testing provide insight into the genetic characteristic of ARVC. Research demonstrates that a family history of ARVC or SCD is found in approximately 20%-30% of cases (Marcus et al., 2013). This is most likely a somewhat conservative estimate however, as within a cardiac setting, family history is often overlooked, rarely documented or never asked. (Hodgkinson, personal communication, 2014; Marcus et al., 1982). Similar to family history, an underestimate of the proportion of genetic-related ARVC is probable on the assumption that undiscovered disease-causing gene mutations exist. ARVC disease-causing gene mutations are present in 50% of patients with ARVC who present to cardiac clinics, evidence that undiscovered disease-causing genes remain (Marcus et al., 2013).

2.1.2 Symptoms of ARVC

Patients with ARVC can experience a wide range of symptoms with varying severity. Initial symptoms of the disease most commonly appear between 15 and 35 years of age, with first symptoms rarely arising in early childhood or beyond 60 years of age (Wichter et al., 2005). Most commonly, symptoms of ARVC include palpitations (irregular heartbeats perceived by patients), pre-syncope (dizziness), syncope (fainting), and chest pain (Hamilton, 2009). Heart failure develops in about 10%-20% of ARVC patients when the heart is no longer functional enough to adequately circulate blood (Cahill et al., 2013; Heart and Stroke Foundation, 2013b).

The most devastating and often the first and only symptom of ARVC is SCD. Research suggests that approximately 20% of all sudden deaths are attributable to ARVC, occurring most frequently in young adults and athletes (Murray, 2012; Romero et al., 2013). Corrado et al. (2003) conclude that ARVC patients who engage in sport or vigorous physical activity are at a five times greater risk for SCD. An increased risk of SCD occurs with vigorous activity resulting from the significant physical stress and increased stimulation of the heart muscles that increase the likelihood for arrhythmias (Basso et al., 2009; Wichter et al., 2005). Such physical activities may also further disease progression as a result of stress induced on the heart (Corrado et al., 2003). Even though physical activity increases the risk for SCD, this does not suggest that SCD cannot occur in the absence of physical activity. A study of 200 ARVC-associated SCDs by Tabib et al. (2003) concluded that death most frequently occurs during sedentary activity.

2.1.3 Diagnosis of ARVC

Diagnosis of ARVC in patients can be difficult due to fluidity in the progression of the disease over time. Hypothetically, initial symptoms may be indicative of a relatively mild heart condition; however, as the disease progresses, the disease may look like other heart conditions (e.g., with left ventricular involvement ARVC can mimic dilated cardiomyopathy) and may not be diagnosed as ARVC (Pirzada et al., 2015). Difficulties with diagnosis led to a consensus by experts on proposed criteria referred to as Task Force Criteria for ARVC (McKenna et al., 1994). The 1994 criteria combined abnormalities in heart structure, pathology, electrical impulses rhythms and family history to establish diagnosis. Each criterion was categorized into major or minor sub classifications based on their known association with ARVC. A diagnosis of ARVC was based on combinations of the number of major and minor criteria for each patient; two major, one major plus two minor or four minor criteria were required for diagnosis.

In an effort to increase sensitivity of the diagnostic criteria, Marcus et al. (2010) subsequently updated the preceding 1994 Task Force criteria. The updates consider changes in clinical understanding, advancement in diagnostic technologies and most notably, newly available genetic mutation testing for ARVC. Marcus et al. (2010) also updated the requirements for diagnosis to include three main diagnostic levels; a definite diagnosis: two major or one major and two minor criteria or four minor from different categories; borderline diagnosis: one major and one minor or three minor criteria from different categories and; possible diagnosis: one major or two minor criteria from different categories. Both original 1994 and updated task force criteria are presented in Appendix A.

Presently, a variety of diagnostic tools are used to assess diagnostic criteria in at risk individuals along with monitoring disease progression in diagnosed ARVC patients. Common tests include electrocardiographs (ECGs), Holter monitors, echocardiograms, magnetic resonance images (MRIs), cardiac biopsies and genetic mutation analyses.

Although task force criteria continue to be the 'gold standard' in ARVC diagnosis, Hodgkinson et al. (2013) note that these descriptive diagnostic characteristics prove difficult for the ARVC population in Newfoundland, particularly in areas that lack tertiary testing, and therefore continue to lack sensitivity. Hodgkinson et al. (2013) argue that the descriptive criteria presented by Marcus et al. (2010) would not efficiently diagnose ARVC in the Newfoundland population as many patients present with death in rural areas, often where availability of clinical testing is scarce (Hodgkinson et al. 2013). In these circumstances, Newfoundland subjects would not meet the descriptive criteria required for diagnosis. Furthermore, the necessary diagnostic equipment to test for task force criteria are not available in Newfoundland (Hodgkinson, personal communication, 2014). Historically, diagnosis in this population has proven difficult prior to the advent of genetic testing and the discovery of the *TMEM43* p.S358L mutation.

In order to utilize the wealth of information from family histories (for example, the presence of early sudden death), a unique set of diagnostic and epidemiological criteria for ARVC in Newfoundland families was created that relies heavily on family history and genetic mutation analysis (Hodgkinson et al., 2013). The criteria identify three separate groups of clinical status; (i) Affected; (ii) Unaffected; and (iii) Unknown. Criteria for these diagnostic groups are presented in Table 2.1.

Table 2.1 Clinical and epidemiological diagnostic criteria for ARVC caused by a p.S358L mutation in *TMEM43* in the Newfoundland population

Clinical Status	Criteria
Affected	- One of the following: • Obligate Carrier • SCD under 50 years of age • Cardioversion for VT or VF under 50 years • Genetic Diagnosis: gene mutation (*TMEM43* p.S358L) positive
Unaffected	• Gene mutation (*TMEM43*, pS358L) negative.
Unknown	• Do not fulfill criteria for affected or unaffected (e.g., no gene mutation screening)

2.1.4 ARVC in Newfoundland Families

Some genetic diseases are common in Newfoundland because of the way the province was settled. The current population was derived from a small number of settlers who formed large families that were usually geographically isolated and had limited immigration and migration. This provides the basis for a founder effect: the reduction in genetic variability occurring when a population is derived from a small number of colonizing ancestors (Teare, 2011). This effect is evident in the ARVC population in Newfoundland caused by *TMEM43* p.S358L where all 25 families are known to be genetically linked to a pair (founders) who settled in Newfoundland in 1799 (Hodgkinson et al., 2013).

ARVC was first identified in the Newfoundland population in the 1980s when a patient presented with a known family history of sudden cardiac death (Guiraudon et al., 1983, case #1). An ongoing search has led to the identification of an additional 24 families. One family pedigree alone (family 64) contains over 1200 individuals spanning

10 generations. The genetic investigation into the disease in the province evolved in 1998 when advancements in genetic testing allowed an American research team to link ARVC in Newfoundland families to chromosome 3p25 (Ahmad et al., 1998). Local genetic research on ARVC began in 1997 at Memorial University of Newfoundland, resulting in the discovery of a novel ARVC disease causing p.S358L mutation in *TMEM43* by Merner and colleagues in 2008.

2.1.5 ARVC caused by p.S358L in *TMEM43*

Studies have shown that this genetic subtype is a severe and particularly lethal autosomal dominant (AD) form of ARVC originally described in Newfoundland families, with more recent identification in families from Denmark, Germany and the United States (Milting et al., 2014). Recall that AD inheritance patterns exhibit a 50% risk of inheriting a genetic mutation from a parent, thus children born to an affected parent have a 50% risk of inheriting the disease causing gene and consequently the disease. Therefore all affected individuals must have been born at a 50% risk, and subsequently all persons born to an affected person had to be born at 50% risk. The term used to describe this population from a risk perspective is *a priori 50%* risk (what risk were you born with?). Even though individuals are born *a priori 50%* risk, their risk status changes as per diagnostic criteria established by Hodgkinson et al. (2013) and outlined in table 2.1. Unaffected individuals thus have a risk reduction to 0%, and those affected have a risk status of 1.[4]

Disease progression and disease severity vary greatly between genetic subtypes of ARVC. The disease causing p.S358L mutation in *TMEM43* subtype of ARVC is highly sex-influenced where men experience earlier onset of symptoms, increased disease

[4]Individuals with unknown status remain at 50% risk.

severity and shorter life expectancies (Hodgkinson et al., 2013). A representation of the influence of sex is demonstrated in the findings of Merner et al. (2008) who found the median age at which affected individuals exhibit signs of the disease is 32 years for males and 44 years for females.

In addition to observed differences between males and females, another characteristic of ARVC caused by p.S358L in *TMEM43* is the disease reaches 100% penetrance in affected individuals. This suggests that all individuals with an affected status will develop symptoms of the disease in their lifetime, assuming they live a normal lifespan (or experience premature death resulting from SCD) (Merner et al., 2008). Full penetrance occurs by a median age for males and females at 63 and 76, respectively (Merner et al., 2008). This study also reports a reduced life expectancy in the population; median life expectancy of 41 years for affected males and 71 years for affected females compared to 83 years for both unaffected sexes.

It is therefore evident that the ARVC caused by a p.S358L mutation in *TMEM43* described in Newfoundland families is severe, sex-influenced and causes premature death in both males and females. The *TMEM43* ARVC population in Newfoundland has important significance for research as the heterogeneity of disease characteristics for ARVC caused by other identified mutations makes understanding different aspects of the disease difficult, whereas the *TMEM43* population allows for accurate, robust information for a homogenous disease population.

2.1.6 Clinical Management of ARVC

Individuals at risk for ARVC and those who have developed the disease are subject to a lifetime of clinical monitoring, disease management and treatment to slow

disease progression and prevent serious events, namely SCD (Basso et al., 2009). ARVC treatment is highly individualized given that some patients remain asymptomatic whereas major variations in symptoms are observed between patients. As a result, treatment is based on clinical presentation, risk assessments for SCD and the preferences of patients and physicians.

Regular cardiac monitoring such as ECGs, Holter monitors and echocardiography are used to identify disease progression which is normally sufficient for asymptomatic patients and healthy affected gene carriers, who do not require immediate treatment (Basso et al., 2009; Wichter et al., 2005). Symptomatic patients, however, are subject to various treatment and management strategies including modifications of physical activities, pharmacological and non-pharmacological interventions, and surgery. Modifications to physical activities act to reduce the risk for exercise-induced arrhythmias and SCD. Avoidance or restriction of vigorous physical activity such as competitive sports, regular training, and strenuous exertion involving abrupt physical effort are usually recommended for high risk and previously diagnosed ARVC patients (Basso, 2009; Romero et al., 2013; Smith, 2011).

Likewise, the use of pharmacological and non-pharmacological interventions to reduce cardiac arrhythmias is common in ARVC management. Drugs such as beta-adrenergic blocking agents (also known as β-Blockers) and the use of antiarrhythmic drugs are often prescribed to reduce the frequency of potentially lethal arrhythmias. β-blockers act to suppress stimulation of the heart muscle from the nervous system reducing the heart rate and workload experienced by the heart (Heart and Stroke Foundation of Canada, 2011b). Antiarrhythmic drugs such as *amiodarone*, *sotalol* and *verapamil* slow

the electrical impulses that occur within the heart in an effort to maintain regular heart rhythms (Heart and Stroke Foundation of Canada, 2011a). Commonly, a combination of β-blockers and antiarrhythmic drugs are used either alone or with other non-pharmacological interventions (Romero et al., 2013). Many of the pharmacological treatments for ARVC cause severe side effects, sometimes disrupting the daily lives of patients.

The most widely accepted non-pharmacological treatment for the prevention of SCD in ARVC patients is the ICD (Romero et al., 2013). ICDs are implanted to normalize irregular heartbeats by monitoring heart rhythms and generating electrical shocks when necessary to restore a normal heart rate and rhythm (Heart and Stroke Foundation, 2013a). ICD implantation is used for both primary and secondary prevention of SCD in ARVC patients (Wichter et al., 2005). Primary prevention includes the implantation of an ICD purely for prophylaxis in a patient who is at a high risk for SCD (such as affected gene carriers) but shows no evidence of arrhythmias (Hodgkinson et al., 2005; Romero et al., 2013). Secondary ICD prevention occurs in patients with known arrhythmias or who have experienced an aborted cardiac arrest.

Primary ICD prevention is used for ARVC patients in Newfoundland at high risk for SCD based on their genetic testing result (Hodgkinson et al., 2005). A number of studies support that ICD therapy improves long-term survival of high risk ARVC patients by terminating lethal arrhythmias (Basso et al., 2009; Hodgkinson et al., 2005; Romero et al., 2013; Wichter et al., 2005). This is particularly evident in the *TMEM43* population where ICD implantation is known to significantly improve survival chances (Hodgkinson et al., 2005). It is also important, however, to recognize that ICD implantation is not

without risk. For example, incidents of inappropriate shocks have been reported and as such, the decision to pursue ICD therapy is highly complex.

Many of the previous surgical treatment approaches for ARVC have been replaced by treatment using ICD implantation (Romero et al., 2013). In some cases, a heart transplant becomes the final treatment option for patients who develop severe heart failure or severe recurrent arrhythmias that do not respond to conventional treatment (Calkins & Marcus, 2008). A heart transplant consists of the surgical removal of the diseased heart and its replacement with a donor heart (Heart and Stroke Foundation, 2012). Calkins and Marcus (2008) suggest that few ARVC patients require heart transplant as a treatment for their disease.

For ARVC patients in Newfoundland, all diagnostic procedures including genetic testing and in many cases, treatment and clinical monitoring, occur at the Cardiac Genetics Clinic at the Health Sciences Centre in the City of St. John's. Genetic testing for this population can occur as early as 10 years of age; however, the decision relies heavily on the preferences of the family and the maturity level of the minor. Patients with ICDs receive consistent follow up every six months to one year, whereas those that that do not require ICD intervention are monitored on a bi-annual basis. Diagnosis and treatment strategies for ARVC patients in Newfoundland are highly interdisciplinary and include researchers, cardiologists, psychologists and genetic counselors.

2.2 Qualitative Perceived Economic Burden Of ARVC Study Summary

A single initial qualitative investigation of the perceived economic burden of ARVC is available (Etchegary et al., 2015). This publication was a previous study involving members of this research team and comprises interview data from 21

individuals including those with an affected, unaffected, or unknown clinical status as well as four spouses. Thematic analysis of interview transcripts revealed four major perceptions of how ARVC affected their families: i) Economic impact at childhood; (ii) Impact on current and future employment; (iii) Impact on current and future financial well-being; and (iv) No perceived economic impact.

Findings for economic impact in childhood suggested that although necessities were available like food and shelter, the family often went without "extras." Additionally, children in affected families alluded to having to work in order to supplement their family income, some feeling they had to contribute. Experiences of the impact on current and future employment included the limitations on the types of jobs that could be safely undertaken, time off work for recovery following ICD surgery and narratives that revealed how the quality of work was lessened. There were also experiences of spouses of affected individuals who returned to work earlier than desired to make up for lost income from their family member affected by ARVC.

With respect to finances, participants noted the effect of the ability to work on disposable income, incurring direct costs for treatment for families living outside a main treatment center, in addition to worries about financial planning. Concerns over having enough insurance or obtaining health or life insurance were voiced, while these worries were lessened for those with good insurance plans at work or a supportive employer. A few participants experienced no perceived burden, often those who were asymptomatic or unaffected but acknowledged that progression may bring forth economic burden in the future.

Despite identified study limitations, such as small sample size, this initial novel investigation provides invaluable insight into the perceived economic burden experienced by ARVC patients and families. Results from this investigation provided one major component informing the planning and construction of the perceived economic burden scale used in this study.

2.3 Measures of Economic Burden

The majority of economic studies measure the economic impact of diseases on a macroeconomic scale, such as disease costs on the medical system or society. While few such studies exist on the economics associated with ARVC, there is a limited body of literature consisting of cost-benefit analysis of inherited cardiac arrhythmias (Goldenberget al., 2005) or prevention of sudden cardiac death using ICDs (Deniz et al., 2009). However, for the purpose of this study, these studies are out of scope as they relate to determining optimal treatment costs for the medical system using a macroeconomic approach.

This study takes a microeconomic approach from the perspective of the at risk individual and their family. It is concerned with exploring the perceived economic burden for patients and their families. Costs incurred by the acquisition of health goods and services as a consequence of disease can significantly impact the ability of individuals and their families to purchase and consume other goods and services (World Health Organization [WHO], 2009). Microeconomic studies are important because if people are consuming healthcare, losing money because of a disease or illness, or are unable to obtain insurance, they have fewer resources for other non-medical goods and services such as food, clothing, housing and leisure/social activities. Therefore, the presence of an

economic burden caused by ARVC would affect both individual and family economic welfare defined by the WHO (2009) as the ability to consume non-health goods, services, and leisure activities. Also there is the stress associated with living with this condition. This must pose an enormous, yet difficult to measure burden on individuals and their families.

Currently, there is a limited literature specifically addressing the microeconomic burden of the ARVC population from the perspective of affected individuals. The above mentioned work of Etchegary et al. (2015) remains the only available research on this topic. Despite the lack of research on the microeconomic burden of ARVC, it is possible to extrapolate findings from microeconomic studies related to chronic diseases and other inherited diseases to the ARVC population. Based on the literature review it appears reasonable to conclude that ARVC patients and families will perceive significant economic burdens.

Within the context of a microeconomic approach, various measures of economic burden are reflected in the literature. Suhrcke et al. (2006) propose four main categories in which the health status of individuals relates to the microeconomic environment. First, labour productivity as a means of assessing the effect of health on earnings and wages; second, the effect of health on labour supply including employment, hours worked, and the probability of retirement; education as part of the human capital theory, and savings and investment make up the third and fourth channels where health affects the economics of households, patients, and families.

The categories presented in the work by Suhrcke et al. (2006) are in line with those presented in the WHO guide to identify economic consequences of disease and

injury (WHO, 2009). The WHO guide includes five measurement categories for microeconomic studies including; expenditures on health by households, labour productivity loss, effects on human, physical, and financial capital formation, consumption of home-produced goods and services (non-market consumption), and, consumption of non-health goods and services (economic welfare). Insurance is a common theme discussed throughout the WHO guide, particularly within household health expenditures category. Although some variations in terminology exist, there tends to be consensus within the literature supporting these measurement categories (Bloom & Canning, 2000; Stuckler & Siegel, 2011).

The limited research into the economic burden of ARVC and genetic conditions more generally requires this study to broadly investigate all possible areas for economic burden that could affect individuals who are at risk for, or who are known to be living with ARVC. The economic categories presented by Suhrcke et al. (2006) are the most comprehensive representation of economic burden topics reflected in the literature. These categories, with slight modifications and the addition of themes from Etchegary et al. (2015), provide the basis for the microeconomic measures used in this study. The five measures of economic burden selected for this study are therefore: (i) human capital attainment; (ii) labour supply and productivity; (iii) investment and savings; (iv) financial burden; and (v) insurance.

2.3.1 Human Capital Attainment

Human capital is the term introduced by Shutlz (1961) that suggests an investment in education and training increases an individual's skills and knowledge that, in turn, affect their capabilities to conduct productive work. Shutlz concludes that an investment

in human capital yields an increase in future wages and income. Human capital theory continues to be widely accepted among economists who agree that increased education levels result in increased chances of employment and higher wages/salaries.

Expanding on the notion of investment in education and training, it is likely that choices relating to careers may also contribute to future higher wages/income. As such, these choices, in theory, contribute to human capital investment. Studies exist that demonstrate how education as a component of human capital investment/attainment can be directly affected by health status. No current literature, however, discusses career choices as a component of human capital attainment affected by health uncertainty, and therefore this study is the first, to our knowledge, to include career choices as a component of human capital.

A reciprocal relationship exists between education and health, where a higher level of education is linked to better health status, but also where poor health status is linked to lower educational performance, progress and completion. Most studies on the relationship between health status and education occur at the primary and secondary school levels, ages where ARVC has not normally manifested, nor has testing occurred. As a result, these studies will not be discussed in detail.

A US study conducted by Teachman (2012) demonstrates the influence of health status on education choices in an age group relevant to ARVC. Teachman (2012) followed over 10,600 participants aged 19-21 for a duration of 25 years, collecting data on post-secondary school enrollment and self-reported health status. He argued that the likelihood of post-secondary school enrollment is dependent on the nature of limitations on future work caused by disease. Specifically, he examines the effect on two forms of

limitations; limits on the *kind* of work that can be performed and limits on the *amount* of work that can be performed. He argues that diseases limiting the kind of work that can be performed increase the odds of post-secondary enrollment by approximately 15%. On the other hand, he argues that diseases that limit the amount of work that can be performed decrease the odds of post-secondary enrollment by approximately 25%. ARVC has the potential to limit both the type and amount of work performed by those at risk, yet it is not known which limitation is more prevalent within this population.

Cervellati & Sunde (2005) suggest that the acquisition of human capital is influenced by two main factors - the ability to acquire education and training and life expectancy. As previously discussed, those at high risk for ARVC experience shorter life expectancies, particularly men, yet the impact of ARVC on human capital attainment is not currently reflected within the literature. Oster et al. (2013a) examine how life expectancy influences human capital attainment in Huntington disease patients, a genetic degenerative neurological disease similar to ARVC in its mode of inheritance, the severity of disease, disease penetrance and variable expressivity. One major difference to note, however, is that ARVC has a number of effective treatments (particularly ICD implantation), whereas Huntington Disease has none. Oster et al. (2013a) found that patients who tested positive for the Huntington mutation completed less education and were 30% less likely to complete post-secondary education than those who were not tested or who tested negative for Huntington Disease. Education was not affected when genetic testing occurred at older ages when education is presumed to have been completed.

Age of onset of symptoms is another predictive factor for the education attainment of Huntington disease patients (Oster et al., 2013a). Symptoms beginning in the teenage years decrease the likelihood of enrollment in post-secondary education, whereas those who develop symptoms between 19 and 28 years of age are at the same likelihood of enrolling in post-secondary education as the general population, yet are less likely to complete it (Oster et al., 2013a).

Similar to genetic conditions, heart disease appears to have a restrictive effect on education for those in young adulthood. An Australian study on heart disease patients 25-64 years of age reports that about half of heart disease and cardiovascular disease patients had their education restricted by their condition (Callander et al., 2013). These results, however, reflect combined restrictions on education and employment and therefore may not represent the true effect on education alone.

Concerns over career choices within families with known genetic conditions appear to begin early in life. Parents of children with genetic conditions have concerns about the future employment and career opportunities for their children (Gallo et al., 2007). These concerns reflect the possibility that their children would be limited in the pursuit of certain careers and potential employment limitations caused by their genetic condition.

For ARVC patients, career limitations are likely based on the physical limitations required for the management of disease progression and prevention of SCD. Physical limitations instilled for disease management may result in ARVC patients choosing different professions and/or careers or even require a change in pre-existing careers. To

date, only limited qualitative findings exist to indicate whether education or career choices are impacted for those at risk for, or affected with ARVC (Etchegary et al., 2015).

2.3.2 Burden on Labour Supply and Productivity

Studies discussed below have shown that people suffering from illness and disease work fewer hours, miss more work, leave paid employment, earn less income, and are more likely to retire at younger ages. These factors, commonly referred to as indirect costs, comprise the economic burden on an individual's labour supply (hours worked, employment status, retirement probability) and their labour productivity (wages, earnings and income). Some suggest that the burden of disease on labour supply and productivity is greater than the monetary amounts spent by individuals on the treatment of their disease (Grover et al., 2003; Jonsson, 1996).

2.3.2.1 Illness and Labour Supply/Productivity Burden

Evidence exists that labour supply and productivity can be affected by illness and disease. Pelkowski & Berger (2004) examined the effect of health problems on annual hours worked and wages using data from the United States Health and Retirement survey. Their study used retrospective longitudinal data on employment histories and health experiences to estimate the impact of health on wages and hours worked. Their results indicate that males who are permanently unhealthy earn approximately 5.6% less than their healthy counterparts. Females with similar health statuses earn significantly less with wages 8.9% lower. The opposite effect between sexes is observed with respect to number of hours worked. In this instance, hours worked by males are reduced by a larger percentage than females at 6.1% and 3.9%, respectively. While permanent illnesses

demonstrate an impact on wages and hours worked, temporary health problems have no significant impact on either of these factors for males or females.

Some people may choose to change their employment status from full time to fewer hours to adjust for chronic disease or ill health. Yen et al. (2011) conducted a study on chronic disease patients over the age of 50 to assess workforce participation among older Australians. Of the chronically ill patients studied, 26% indicated that they were working part time. Of those, 12% named ill health as the primary reason for working part time hours.

In addition to evidence that ill health reduces wages and hours worked, people with chronic disease are less likely to be in any form of paid employment. Gannon and Nolan (2003) used cross-sectional data compiled from two Irish surveys to examine the impact of chronic disease on labour force participation for people aged 16 to 64. The probability of labour force participation was 61% lower for males and 52% lower for females whose chronic illness 'severely' affected their daily activities. For males and females whose chronic condition affected their daily activities 'to some extent', the probability of labour force participation was reduced by 29% and 22%, respectively. Not only do these findings indicate that chronic disease affects participation in paid employment, but they also indicate the role that severity of disease plays in the labour force participation of individuals.

Alavina and Burdorf (2008) studied the associations between self-perceived health status and labour participation in ten European countries. Using data from the Survey on Health and Ageing in Europe, Alvina & Burdorf found perceived poor health to be strongly associated with non-participation in the labour force. Only 18% of the Europeans

who reported having poor health remained employed. Poor health, however, is commonly reported in unemployed and retired individuals accounting for 39% and 37% of individuals with these employment statuses.

Smith (1999) suggests that people may choose early retirement as a means to compensate for ill health. The previously discussed study by Yen et al. (2011) on chronic disease patients concluded that 17.3 % of respondents had retired early due to ill health with the average age of retirement being 58 years compared to the normal retirement age of 63. Schofield et al. (2008) report a much higher retirement rate amongst chronically ill Australians. Their study on premature retirement rates using data from the Survey of Disability, Ageing and Careers reports that 46% of chronic illness patients had retired prematurely as a direct result of their condition. These results are supported by a similar Italian study that reported a significant positive association between chronic disease and early retirement (Ranzi et al., 2013).

Contrary to the majority of literature on the relationship between workforce participation, early retirement, and chronic illness, an American study by Miah and Wilcox-Gok (2007) reports an opposite effect. Using retrospective data from the American Health and Retirement Study, they estimated how chronic illness influences asset accumulation and subsequent retirement. Asset accumulation in this study referred to the sum of household assets, social security benefits and expected retirement benefits. As a result of their analysis, they inferred that chronic illness is associated with reduced likelihood of retirement, which they argued is attributable to lower asset accumulation.

Available literature suggests that living with ARVC may contribute to a reduction in wages/income, hours worked or a cessation of employment altogether. Furthermore,

decisions concerning retirement may also be affected. These questions have yet to be studied in ARVC populations; however, the following section presents evidence from diseases with some similar characteristics to ARVC.

2.3.2.2 Evidence in Heart & Genetic Diseases

In the absence of microeconomic studies specific to ARVC, it is possible to draw similarities to existing studies related to other heart and genetic diseases. By examining similar studies of these related chronic diseases, it is reasonable to assume certain trends can be applied to ARVC. A single Canadian study examined the effect of heart disease on labour supply and productivity. Using cross-sectional data from Statistics Canada's National Population Health Survey, Johansen (1999) studied characteristics of the working- age population aged 35 to 64, with and without heart disease. The author reported that only 48% of men with heart disease in the working-age population worked for pay, compared to 83% of men without heart disease. A similar effect was reported for women, where 36% of women with heart disease report working for pay compared to 64% without heart disease. The primary reason for heart disease patients not working is due to recovery from illness connected to their heart disease. Almost one third of heart disease patients (30%) reported being on disability compared to only 6% of non-heart disease patients. Even though not statistically significant, Johansen indicated that 17% of working-age heart disease patients reported being retired, more than double the figure (8%) for those without heart disease.

An Australian study measured various disadvantages experienced by those with heart disease, other circulatory diseases and no health condition. Their study used data on patients 25 years of age and older from the Survey of Disability, Ageing and Careers.

Once adjusted for age and gender, the odds of heart disease patients having low income were twice as high compared to people with no health condition (Callander et al., 2013). It is not surprising then that half of the heart disease patients in their study reported having employment restricted by their condition offering a potential explanation for lower household incomes.

A British qualitative study on the perspectives of patients living with heart failure and their caregivers coincides with quantitative results on the effect of heart disease on labour. Pattenden et al. (2007) interviewed 36 patients and 20 caregivers using semi-structured questions to explore participants' experiences of living with heart failure. It was found that many patients indicate an inability to work, whereas only a limited number of caregivers report having to giving up work.

Few studies have demonstrated the effect of genetic conditions on labour supply and productivity, yet one study reveals that trends in early retirement are similar to those reported in general chronic illnesses. Oster et al. (2013b) conducted a study on behaviors of Huntington disease patients as a result of their genetic mutation results. They report that patients carrying the gene mutation for Huntington disease were more likely to retire early compared to those who did not have the mutation (Oster et al., 2013b).

2.3.2.3 Labour Supply & Productivity Burden in Family Members

Similar to unhealthy patients, healthy family members may also experience a burden on their personal labour supply and productivity as a result of the presence of illness in the family. Studies have indicated spouses and children of ill family members experience labour burden reflected in changes to labour supply and productivity. These burdens are most often reported in literature where healthy family members become

informal caregivers, such as the case for heart failure patients in the Pattenden et al. (2007) study presented in section 2.3.2.2 above.

Not all changes to a healthy family member's labour supply or productivity reflect cases of leaving the workforce to become an informal caregiver. For example, Smith (1999) suggests that even though a decrease in earnings from an ill household member may occur, attempts to compensate for this loss by a spouse increasing their work may occur. Spousal compensation is evident in a study on female spouses of chronic pain patients conducted by Kemler and Furnee (2002) who report a change in labour responsibilities within the family. They indicated that the female spouses increased their employment to make up for the income and productivity losses of their ill spouse. Females have also been shown to have different probabilities of retirement as a result of their spouse's illness. Jiminéz-Martin and Martinez-Grando (1999) reported that a female whose spouse is out of the labour force due to chronic illness has a reduced probability of retirement by 24%.

Contrary to females, a male whose spouse is out of the labour force with a chronic condition has an increased probability of retiring by 13%. This gender trend is also observed with respect to labour supply in a study on spousal reactions to ill health using data from the American Health and Retirement survey. In this study, Charles (1999) reports that males reduce their labour supply substantially when their spouse encounters ill health, whereas females tend to substantially increase their labour supply in similar situations. It appears that the spousal trends reflect that males become caregivers while females become "breadwinners" in response to chronic disease.

2.3.3 Savings and Consumption

Illness and disease are shown to affect both the rates at which people save money (financial planning) and also consume (spend money) health and non-health related goods and services. Financial planning in the form of savings is relatively straightforward; however, consumption in the context of this study focuses on two main concepts; (i) out-of-pocket costs related to ARVC health goods and services; and (ii) general spending habits. Although both savings and consumption appear to be affected by ill health individually, relationships between savings and consumption as a result of ill health are also reflected in the literature below.

2.3.3.1 Ill Health and Savings

A bi-directional relationship between health and wealth is widely recognized within the literature; where ill health affects the accumulation of wealth, and where wealth increases the likelihood of being healthy. Smith (1999) argues that savings decrease as health deteriorates due to a potential reduction in income and increase in expenditure on health and health-related expenses. A direct effect of health on savings exists if a disease forces households to utilize existing or anticipatory savings to finance health expenditures (WHO, 2009).

Historically, some studies exist that link future health uncertainty and savings behaviour, commonly referred to as precautionary saving (Lillard & Weiss, 1997; Palumbo, 1999). More recently, an Italian study by Jappelli et al. (2007) implied that health risk has an important effect on saving rates. Using socioeconomic data from two cycles of the Survey of Household Income and Wealth and self-reported health status data, the authors concluded that people at risk of falling into poor health save more.

Factors such as fewer children and higher income are shown to reduce savings rates, whereas increased health, higher education levels and larger families tend to increase savings rates (Jappelli et al., 2007).

One theory presented by WHO (2009) states that people with good health generally have longer life expectancies and, as a result, the increased likelihood of achieving retirement. They expand on this theory to state that the increased likelihood that a healthy person will reach retirement causes that individual to save more money in order to guarantee income in their retirement. Contrary to good health and longer life expectancies, the WHO (2009) does not indicate whether ill health or a shorter life expectancy would result in fewer savings. The authors did, however, suggest that ill health may lead to possible savings as households account for future healthcare or non-health related needs (precautionary saving).

Schofield et al. (2012a) concluded in their Australian study that people who retire early due to heart disease face long term financial disadvantages compared to people who remain in full time employment. Those who had retired early due to heart disease had accumulated 99.6% less savings by age 65 compared to those who remained in the workforce full time (Schofield et al., 2012a). Their study demonstrated a relationship between early retirement because of heart disease and inadequate accumulated savings.

Based on the current literature, the effect of ARVC on savings remains unknown. Precautionary savings may be evident in the ARVC population as the disease characteristics indicate ill health in all affected individuals, in addition to a known reduction in life expectancy. This study attempts to provide insight into the effect of ARVC on savings.

2.3.3.2 Out-of-Pocket spending on Health Related Expenses

For the purposes of this study, out-of-pocket costs will refer to monetary transactions for medical (hospital services, physician services, drugs, medical devices, homecare) and non-medical (transportation, accommodation) products and services. In the literature, these costs are commonly referred to as direct costs, since they are directly related to the treatment of a disease or illness. Despite public health funding for all, and extended private coverage for many Canadians,[5] most households report having out-of-pocket health expenditures on health care services or products. Out-of-pocket health expenditures reduce monetary resources available for households to spend on non-health goods and services, as well as a reduction of current and future savings.

A recent Statistics Canada article by Sanmartin et al. (2014) revealed that out-of-pocket health care expenditures for Canadian households are increasing, particularly for lower income households. Using annual[6] data from the Survey of Household Spending (SHS) between 1997 and 2009, the authors analyzed out-of-pocket expenditures by income quintiles. They found that out-of-pocket spending increased in all income quintiles for insurance premiums and prescription drugs, with the largest increases occurring in lower income-households. This article demonstrated that Canadians experience a certain level of out-of-pocket costs related to their health, regardless of public insurance and other government assistance programs. What this article does not indicate, however, is the potential differences experienced in households with a family

[5] See section 2.5 for details on public and private insurance
[6] SHS data is collected annually in the 10 provinces, and bi-annually in the territories.

member who suffers from a chronic disease, but it is likely that lower income individuals would be more adversely affected.

McGillion et al. (2008) used data collected on chronic angina patients enrolled in a self-management program in Ontario, Canada to determine the short-term financial impact of their program on their patients. Even though the objective was to demonstrate the impact of an intervention program on costs, they calculated an estimate of the annual cost of illness for chronic angina patients. Total annual out of pocket costs included money paid to health care professionals related to homecare; costs to attend healthcare appointments outside of the home (e.g., travel); angina-related medication; and supplies/equipment related to heart disease. The mean annual out of pocket costs amount to $3,265, ranging from $0 to $40,908. Although their results may not be generalizable outside of their chronic angina patients enrolled in their program, the study is one of few that provide insight into out-of-pocket costs for heart disease patients in Canada.

Conrad et al. (2006) conducted a study to determine the economic burden faced by heart-failure patients from thirteen American outpatient clinics. Both cross-sectional and longitudinal analysis were used to measure health status and perceived economic burden. Their results indicated that 44% of patients perceived their medical costs as creating a significant economic burden. Those patients reporting economic burden were usually younger and more likely to have a lower household income. They also concluded that patients who perceived economic burden reported a lower health status compared to those experiencing no economic burden.

Despite the lack of evidence pertaining to ARVC in this area, out-of-pocket costs for travel, medication or other health related goods/services related to ARVC are incurred

by patients. Such costs have not only been shown to occur but also pose a financial/economic burden in many heart disease patients presented in literature thus far.

2.3.4 Insurance

Insurance coverage provides individuals with protection against major financial losses as a result of illness, disease, disability or death. Within Canada, both public and private health insurance plans exist in the form of a publically funded health care system and private supplemental medical insurance as described in the following sections. Even though a variety of insurance types exist, the focus in this study is public and private medical insurance with additional possible references to life insurance and disability insurance.

2.3.4.1 Canadian Health Care System

In Canada, a publically funded universal health care system is legislated under the *Canada Health Act* (CHA) of 1984. Public funding utilizes a proportion of federal revenue from consumption and income taxes as the main resource for the provision of health care services provided to residents (Hurley & Guindon, 2008). The CHA requires provinces and territories to provide medically necessary health care services to their residents using funds received from the Federal Government through the Canada Health Transfer[7]. In order to qualify for the transfer, provincial and territorial public health care plans must comply with five main principles: public administration, comprehensiveness, universality, portability and accessibility (CHA, 1984).[8]

[7] Health care services funded directly by the Federal Government for First Nations people living on reserves; Inuit; serving members of the Canadian Forces; eligible veterans; inmates in federal penitentiaries; and some groups of refugee claimants (Health Canada, 2012b).
[8] Descriptions of the five main principles can be found in Appendix B.

Physician and hospital services fall under the umbrella term "medically necessary" health care services, which are required to be publically funded. All physician costs (consultation, laboratory tests, administration of medication, treatment etc.) as well as in-hospital costs (standard accommodation, food, equipment, non-physician care) are publically funded services nationwide. In addition to the coverage of services noted above, provinces and territories have the option to either partially or fully fund additional health services for their residents. Coverage of such supplemental services is usually targeted towards certain groups such as seniors, children or low-income residents and often includes out-of-hospital prescription drugs, ambulance costs, dental and vision care, medical equipment and various health professional services (Health Canada, 2012a).

Even though provincial healthcare plans cover many of the healthcare costs, public funding only accounts for 70% of the total health expenditure in Canada (Paris et al., 2010). Private payers composed of patients and private health insurance companies incur all remaining health expenditures contributing 14.9% and 12.8%, respectively (Paris et al., 2010). Private health expenditures include costs for out of hospital prescription/over the counter drugs, medical equipment, dental and vision care, private health professional services (physiotherapy, dentistry, specialty nurse etc.) in addition to medically related transportation and accommodation costs.

Generally, additional provincial government subsidies are available to supplement provincial public health plans, with observed variations between provinces. In the case of Newfoundland and Labrador, the Department of Health and Community Services offers a variety of financial assistance programs to prevent catastrophic financial spending on health services. These programs commonly require specific qualification criteria, usually

demographic characteristics, such as specific age or income groups. Provincial programs in Newfoundland potentially available to ARVC patients include: Prescription Drug Programs, Medical Travel Assistance Program; and Special assistance program – Medical equipment and supplies (Government of Newfoundland and Labrador, 2014). Even though utilization of these government programs is not directly measured in this study, they represent important considerations in the overall financial burden of ARVC as possible protective factors.

2.3.4.2 Private Medical Insurance

In addition to public insurance, 67% of Canadians are enrolled in extended private health insurance plans (Paris et al., 2010). The primary role of private insurance is to provide complementary coverage for services not covered by the publically funded health care system. Approximately 91% of extended health care insurance coverage in Canada is offered by way of a group plan such as part of an employee benefits package in which many employers pays insurance premiums[9] (Canadian Life and Health Insurance Association [CLHIA], 2013). It is possible, however, for those who are self-employed, unemployed or without group plans to purchase an individual insurance plan, usually at significantly higher premiums (Hurley & Guindon, 2008). In addition to elevated premiums, individual extended health plans often exclude expenses incurred as a result of pre-existing medical conditions (CLHIA, 2012).

Extended healthcare plans range in their coverage of eligible expenses yet typically do not pay 100% of the covered costs. Normally, plans require a deductible (commonly $25-$50, per individual), a co-pay (usually 10-20%) and/or limit the

[9] Premiums refer to rates charged for insurance coverage

maximum monetary amount an insured member can claim for a given time period (CLHIA, 2012). Depending on the type of plan, eligible expenses consist of various combinations of costs for prescription drugs, semi-private or private hospital accommodation, special nursing services, ambulance services, medical appliances or equipment, medical services excluded from government plans (e.g. services from chiropractors, physiotherapists, optometrists etc.), and vision care (CLHIA, 2013).

The exact methodology used by insurance companies to calculate individual amounts paid for premiums, deductibles, co-pays or maximums is highly proprietary. It is likely, however, that factors such as age, health status, medical history and assessment of "risk" for the insurance company, factor into premium rates. It is important to note that no federal or provincial regulation exists in Canada to control the premiums that private insurance companies can charge for health insurance (Hurley & Guindon, 2008). In addition to the potential for elevated premiums, previous medical histories may also affect eligibility for health insurance, rendering the purchase of private health insurance increasingly challenging for some individuals.

2.3.4.3 Life Insurance

Approximately 22 million Canadians are enrolled in a life insurance policy (CLHIA, 2015b). Although a variety of life insurance policies exist such as term or whole life insurance, the purpose of life insurance is to protect families against financial hardship in the event of death (CLHIA, 2015a). The provision of life insurance is similar to previously discussed private medical insurance as both individual and group coverage are available, yet the focus of assessment is on mortality rather than illness or disease. Insurance companies make long term projections based on statistical or actual experience

of mortality rates suggesting the risk for future expense and to calculate interest rates (CLHIA, 2015a). Like extended medical insurance, risk stratification remains highly proprietary and depending on the risk stratification of an individual, they may be required to pay higher premiums or be denied life insurance.

2.3.4.4 Genetic Discrimination

Genetic discrimination refers to the discrimination against an individual or members of their family on the sole basis of actual or perceived genetic differences rather than physical features (Billings et al., 1992). Discrimination can occur with respect to employment, medical, life and other types insurance, and even socially. For our study, genetic discrimination is mostly assessed on the basis of medical/life insurance, and is the focus of this review.

Currently, no legislation exists in Canada that protects individuals specifically against genetic discrimination despite wide recognition of the issue and precedents set internationally. In fact, Bill C-508, which was introduced in 2010 proposing amendments to the *Canadian Human Rights Act* to include genetic characteristics as a prohibited grounds for discrimination did not pass. Internationally, many countries have enacted laws to protect or limit the use of genetic information for insurance purposes. For example, in the United States, the *Genetic Information Nondiscrimination Act* (GINA) enacted in 2008, protects individuals against genetic discrimination with regards to employment and health insurance (U.S Department of Health and Human Services, 2008). In the Canadian context, Pullman and Lemmens (2010) argue that the provision of essential health services under the current public health care system does not warrant a need for statutes such as GINA at this time in Canada. They do, however, recognize that

genetic technology could be used inappropriately to affect at-risk individuals in contexts such as life or disability, or additional health insurance. It is important to note that the GINA statute does not prohibit discrimination with regard to life or disability insurance.

In a position statement on genetic testing, The Canadian Life and Health Insurance Association (CLHIA) indicated that the policy of the Canadian private healthcare or life insurance industry does not require an insurance applicant to undergo genetic testing (CLHIA, 2010). Conversely, this does not prevent such practices nor does it prevent the use of pre-existing genetic information. For example, the CLHIA recognizes the use of pre-existing genetic test results by insurance companies as equivalent to information pertaining to family history.

2.3.4.5 Genetic Discrimination in the Literature

No studies were found on cases of genetic discrimination for ARVC patients or related inherited cardiomyopathies. Huntington disease was one of the first genetic conditions utilizing genetic testing and as a result is the focus of much of the literature in this area. A Canadian cross sectional study of asymptomatic Huntington patients by Bombard et al. (2009) used self-reported data to assess perceived genetic discrimination. Genetic discrimination was perceived by about 40% of Huntington respondents. The majority of discrimination was in relation to insurance where 29% of respondents perceive genetic discrimination; other areas indicate discrimination by family (15%) socially (12%) and less often in employment/healthcare. Insurance discrimination is described in the form of insurance rejection, premium increases, or requests to take predictive tests. The study also reports that the main reason for discrimination is family

history, where a significantly smaller proportion of respondents attribute their discrimination to actual genetic test results.

For Huntington patients in Australia, Canada and the United states, genetic discrimination is reported by 26% when trying to purchase any type of insurance, while over 70% patients worry about being denied insurance (Erwin et al., 2010). This study also confirmed that discrimination occurs because of genetic test results and family history of the disease. Another study conducted by Bombard et al. (2011) on Huntington disease patients used cross sectional data to explore the factors associated with having experienced genetic discrimination. Factors that increased the likelihood of genetic discrimination included higher education, risk identification at a younger age and a mutation positive status.

More than half of the parents of children with genetic conditions raised concerns in a qualitative study over health insurance, stating issues of having claims denied, reaching lifetime maximums and not being able to obtain insurance because of pre-existing conditions (Gallo et al., 2008). This concern was also mirrored with respect to life insurance for this population.

ARVC patients may encounter elevated insurance premiums as well as the denial of medical or life insurance on the basis of genetic discrimination or reported medical/family history. It seems possible to expect these findings in the ARVC population based on reported evidence from other genetic conditions such as Huntington Disease. Many similarities exist between Huntington Disease and ARVC, yet perhaps the most important similarity to note is that both are genetic conditions identifiable with

available genetic testing. It is therefore expected that the ARVC population will experience similar problems with purchasing medical or life insurance.

2.4 Summary

ARVC is a severe and often lethal inherited disease of the heart muscle with variable disease progression affecting approximately 1 in 2000-5000 in the general population. The disease is likely more common in Newfoundland families where the disease is caused by a p.S358L mutation in the *TMEM43* gene. This disease is known to cause a variety of symptoms in affected patients, the most notable of which is SCD. ARVC caused by a p.S358L mutation in *TMEM43* is highly sex-influenced where men experience more severe symptoms at earlier ages in addition to significantly reduced life expectancies in the absence of treatment. Advancements in both diagnostic criteria and techniques such as genetic mutation analysis have enabled the early detection of the disease in at risk populations, allowing clinical management of the disease using medications, ICDs and sometimes surgery.

There is a significant gap in existing literature pertaining to the economic burden experienced by ARVC patients and their families. Previous qualitative work by members of this research team has identified perceived burden for ARVC patients including experiences beginning in childhood, employment limitations and disruptions, financial concerns and problems with insurance. Despite the limited research into the microeconomic burden of ARVC, it is possible to extrapolate findings from studies on conditions with similar disease characteristics to ARVC when determining the possible economic burdens experienced by this population. Relevant literature indicates that chronic disease, ill health, health uncertainty, life expectancy, and genetic predisposition

are all contributing factors to changes or burdens within the economic measures used in our study. These measures include (i) human capital attainment; (ii) labour supply and productivity; (iii) consumption and savings; (iv) financial burden and (v) insurance.

Any perceived economic burden experienced by ARVC patients and their families has the potential to disrupt various aspects of their lives and contributes an additional burden to families already facing a severe and fatal disease. It is therefore imperative to conduct research in this area. Available literature on the various economic burden areas being examined in this study provide sufficient evidence to indicate a possible economic burden experienced by ARVC patients and their families. This study attempts to address the significant gap in literature on the economic burden of ARVC on individuals, families and households.

Chapter 3: Methods

3.1 Survey Instrument

Objective one of the study was to develop a survey tool to collect data on the perceived economic burden of ARVC caused by the p.S538L mutation in *TMEM43* in the Newfoundland population. Survey instrument development began with the identification of general themes and topics thought to contribute to perceived economic burden based on prior qualitative interviews with ARVC families (Etchegary et al., 2015). Findings from this study were used to identify general topics and themes pertaining to economic burdens experienced by participants.[10] The qualitative data focused on participants' thoughts about growing up with ARVC in their families or marrying into a family with a history of ARVC and how this influenced their family's spending, education and career choices and other economic factors.

The study conducted by Etchegary et al. (2015) found that most families could afford necessities such as food, clothing or shelter but identified a lack of disposable income for non-essential spending ranging from toys or entertainment supplies to family vacations or buying brand named. They recalled how their unaffected parent (usually their mother) had to take on extra work as a result of the loss of income from their affected father. As adults, participants noted how ARVC affected their ability to work, and as such, their disposable income. Similar to findings in parents, spouses of affected individuals indicated having to return to work or increase work hours to compensate for a reduction in family income caused by their affected spouse's work limitations. Other participants discussed the expense of managing ARVC, particularly those who had

[10] A detailed summary of this investigation is presented in Section 2.2

to travel to the Health Sciences Centre in St. John's for treatment, appointments, and following a cardiac event (e.g a shock from their ICD). Finally, others noted their difficulty securing additional life or health insurance and their worry for their children's eventual ability to do so.

The approach to participant consultation in survey development was the use of existing qualitative data from Etchegary et al. (2015). [11] In addition to pre-existing qualitative data, topic development focused on consultation with various clinicians who provided patient experiences from anecdotal evidence. Finally, literature was explored to supplement, structure and finalize topics leading to the drafting of survey items. Once survey items were drafted, additional input was sought from various experts in the field resulting in minor changes to content, question structure, and editorial changes. The final version of the survey was reviewed and agreed upon by the academic supervisory committee.

A five point Likert scale was selected as the most appropriate to provide self-reported descriptive data. Higher scores indicate a greater perceived burden. Data gathered by the survey instrument reflected topics in areas such as perceived burdens, experiences and beliefs pertaining to education and career choices, indirect and direct costs, insurance, and finally finances, all related to a respondent's personal and familial risk for ARVC.

[11] Direct consultation with participants specific to this quantitative study was not conducted due to the pilot nature of the project, ethical considerations of the known research burden within this population, and academic time constraints.

The final survey instrument comprised eight sections (education choices, career choices, personal indirect costs, indirect costs for other family members, income, direct costs, insurance, and finances/spending) with a total of 76 items.[12] Respondents were also given the opportunity to respond to an open-ended question on the final page of the survey instrument that facilitated the collection of any information they believed to be pertinent to economic burden not covered by the existing questions. The final component to the survey was a five-question demographic sheet collecting information about respondents on their education level, employment status, marital status, number of children and income. The survey was estimated to take respondents approximately 20-30 minutes to complete.

3.2 Study Population

A Cardiac Genetics Clinic located at the Health Sciences Center in St. John's Newfoundland, manages the testing and treatment of families at risk for ARVC. As such, there is an extensive, previously established population from which a sample was selected. The ongoing clinical research of ARVC in Newfoundland for over 30 years has identified 25 family pedigrees expressing ARVC caused by the p.S538L mutation in the *TMEM43* gene. These 25 families account for 885 individuals all of whom were born at an *a priori* 50:50 risk of inheriting ARVC causing P.S538L mutation in *TMEM43*. Both research and clinical information for these individual family members are maintained in a database, which for the purpose of this study will be referred to as the ARVC *TMEM43* registry.

[12] Readability level of the survey was determined using Microsoft Word © readability function with a Flesch-Kincaid Grade level score of 8. Refer to Appendix C2 for original survey and demographic sheet content.

Purposive sampling utilizing the pre-existing ARVC *TMEM43* registry was the method selected to identify a population from which to sample. The registry contained a total of 885 individuals from 25 families who were further screened based on ascertainment and other inclusion criteria. Individuals from four newly identified families (n = 34) were excluded from the sample based on considerations of them coping with a new diagnosis and the limited amount of data available for these individuals. All potential participants were born at an *a priori* 50% risk of inheriting the ARVC causing p.S538L mutation in *TMEM43* and were also limited to well-ascertained individuals (n = 699) where the clinical status (either affected or unaffected) of ≥ 50% of siblings was known (Hodgkinson et al., 2013).

Those who were poorly-ascertained (n = 152), where clinical status was known for < 50% of siblings were excluded from the study (Hodgkinson et al, 2013). Both males and females were included in the study and the minimum age for participation was 14 years. Individuals born at a risk other than 50% of inheriting the ARVC causing mutation are not part of the dataset, so are not included. Well- ascertained individuals known to be deceased (n = 214) were also excluded from the population. Ascertainment data is presented in figure 3.1. Furthermore, to be included in the analysis participants must have returned their surveys within the given data collection period of December 1, 2013 to May 30, 2014.

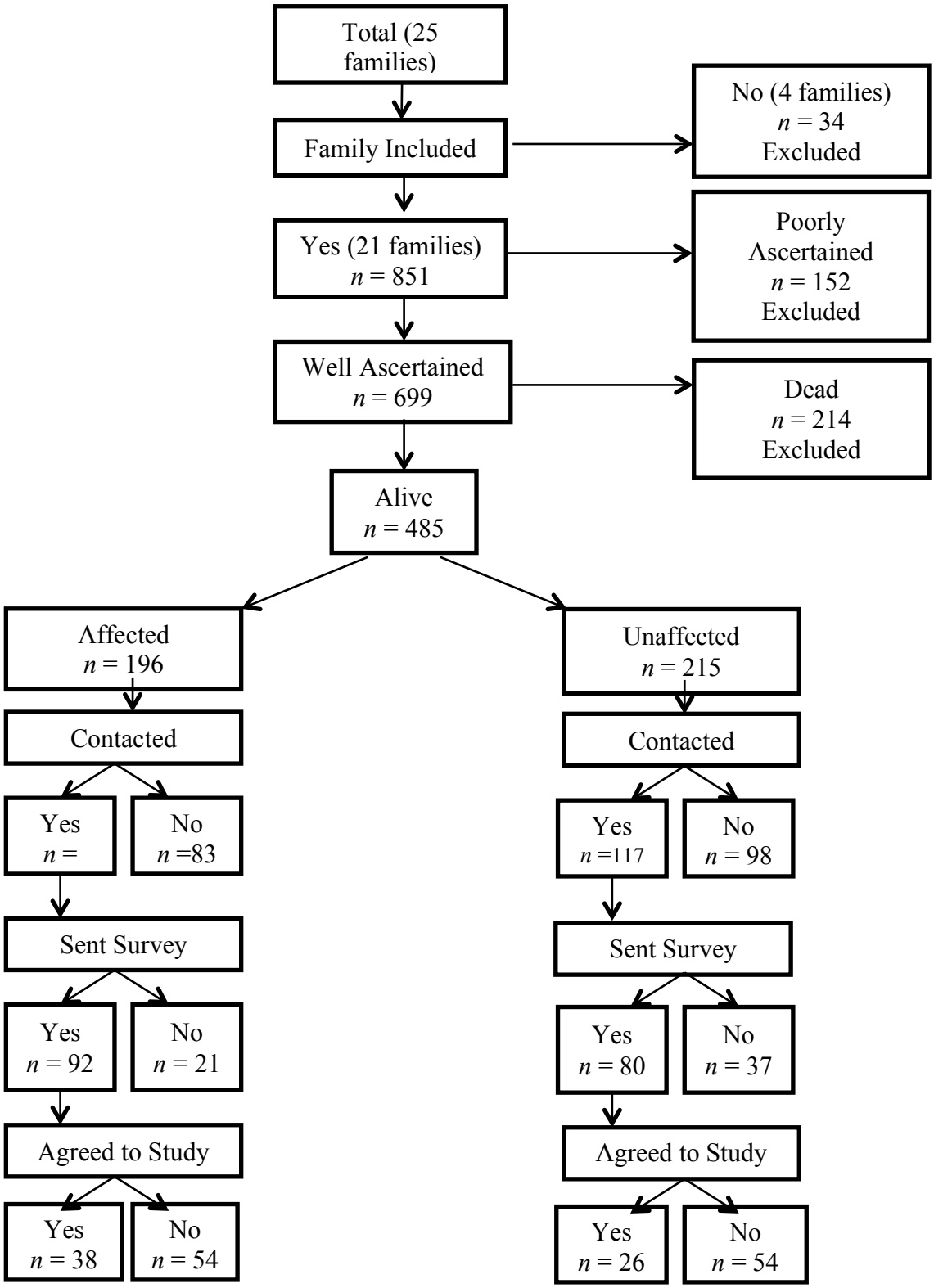


Figure 3.1 Ascertainment, sampling and data collection occurring between December 1, 2013 and May 30, 2014

3.3 Recruitment

Well-ascertained individuals meeting inclusion criteria (n = 485) were randomly selected from each clinical status group (affected, unaffected and unknown), representing approximately half from each group. Potential participants were contacted by phone either directly by someone with a pre-existing clinical relationship with the family, or on behalf of a clinician by a researcher involved with various ARVC research projects. Those opting to receive study documents were then given the option to receive the surveys either by mail or electronically in fillable PDF files through email.

A total of 230 affected and unaffected individuals representing half from each clinical status group were contacted and invited into the study. The justification to only invite half of the eligible population was determined based on time constraints of the academic program, and to isolate the other half of the eligible population for future study using the preliminary validated perceived economic burden scale produced by this study.[13] Of the individuals contacted, 172 agreed to participate and receive study documents. A summary of the number of individuals contacted based on clinical status is presented in figure 3.1.

3.4 Data Collection

Survey packages were sent to participants either by mail or in electronic format by email based on participant preference. All packages contained a consent form, the economic impact of ARVC survey, a demographic sheet, and a survey for a related study

[13] Please note this is an already oversampled population, therefore only contacting half of the eligible population was purposefully chosen in order to reduce the risk of research burden.

on the psychosocial impact of ARVC.[14] Refer to Appendix C for a copy of the original study documents. Additionally, mail packages included a self-addressed postage paid envelope for participants to return their completed surveys. To maximize response rate, follow up calls were conducted approximately three weeks following the distribution of the survey packages, and an additional mail out to all email participants was also completed following problems with document compatibility. Data collection occurred from December 1st 2013 to May 30, 2014.

3.5 Secondary data from the ARVC TMEM43 registry

The ARVC *TMEM43* registry was created in 2004 as a means of tracking individuals and families that were at risk of developing the ARVC condition. This effort was undertaken to establish not only patient records for this population but also as a means to readily access data on this population for research purposes.[15] The registry continues to be a working research dataset for research projects targeted towards the *TMEM43* population. In total there are over 1500 variables for each patient containing information such as demographics, diagnostic procedures and results, pharmaceutical treatments, cardiac interventions, cardiac events, hospital and clinic visits, and clinician notes. For the purpose of this study, the registry was used to identify the study sample but was also a source of secondary data for information on participant age, sex and ARVC clinical status.

[14] The 20-30 minute time estimate for survey completion stated in Section 3.1 was for the economic survey only, and not the related psychosocial survey.
[15] This approach to a genetic registry system was based on Emery et al. (1972) and Emery & Brough (1978) and the World Health Organization

3.6 Data Management

Data were entered into a de-identified copy of the ARVC TMEM43 registry and analyzed using SPSS® statistical software (Version 22). Study participants responses were coded using unique identification numbers already established within the ARVC *TMEM43* registry. Each Likert survey item was coded using its respective score from 1 (strongly disagree) to 5 (strongly agree), binomial responses were coded as 1 (yes) to 2 (no) and all N/A (not applicable) responses were coded with a numerical value of 6 and excluded from mean calculations. Open-ended responses were transcribed as string data in text format and all demographic responses were coded with unique numerical values. [16]All missing data was entered using a numerical value of -99 and were excluded from analysis. To improve data accuracy, each entry was cross-referenced twice with the original survey and descriptive statistics were run on each item to ensure no invalid values were entered.

3.7 Scale Construct

The second objective of this study was to construct and provide some initial validation data on the Perceived Economic Burden (PEB) of ARVC scale. The construct of the scale began with the assignment of the original 76 survey items into the five measures of perceived economic burden reflected in the literature to create five hypothesized subscales[17]. The five hypothesized subscales are: (i) human capital attainment (HC); (ii) labour supply and productivity (LSP); (iii) consumption and saving (CS); (iv) financial burden (FB); and (v) insurance (IN). Initially, survey items were

[16] Analysis was not performed on the open-ended string data. Rather, this data will be used to inform future studies by members of the research team.
[17] Refer to Table F1 in Appendix F for the assignment of original survey items into hypothesized subscales.

divided into the eight separate sections to increase readability and simplicity for respondents. The grouping of survey questions into the five subscales increased reliability values of the survey items in addition to reflecting those presented in the literature.

Original survey items were examined for face and content validity for each hypothesized subscale and distributed accordingly resulting in the exclusion of seven original survey items determined to be independent items. The process of item reduction occurred through consultation between the author and members of the supervisory committee until a consensus was achieved. Furthermore, all binomial survey items were excluded from the hypothesized scales for separate analysis. All items in each subscale were examined to ensure all were scored in the same direction (i.e., higher response value indicated greater burden), which resulted in the reverse coding of one subscale item (IN1). The final step prior to scale validation involved the summation of subscale item scores, and the calculation of multi-item mean scale scores. The result was a subscale score for each participant ranging from 1 to 5.

3.8 Statistical Analysis

3.8.1 Survey Response Rates & Representativeness of Sample

Response rates for the survey were calculated based on the number of respondents with completed surveys and consent forms. Those with incomplete consent forms or blank surveys were excluded from the final sample. Demographic characteristics of the final sample population were calculated based on complete demographic sheets and secondary data obtained from the ARVC *TMEM43* registry.

Descriptive and frequency statistics were calculated to determine the demographic information of the study population. Chi-square test for independence was performed to

determine the representativeness of the study population. The purpose of a Chi-square test is to explore the relationship between two or more categorical variables (Pallant, 2010, p.215). Using Chi-square tests, select demographic data on all individuals who met inclusion criteria were compared to the demographic data of the final sample population. Two chi-square tests were conducted to determine representativeness of the sample with respect to clinical status and sex. These demographic variables were selected on the basis of the completeness of data. A variable would be representative of the original population if a significant difference ($p < .05$) between the original and final sample was not observed. Tests for representativeness of a population are useful to determine the generalizability of the study results.

3.8.2 Scale Validation

Validation of the scale followed work based on Ware and Gandek (1998) and used by others in the testing of scales[18]. All statistical tests for scale level assumptions were conducted using SPSS© version 22. The purpose of scale validation is to provide an evaluation of the evidence to support the appropriateness, meaningfulness and usefulness of the inferences that can be made from an instrument score (Zumbo & Chan, 2014).

3.8.2.1 Item level descriptive statistics and subscale score calculation

The first step in the scale validation involved the calculation of item level descriptive statistics for each survey item to determine the amount of missing data, frequency of responses, item means and standard deviations. It is expected that scales have only a small amount of missing data, all response choices are utilized for each item, item means are roughly consistent within each scale item and standard deviations are

[18] See Watkins et al., 2013; Radwin et al., 2005

roughly equivalent and around 1.0 for a five-choice Likert response scale (Ware & Gandek, 1998).

As previously discussed in Section 3.7, multi-item scale scores were computed as a mean scale score based on response values from individual items within each hypothesized scale. A mean score was used as opposed to a summated scale score based on the amount of missing data for individual items and for ease of comparison between scales.

3.8.2.2 Tests for Likert scale assumptions

The second step in scale validation involved the creation of a multitrait/multi-item correlation matrix to examine the relationship of each item to its hypothesized subscale in addition to other subscales (Ware & Gandek, 1998). A multitrait/multi-item matrix approach tests three Likert scaling assumptions: (i) item internal consistency; (ii) equality of item-scale correlations; and (iii) item discriminant validity. Item internal consistency tests the assumption that items should be linearly related to the overall subscale concept being measured, and is tested by comparing the correlation of each item score with its corresponding overall scale score (computed using the mean scores of all items within a given scale). A substantial and satisfactory item internal consistency is considered a correlation of 0.40 of an item with its hypothesized scale (Ware & Gandek, 1998).

Assumption two, equality of item-scale correlations, tests that scale items contribute roughly equal proportions of information to total scale score. This assumption was tested by visually inspecting the multitrait/multi-item matrix to determine the extent of equality between the correlations of items and their hypothesized subscales. This standard is satisfied if all items contribute substantially to the total scale score even if

item-scale correlations vary. Ware & Gandek (1998) suggest that it is satisfactory for item-scale correlations to vary (e.g., from 0.40 to 0.70) across the same scale.

The third Likert scale assumption, item-discriminant validity, tests the extent to which each item measures concepts other than what it is expected to measure, ultimately determining the integrity of the hypothesized item groupings into scales. This assumption was tested using the multitrait/multi-item correlation matrix to compare the correlation of an item with its hypothesized scale to the correlation of that same item with all other scales in the matrix. Item discriminant validity is supported if the correlation between an item and its hypothesized scale is significantly higher than its correlation with all other scales in the matrix. The significance level for correlation comparison is approximately a 95% confidence interval determined using two standard errors which is equal to 1 divided by the square root of the sample size. The number of item-discriminant tests is equal to the number of items in a scale multiplied by the number of scales in the matrix minus 1.

3.8.2.3 Test for Scale Reliability

The third step in the validation process involved establishing reliability of measurement for each subscale. Ware & Gandek (1998) describe reliability of measurement as the extent to which the measured variance in a score reflects the true score and not random error. Simplified, the definition of reliability of a subscale is the extent to which the measures give consistent and accurate results. Item internal consistency, determined by Cronbach's alpha coefficients, was selected as the method to determine reliability of subscales. Cronbach's alpha coefficient calculation takes into account the number of scale items and item homogeneity (Cronbach, 1951). Cronbach's alpha coefficients were calculated for the five hypothesized subscales to determine their

internal consistency. Literature suggests that an acceptable Cronbach's alpha coefficient value for group level comparison is 0.70 (Nunnally & Bernstein, 1994).

3.8.2.4 Correlations between Scales (Validity of PEB Scale)

The final step in the validation process involved the evaluation of each subscale to determine if each subscale was making a distinct contribution (unique reliable variance) to the overall PEB scale. To determine the validity of the overall PEB scale, correlations between the five subscales were compared with reliability estimates (Ware & Gandek, 1998). A subscale is making a distinct contribution if its correlations with the other scales are less than its own reliability coefficient (Guilford, 1954). Correlations between two scales that have equal reliability coefficients indicate the possibility of scales performing like alternate measures of similar concepts (Ware & Gandek, 1998). Ware & Gandek (1998) suggest that factor analysis may also be performed to further test construct validity; however, as a larger sample size is a requirement for factor analysis it was not conducted[19].

3.8.3 Empirical Analysis

3.8.3.1 Regression Technique and Analysis

Multiple linear regression is a technique for examining the relationship between independent variables (referred to as predictors) and a single continuous dependent variable (Aiken, West & Pitts, 2003). Multiple linear regression is typically used to explore and maximize prediction for independent variables (Pedhazur, 1997). For this study the five mean scale scores (HC, LSP, CS, FB, IN) were selected as continuous variables for regression analysis, and as such five distinct regression analysis were

[19] Final sample size for this study n = 64

conducted. Mean scale scores could range from a minimum of 1 to a maximum of 5; an increase in the value of the score is associated with an increased perceived burden.

The suggested practice for the selection of the number of independent variables in multiple regression analysis is one independent variable per 15 respondents (Stevens, 1996, p.72). Due to the pilot and the exploratory nature of the study a larger than normal number of independent variables was selected for regression analysis to determine which predictors may account for the variation in scale scores. Predictors were chosen based on variables that were indicated in literature and also from preliminary data analysis such that predictors with low correlations with the dependent variable were not included in regression models.

Demographic variables were used to suggest potential predictors of perceived burden. Predictor variables for regression analysis included sex, clinical status and various demographic variables either collected as part of the study or contained within the *TMEM43* data registry. Many of the demographic predictor variables were re-grouped into a smaller number of categories and transformed into binary variables to simplify regression model interpretation. The coding for binary variables consisted of a coding value of 1 for the category of interest and 0 for all other categories within a given predictor type. A value of 1 indicates the presence of the specific predictor attribute; conversely, a value of 0 indicated the absence of a predictor. Predictor variables used in the study's regression analyses are presented in Table 3.1.

Table 3.1 Predictor variables used in multiple regression analysis.

Predictor Type	Category/Description	Variable Name	Coding*
Clinical Status/Sex	Affected Male	Affectedmale	AA = 0 AP = 1
	Affected Female	Affectedfemale	AA = 0 AP = 1
	Unaffected Male	Unaffectedmale	AA = 0 AP = 1
	Unaffected Female	Unaffectedfemale	AA = 0 AP = 1
Age	N/A	Age	Continuous variable
Children	Has Children?	Haschildren	0 = no 1 = yes
Education Level	Some High School (HS) or HS diploma	eduuptoHS	AA = 0 AP = 1
	Some or completed post secondary education	Edupostsecondary	AA = 0 AP = 1
Employment Status	Employed either full time or part time	employed*	AA = 0 AP = 1
	Retired or unemployed	unemployed_retired	AA = 0 AP = 1
Income	Household Income less than $50,000	incomeless50	AA = 0 AP = 1
	Household income greater than $50,000	incomegreater50	AA = 0 AP = 1
Marital Status	Single or divorced	single_divorce	AA = 0 AP = 1
	Married or living with partner	married_livingwithpartner	AA = 0 AP = 1
Missing Demographics**	Respondents with missing demographic information	missing_dem	AA = 0 AP = 1

* AA = Attribute absent ; AP = Attribute present

** Respondents with missing demographic information were assigned modal values for demographic information

In order to validate the multiple linear regression analysis, a number of assumptions regarding the data must be met, such as tests for multicollinearity, normality, homoscedasticity and independence of residuals (Pallant, 2010, p.150). Tests for multicollinearity examine the relationships between predictor variables to ensure that these variables are not highly correlated. To satisfy the multicollinearity assumption, both Tolerance scores and Variance Inflation Factor (VIF) values were examined for each regression model. To satisfy the multicollinearity assumption, Tolerance scores should exceed 0.10 and VIF values should be greater than 10 (Pallant, 2010, p.158).

Normality and linearity assumptions require that residual values be relatively normally distributed and have a straight-line relationship with the predicted dependent variable score. These assumptions were tested for each of the regression models by visual inspection of the Normal Probability plots. The normality and linearity assumptions are not violated if the residual points lie in a reasonably straight diagonal line from the bottom left to top right of the Normal Probability Plot (Pallant, 2010, p.158). Finally, tests for homoscedasticity assumptions are used to determine if the variance of the residuals about the predicted scores are the same for all predicted scores. Homoscedasticity assumptions were tested by visually inspecting the residuals scatterplot for each regression where all residuals should be roughly rectangular distributed and concentrated in the center around the zero point (Pallant, 2010, p.158).

Regression analysis was conducted on the five subscales representing the five selected areas of economic burden. Table 3.2 presents variables selected for each of the regression analyses including reference groups for the dummy variables.

Each regression model was examined to determine the proportion of variance explained in the dependent variable by the distinct combination of predictors (R square value). The test of significance for the R square value is represented by the p value presented in the ANOVA table. Regression coefficients (B values) were subsequently examined to determine significant predictors for each subscale mean score as indicated by the p value.

Table 3.2 Variables selected for regression analysis.

Sub Scale	Dependent Variable	Predictors (Independent Variables)	Reference Group
Human Capital (HC)	HC mean scale score	affectedmale, affectedfemale, unaffectedfemale, edupostsecondary, age haschildren unemployed_retired missing_dem	} unaffectedmales eduuptoHS employed
Labour Supply and Productivity (LSP)	LSP mean scale score	affectedmale, affectedfemale unaffectedfemale age haschildren incomegreater50 married_livingwithpartner missing_dem	} unaffectedmales incomeless50 single_divorce
Consumption and Savings (CS)	CS mean scale score	affectedmale affectedfemale unaffectedfemale haschildren incomegreater50 unemployed_retired eduuptoHS missing_dem	} unaffectedmales incomeless50 employed edupostsecondary
Financial Burden (FB)	FB mean scale score	affectedmale affectedfemale unaffectedfemale	} unaffectedmales

Sub Scale	Dependent Variable	Predictors (Independent Variables)	Reference Group
		haschildren unemployed_retired incomegreater50 age missing_dem	employed incomeless50
Insurance (IN)	IN mean scale score	affectedmale affectedfemale unaffectedfemale haschildren unemployed_retired incomegreater50 age edupostsecondary missing_dem single_divorce	} unaffectedmales employed incomeless50 eduuptoHS married_livingwithpartner

3.8.3.2 Chi-Square tests for Independence Technique and Analysis

Chi-square tests explore the relationship between two or more categorical variables (Pallant, 2010, p.217). The test measures how observed cell counts in cells diverge from predicted values, where a large difference between expected and observed counts is indicative of a significant relationship. Chi-square statistics were selected for the analysis of all binomial survey items. A 2x4 table was used to determine whether a relationship between clinical status/sex and item responses was present. Tests were on the following survey items: Ind13, Ind14, Ind15, Ind16, Indof8, Insur7 and Insur8 (Figure C1, Appendix C). Clinical status/sex categorical variables were affected males, affected females, unaffected males and unaffected females.

3.9 Data Merger and Storage

The original de-identified version of the dataset was merged with the original *TMEM43* registry dataset for storage of data for 20 years[20]. Hard copies of the consent forms and all survey questions were stored separately in a locked filing cabinet in a secure office at the Health Sciences Centre campus of Memorial University of Newfoundland.

3.10 Ethics Approval

This study received ethics approval from the Health Research Ethics Board (HREB) overseen by the Health Research Ethics Authority (HREA) at Memorial University of Newfoundland under reference number 13.096. Full board approval was granted October 3, 2013 (Appendix E). Three amendments were submitted to include use of email in the study protocol, the additional collection of demographic information and the addition of a research team member to enroll participants. The three amendments were approved on November 15, 2013, February 6, 2014 and February 13, 2014 respectively (Appendix E).

[20] Consent forms indicated that data would be kept for 20 years. Participants were able to choose not to have their data stored in which case their data was destroyed prior to the data merger.

Chapter 4: Results

4.1 Survey Response Rates

Survey response rates are presented in Figure 3.1 in Chapter 3. There were 485 individuals identified from the ARVC *TMEM43* registry *(n* = 885) who met the study inclusion criteria. When contacted, 172 eligible individuals agreed to receive and review the study documents of which there were 64 (37.2%) individuals who enrolled in the study and 108 (62.8%) non-respondents.[21] The final sample consisted of 28 (43.8%) affected females, 21 (32.8%) unaffected females 10 (15.6%) affected males, and 5 (7.8%) unaffected males.

4.2 Demographic Characteristics of Sample

Table 4.1 describes the demographic characteristics of the sample population in this study. The mean age of the population was 52 years (SD 13.92) with a minimum of 24 years and maximum of 83 years. The largest age demographic in the sample was those in the middle age range comprising 41-60 years, representing 45.5% of the sample. More than three quarters (76.5%) of respondents were female, with the majority of respondents indicating their marital status as married or living with a partner (65.2%). Respondents on average had 1.81 children (SD 1.30) with the minimum number of children reported as 0 to a maximum of 6. Roughly one third of the sample (29.7%) had achieved a non-university post-secondary education, with high school diploma (14.1%), some university (10.9%) and bachelors degree (12.3) educational achievement comprising approximately one third of the rest of the sample. The two most frequently indicated employment

[21] Data collection from December 1st 2013 to May 30, 2014. There were 176 individuals contacted, of which four with unknown clinical status (poorly ascertained) were contacted in error and subsequently excluded from the study.

statuses were employed full-time and retired, which comprised 34.4% and 32.9% of the sample respectively. Just over one quarter of the sample (26.6%) indicated an annual household income of $26,000-$50,000.

Table 4.1 Demographic characteristics of study participants.

Characteristic	**n (%)**	**Range**	**Mean (SD)**
Age (n=64)		24 - 83	52.0 (13.92)
<20	0 (0.0)		
21- 40	16 (24.2)		
41- 60	30 (45.5)		
61- 80	17 (25.8)		
> 80	1 (1.5)		
Sex (n=64)			
Male	15 (23.5)		
Female	49 (76.5)		
Marital Status (n=57)			
Single, Never married	7 (10.6)		
Married or Living with partner	43 (65.2)		
Divorced or separated	7 (10.6)		
Widowed	0 (0)		
Number of Children (n=57)		0 – 6	1.81 (1.30)
Highest education obtained (n=56)			
Some High School	6 (9.4)		
High School Diploma	9 (14.1)		
Trade School or non University	19 (29.7)		
Some University	7 (10.9)		
Bachelor's Degree	8 (12.5)		
Graduate Degree	4 (6.3)		
Other	3 (4.7)		
Current Employment Status (n=56)			
Employed Full-time	22 (34.4)		
Employed Part-time	8 (12.5)		
Student	0 (0)		
Retired	21 (32.8)		
Unemployed	5 (7.8)		
Annual Household Income (n=55)			
< $25,000	8 (12.5)		
$26,000 - $50,000	17 (26.6)		
$51,000 - $75,000	12 (18.8)		
$76,000 -$100,000	6 (9.4)		
> $100,000	10 (15.6)		
I'd Rather Not Say	2 (3.1)		

4.3 Representativeness of Sample

To assess the representativeness of the sample, sex and ARVC clinical status of respondents (final sample) for the pilot phase were compared to all participants who met inclusion criteria in the study (original sample). Chi-square test results for these analyses are presented in Table 4.2. Clinical status was determined to not be representative of the original population $X^2(1, n = 411) = 4.15$, $p < .05$. Sex was also not representative of the original sample population $X^2 (1, n = 485) = 14.56$, $p < .05$.

Table 4.2 Chi-square comparison on clinical status and sex of final sample population and original population.

Characteristic	Study Sample n (%)	Original Population n (%)	X^2	df
Clinical Status*			4.15	1
Affected	38 (59)	158 (45)		
Unaffected	26 (41)	189 (54)		
Sex**			14.56	1
Male	15 (23)	206 (49)		
Female	49 (77)	215 (51)		

*p = 0.042
** p = 0.000

4.4 Scale development and validation

The results of the scale development and validation are based on the pilot testing of the survey instrument, and should be interpreted as preliminary. Mean scale scores were used in the data analysis methods to minimize the effect of missing data.

4.4.1 Construction of Hypothesized subscales

Five hypothesized subscales comprising the Perceived Economic Burden (PEB) of ARVC scale were constructed using original survey items on the basis of face validity,

content validity and the literature. Seven original survey items were determined to not contribute to face validity and were excluded from the hypothesized scales. The remaining 62 survey items were divided into their respective hypothesized subscales as follows: Human Capital Scale (12 items); Labour Supply and Productivity scale (29 items); Consumption and Savings scale (9 items); Financial Burden Scale (8 items); Insurance scale (4 items). Seven binomial survey items were also included in the original survey tool and although not included in the hypothesized subscales were retained as independent descriptive items. The classification of original survey items into their respective subscales is presented in Table F1 in Appendix F.

4.4.2 Item Level and Subscale Descriptive Statistic Analysis

Table F2 in Appendix F displays descriptive statistics for each survey item. Mean scores on items ranged from 1.48 (SD 0.75) to 4.11 (SD1.18). The majority of items had mean scores less than 3 with missing values ranging from 0% to 13.6%. All items minimum and maximum values for response values were 1 to 5 for ordinal survey items and 1 to 0 for binary (Y/N) survey items. All response choices were used for the majority items (94.7%); however, four items indicated 0 responses for a particular choice (Indir11, Indir12, Indirofm6, Income8).

Items included in hypothesized subscales were examined to determine if the means were roughly equivalent for all scale items and that standard deviations were roughly equivalent and around 1.0 (Ware & Gandek, 1998). These results are presented in Table F3 in Appendix F. All item means within their respective scale are roughly equivalent with ranges from 1.81 – 3.03 for HC, 1.48 – 3.08 for LSP, 2.10-3.03 for CS, 1.98-2.78 FB, 2.70-3.94 for IN. Standard deviations are also roughly the same for all

items within subscales and around 1.0: HC (1.01 – 1.54), LSP (0.74 – 1.65), CS (1.20 – 1.52), FB (1.14 – 1.48), IN (1.25 – 1.37).

4.4.3 Scale Level Assumptions

Validity of the hypothesized subscales was tested using scale level assumptions for Likert scaling indicated by Ware & Gandek (1998). The multitrait/multiitem correlation matrix used for these analyses are presented in Table F3 in Appendix F.

The first assumption tested was for item internal consistency. Results demonstrated that all items' correlation coefficients with their respective scales are larger than 0.40 (range 0.41 to 0.86), which indicates a substantial and satisfactory item internal consistency (Ware & Gandek, 1998). The second assumption tested was for equality of item-scale correlations. Results indicated that the individual items comprising the scales contributed roughly equal proportions of information to their respective total scale score; HC scale range 0.66 – 0.84; LSP scale range 0.41- 0.77; CS scale range 0.62-0.85; FB scale range 0.70 – 0.86; and IN scale range 0.56 – 0.85. Ware & Gandek (1998) indicate that it is satisfactory for item-scale correlations to vary (e.g., from 0.40 to 0.70,) across the same scales, and therefore the scales appear to satisfy the assumption for equality of item-scale correlation.

The final assumption tested used item discriminant validity to determine the extent to which an item measured concepts outside of its hypothesized subscale in the competing subscales. Item discriminant validity was supported if the correlation of an item with its hypothesized scale is significantly higher than with other scales; significance level was equal to 2 standard errors (approximately a 95% confidence interval) (Ware & Gandek, 1998). A total of 244 item discriminant tests were completed determined by the

number of items in each scale multiplied by the number of scales in the matrix minus 1. A summary of possible test results is presented in Table 4.3.

Table 4.3 Possible test results for item discriminant validity tests

Test Result Value	Result	Item Discriminant Validity Supported
+2	Correlation significantly greater for hypothesized scale compared to competing scale	Yes
+1	Correlation greater, but not significantly, for hypothesized scale compared to competing scale	Yes (on preliminary basis)
-1	Correlation lower, but not significantly, for hypothesized scale compared to competing scale	No
-2	Correlation significantly lower for hypothesized scale compared to competing scale	No

Item discriminant validity test are presented in Table F4 in Appendix F. The majority of the 244 tests indicated that item discriminant validity was supported with test result values of +2 and +1. Three items failed the test for discriminant validity (LSP6, LSP7, CS3) all receiving a test value of -1 for one of the competing scales. Items that failed tests for discriminant validity were retained in the scales as their correlations were not significantly lower and items were determined to contribute content validity to their respective scales. Ware & Gandek suggest that failure of item discriminant validity tests may result in less efficient scales and recommend translation of these items for future studies. As this study represents initial validation work, they were retained for their descriptive value and as a basis for translation in future work.

4.4.4 Reliability of Proposed Subscales

Descriptive statistics for the five subscale mean scores are presented in Table 4.4. For each respondent, the mean score for each subscale was calculated and used for the analysis. The mean scale scores of respondents for all five subscales ranged from a minimum of 1.00 to a maximum of 5.00. The means for the mean scores ranged from 2.07 (SD 0.83) for the LSP subscale to 3.45 (SD 1.08) for the IN subscale.

Table 4.4 Descriptive statistics for subscale means scores.

Scale	Mean	SD	Minimum	Maximum
HC	2.43	1.07	1.00	5.00
LSP	2.07	0.83	1.00	5.00
CS	2.40	1.02	1.00	5.00
FB	2.28	1.03	1.00	5.00
IN	3.45	1.08	1.00	5.00

Cronbach's alpha (reliability) coefficients for each subscale were calculated to determine internal consistency. The reliability coefficients for the five subscales ranged from 0.75 for IN to 0.94 for LSP with values of 0.90, 0.91 and 0.93 for the CS, FB and HC scales. All of the reliability coefficients were above the minimum acceptable level of 0.70 suggested for group level comparisons (Nunnally & Bernstein, 1994). Therefore all five subscales were found to have good internal consistency and were considered reliable.

4.4.5 Validity of Perceived Economic Burden Scale

The overall perceived economic burden (PEB) of ARVC scale was analyzed to determine whether each of the five subscales were making distinct and unique contributions to the overall scale. Reliability coefficients for each subscale were compared with Pearson correlations for each competing subscale: results are presented in Table 4.5.

Table 4.5 Reliability coefficients and inter-scale correlations

Scale	HC	LSP	CS	FB	IN
HC	(0.94)				
LSP	0.61	(0.94)			
CS	0.55	0.64	(0.90)		
FB	0.53	0.70	0.91	(0.91)	
IN	0.53	0.47	0.39	0.35	(0.75)

*Scale reliability coefficients (Chronbach's alpha coefficient) presented on the diagonal

The alpha coefficients for four out of the five subscales were larger than the correlation coefficients indicating that there is unique reliable variance measured by each of these subscales (Ware & Gandek, 1998). The alpha coefficient for the FB scale was the same as its correlation coefficient with the CS, indicating that these scales may be performing like alternate measures of similar concepts. The final constructed and preliminary validated PEB scale survey tool is displayed in Appendix H.

4.5 Empirical Results: Predictors of Perceived Economic Burden

4.5.1 Human Capital Attainment

4.5.1.1 HC Regression Analysis

Multiple regression analysis was conducted to examine the relationship between HC scale scores and various other possible predictors (n = 64). Normality Probability Plot of Regression Standardized Residuals and Scatterplot are presented in Appendix G. Preliminary analysis of the regression Normal Probability Plot / scatterplot indicated that no violation of normality, linearity, and homoscedasticity assumptions had occurred. Additionally, tests for multicollinearity indicated no violation with all tolerance levels> 0.10 (0.33 – 0.89) and Variance Inflation Factor (VIF) scores < 10 (1.1 – 4.2).

Model summary result SPSS® outputs are presented in Figure 4.1. The coefficients affectedmale, affectedfemale, unaffected female, edupostsecondary, age, haschildren and unemployed_retired entered in the model accounted for 17.5% of the variance (R square 0.175) in HC scale scores F (8,55) = 1.46, p > .05.

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.419[a]	.175	.055	1.02440

a. Predictors: (Constant), missing_dem, affectedfemale, haschildren, age, edupostsecondary, affectedmale, unemployed_retired, unaffectedfemale
b. Dependent Variable: HC

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	12.278	8	1.535	1.463	.192[b]
	Residual	57.717	55	1.049		
	Total	69.995	63			

a. Dependent Variable: HC
b. Predictors: (Constant), missing_dem, affectedfemale, haschildren, age, edupostsecondary, affectedmale, unemployed_retired, unaffectedfemale

Figure 4.1 SPSS® Multiple Regression Model Output HC scale.

Model coefficient SPSS® outputs are presented in Table 4.6. Examination of the regression coefficient revealed a single statistically significant coefficient, affectedmales, B = 1.23 (SE 0.61), p < .05. This result indicates that after controlling for other predictors

in the model, affected males reported higher perceived HC scale scores. All other predictor variables were not statistically significant predictors of HC scale scores.

Table 4.6 Regression coefficients output summary for HC scale.

Coefficient	Reference Category	B	SE	t	p
Affected Males	Unaffected Males	1.23	0.61	2.02	.048
Affected Females	Unaffected Males	0.49	0.53	0.92	.362
Unaffected Females	Unaffected Males	0.18	0.52	0.35	.727
Some or Completed Post Secondary Education	Some High School (HS) or HS Diploma	0.10	0.32	0.32	.752
Age	N/A	- 0.01	0.01	- 0.71	.487
Has Children	N/A	0.45	0.37	1.22	.228
Unemployed or Retired	Employed	0.30	0.35	0.09	.932

* Missing demographic information was controlled for by inclusion of a missing demographic variable in the regression model (data not shown).

4.5.2 Labour Supply and Productivity Results

4.5.2.1 LSP Regression Results

Multiple linear regression was conducted to examine the relationship between LSP scale scores and various potential predictors (n = 64). Normality Probability Plot of Regression Standardized Residuals and Scatterplot are presented in in Appendix G. Test for multicollinearity indicated no violation of this assumption with all tolerance levels > 0.10 (0.23 – 0.71) and VIF scores < 10 (1.3 – 4.3). Inspection of the regression Normal Probability plot and scatterplot indicated no violations for normality, linearity, multicollinearity and homoscedasticity assumptions.

Model summary SPSS® output results are displayed in Figure 4.2. The coefficients affectedmale, affected female, unaffectedfemale, age, haschildren, incomegreater50, married_livingwithpartner and missing_dem entered accounted for

18.5% of variance (R square 0.185) in LSP scores F (9,54) = 1.36, p = > .05.

Examination of the regression coefficients presented in Table 4.7 revealed no significant predictors for LSP scale scores.

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.430[a]	.185	.049	.80643

a. Predictors: (Constant), missing_dem, affectedfemale, haschildren, age, married_livingwithpartner, incomegreater50, affectedmale, unemployed_retired, unaffectedfemale

b. Dependent Variable: LSP

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	7.955	9	.884	1.359	.230[b]
	Residual	35.118	54	.650		
	Total	43.073	63			

a. Dependent Variable: LSP

b. Predictors: (Constant), missing_dem, affectedfemale, haschildren, age, married_livingwith, incomegreater50, affectedmale, unemployed_retired, unaffectedfemale

Figure 4.2 SPSS® regression model output for LSP scale.

Table 4.7 Regression coefficients output summary for LSP scale.

Coefficient	Reference Category	B	SE	t	p
Affected Males	Unaffected Males	0.84	0.49	1.70	.096
Affected Females	Unaffected Males	0.26	0.42	0.54	.535
Unaffected Females	Unaffected Males	- 0.05	0.42	- 0.12	.906
Age	N/A	0.03	0.01	0.23	.816
Unemployed or Retired	Employed	- 0.14	0.28	- 0.50	.617
Income > $50,000	Income < $50,000	- 0.22	0.25	-0.89	.377
Married or Living With a Partner	Single or Divorced	0.27	0.29	0.93	.358
Has Children	N/A	0.22	0.30	0.73	.469

* Missing demographic information was controlled for by inclusion of a missing demographic variable in the regression model (data not shown).

4.5.2.2 Chi-square LSP analysis

A chi-squared test for independence was performed to determine the relationship between sex/clinical status and binomial survey item responses Indir13 (unable to work due to own risk), Indir14 (short-term disability), Indir15 (long-term disability), Indir16 (unable to work due to other family member's risk), Indof8 (family member unable to work due to respondent's risk). No significant relationship was observed for LSP items Indir13, Indir16 and Indof8. Table 4.8 presents the results for the chi-square model for items Indir14 and Indir15.

The relationship between going on short-term disability (Indir14) and the clinical status/sex variables was significant, X^2 (3, n = 62) = 16.64, p <.05 with a large effect size Cramer's V = 0.52. Affected males were more likely to report having to go on short-term disability as a result of their risk for ARVC than were unaffected males, affected females, and unaffected females. Similarly, the relationship between going on long-term disability (Indir15) and the clinical status/sex variables was significant, X^2 (3, n = 62) = 10.75, p <

.05 with a moderate effect size (Cramer's V = 0.42). Affected males were more likely to report having to go on long-term disability as a result of their risk for ARVC than were unaffected males, affected females, and unaffected females.

Table 4.8 Chi-square model summary for binomial items Indir14 and Indir15.

Item		Affected Males	Unaffected Males	Affected Females	Unaffected Females	Total	X^2	df
Had to go on short-term disability (Indir14)*	Yes	4	0	1	0	5	16.64	3
	No	6	5	26	20	57		
	Total	10	5	27	20	62		
Had to go on long-term disability (Indir15)**	Yes	2	0	0	0	2	10.75	3
	No	8	5	27	20	60		
	Total	10	5	27	20	62		

* p = .001
** p = .013

4.5.3 Consumption and Savings Results

4.5.3.1 CS Regression Results

Multiple linear regression was performed to examine the relationship between CS scale scores and various possible predictors (n = 62). Multicollinearity assumption tests indicated no violation with all tolerance levels > 0.10 (0.26 – 0.89) and VIF scores < 10 (1.2 – 3.9). Normality Probability Plot of Regression Standardized Residuals and Scatterplot are presented in Appendix G. Visual inspection of the regression Normal Probability plot and scatterplot indicated no violations for normality, linearity, and homoscedasticity assumptions.

Figure 4.3 present the SPSS® model summary output for the CS regression analysis. The coefficients missing_dem, affectedfemale, haschildren, eduuptoHS,

unemployed_retired, affectedmale, incomegreater50, unaffectedfemale entered accounted for 25% of variance (R square 0.250) in CS scores, F (8,53)= 2.21, p < .05.

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.500[a]	.250	.137	.94329

a. Predictors: (Constant), missing_dem, affectedfemale, haschildren, eduuptoHS, unemployed_retired, affectedmale, incomegreater50, unaffectedfemale
b. Dependent Variable: CS

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	15.724	8	1.966	2.209	.041[b]
	Residual	47.160	53	.890		
	Total	62.884	61			

a. Dependent Variable: CS
b. Predictors: (Constant), missing_dem, affectedfemale, haschildren, eduuptoHS, unemployed_retired, affectedmale, incomegreater50, unaffectedfemale

Figure 4.3 SPSS® regression model output for CS scale.

Model coefficients are presented in Table 4.9. The affectedmales coefficient was a significant predictor for CS scale scores B =1.49 (SE 0.54), p < .05. These results indicate that after controlling for other predictors in the model, affected males reported higher consumption and savings perceived burdens. It should be noted that the affectedfemale coefficient is significant at a 10% level of significance B =0.88, (SE 0.48), p < .1. All other predictor variables were not statistically significant predictors for CS scale scores.

Table 4.9 Regression coefficients output summary for CS scale.

Coefficient	Reference Category	B	SE	t	p
Affected Males	Unaffected Males	1.49	0.54	2.76	.008
Affected Females	Unaffected Males	0.88	0.48	1.82	.071
Unaffected Females	Unaffected Males	0.23	0.50	0.46	.651
Has Children	N/A	0.23	0.35	0.67	.506
Income > $50,000	Income < $50,000	- 0.51	0.33	- 1.54	.128
Unemployed or Retired	Employed	- 0.08	0.27	- 0.31	.759
Some High School (HS) or HS Diploma	Some or Completed Post Secondary Education	- 0.45	0.35	- 1.30	.201

* Missing demographic information was controlled for by inclusion of a missing demographic variable in the regression model (data not shown).

4.5.4 Financial Burden

4.5.4.1 FB Regression Results

Multiple regression analysis was conducted to examine the relationship between FB scale scores and various potential predictors (n = 62). Results revealed that no violations for multicollinearity assumptions occurred as all tolerance levels were > 0.10 (0.23 – 0.71) and VIF scores < 10 (1.3 – 4.3). Normality Probability Plot of Regression Standardized Residuals and Scatterplot are presented in Appendix G. Interpretation of the Normal Probability plot /scatterplot for the regression revealed no violations for normality, linearity, and homoscedasticity assumptions.

Results for the model summary are presented in Figure 4.4. The coefficients missing_dem, affectedfemale, haschildren, age, incomegreater50, affectedmale, unemployed_retired, unaffectedfemale entered accounted for 24.3% of variance (R square = 0.243) in FB scale scores, F (8,53) = 2.13, p < .05.

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.493[a]	.243	.129	.95817

a. Predictors: (Constant), missing_dem, affectedfemale, haschildren, age, incomegreater50, affectedmale, unemployed_retired, unaffectedfemale
b. Dependent Variable: FB

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	15.643	8	1.955	2.130	.049[b]
	Residual	48.658	53	.918		
	Total	64.302	61			

a. Dependent Variable: FB
b. Predictors: (Constant), missing_dem, affectedfemale, haschildren, age, incomegreater50, affectedmale, unemployed_retired, unaffectedfemale

Figure 4.4 SPSS® regression model output for FB scale.

Model coefficients are presented in Table 4.10. Two coefficients were significant predictors for FB scale scores; affectedmales B = 1.84 (SE 0.57), $p < .05$; affectedfemales B = 1.28 (SE 0.50), $p < .05$. These results indicate that after controlling for other variables in the model, both affected males and affected females score higher on perceived FB scale scores. All other predictor variables were not statistically significant predictors for FB scale scores.

Table 4.10 Regression coefficients output summary for FB scale.

Coefficient	Reference Category	B	SE	t	p
Affected Males	Unaffected Males	1.84	0.57	3.20	.002
Affected Females	Unaffected Males	1.28	0.50	2.56	.013
Unaffected Females	Unaffected Males	0.55	0.50	1.08	.284
Has Children	N/A	0.36	0.36	1.01	.318
Unemployed or Retired	Employed	- 0.47	0.35	- 1.32	.192
Income > $50,000	Income < $50,000	- 0.21	0.29	- 0.73	.466
Age	N/A	0.02	0.01	1.37	.177

* Missing demographic information was controlled for by inclusion of a missing demographic variable in the regression model (data not shown).

4.5.5 Insurance Results

4.5.5.1 IN Regression Analysis

Multiple linear regression was conducted to examine the relationship between IN scale scores and various potential predictors (n = 61). No violation of multicollinearty occurred with all tolerance levels > 0.10 and VIF scores <10. Normality Probability Plot of Regression Standardized Residuals and Scatterplot are presented in Appendix G. Normal Probability Plot and scatterplot analysis indicated no violations for normality, linearity or homoscedasticity assumptions.

Model summary results are reported in Figure 4.5. The coefficients single_divorce, incomegreater50, affectedfemale, unemployed_retired, edunpostsecondary, haschildren, affectedmale, missing_dem, age, unaffectedfemale entered accounted for 30% of variance (R square 0.30) in IN scale scores, F (10,50) = 2.14, p < .05.

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.547[a]	.299	.159	.94731

a. Predictors: (Constant), single_divorce, incomegreater50, affectedfemale, unemployed_retired, edunpostsecondary, haschildren, affectedmale, missing_dem, age, unaffectedfemale
b. Dependent Variable: IN

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	19.169	10	1.917	2.136	.039[b]
	Residual	44.870	50	.897		
	Total	64.039	60			

a. Dependent Variable: IN
b. Predictors: (Constant), single_divorce, incomegreater50, affectedfemale, unemployed_retired, edunpostsecondary, haschildren, affectedmale, missing_dem, age, unaffectedfemale

Figure 4.5 SPSS® regression model output for IN scale.

Model coefficients are presented in Table 4.11. Two coefficient were significant predictors for IN scale scores: affectedmales B = 1.64 (SE 0.66), $p < .05$, and educationpostsecondary B = 0.87 (SE 0.37), $p < .05$. These results indicate that after controlling for other predictors, both affected males and those with some or completed post-secondary education report higher IN scale scores. It should be noted that the affectedfemales coefficient was significant at 10%, B = 1.12 (SE 0.6), $p < .1$. All other predictor variables were not statistically significant predictors for IN scale scores.

Table 4.11 Regression coefficients output summary for IN scale.

Coefficient	Reference Category	B	SE	t	p
Affected Males	Unaffected Males	1.64	0.66	2.49	.016
Affected Females	Unaffected Males	1.12	0.60	1.87	.067
Unaffected Females	Unaffected Males	0.60	0.61	0.99	.328
Has Children	N/A	0.58	0.36	1.60	.117
Unemployed or Retired	Employed	- 0.39	0.36	- 1.08	.285
Income > $50,000	Income < $50,000	- 0.35	0.35	- 1.00	.323
Age	N/A	0.00	0.01	0.07	.943
Some or Completed Post Secondary Education	Some High School (HS) or HS Diploma	0.87	0.37	2.35	.023
Single or Divorced	Married or Living With a Partner	- 0.10	0.38	-0.27	.791

* Missing demographic information was controlled for by inclusion of a missing demographic variable in the regression model (data not shown).

4.5.5.2 Chi-square IN analysis

A chi-squared test for independence was performed to determine the relationship between sex/clinical status and binomial survey item responses Insur7 (payment of higher premiums for medical insurance) and Insur8 (denial of medical insurance). No significant relationship was observed for Insur8. Table 4.12 presents results for the chi square model for item Insur7. The relationship between paying higher premiums for medical insurance and the clinical status/sex variables was significant, X^2 (3, n = 61) = 13.02, $p < .05$ with a moderate effect size Cramer's V = 0.46. Affected males were more likely to report to perceive paying higher insurance premiums as a result of their risk for ARVC than were unaffected males, affected females, and unaffected females.

Table 4.12 Chi-square model summary for binomial item Insur7.

Item		Affected Males	Unaffected Males	Affected Females	Unaffected Females	Total	X^2	df
Paid Higher premiums for medical insurance (Insur7)*	Yes	6	0	10	1	17	13.03	3
	No	4	5	17	18	44		
	Total	10	5	27	19	61		

* p = .005

4.6 Summary

Overall, the results section demonstrates the final characteristics of the sample population, the construction of the PEB scale, its validation, and the use of multiple linear regression and chi-square analysis in an attempt to explain some of the data collected from the sample. A brief summary of the results section is presented below.

A final sample of n = 64 was obtained from the data collection timeframe of December 1, 2013 to May 30, 2014 as indicated in section 4.1 of this chapter. The sample was determined to not be representative of the population for clinical status (affected/unaffected) nor for sex (section 4.3). Approximately 60% of the sample were affected and the majority of the respondents were female (77%).

The Perceived Economic Burden scale was constructed to be composed of five subscales[22] and was analyzed for both validity and reliability according to previous work by Ware & Gandek (1998) in the second section of this chapter (Section 4.4). All items within the five hypothesized subscales had roughly equivalent means and standard deviation of approximately 1.0. Furthermore, tests for Likert scale assumptions for item

[22] Human Capital Scale (HC); Labour Supply and Productivity scale (LSP); Consumption and Savings scale (CS); Financial Burden Scale (FB); Insurance scale (IN)

internal consistency and equality of item-scale correlation achieved satisfactory results. The final test for the item discriminant validity assumption achieved satisfactory results for all but three items, which were not removed from their subscales due to their content validity and the pilot nature of this work. All reliability coefficients (Cronbach's alpha) were above the minimal acceptable range of 0.70 indicating that all five subscales had good internal consistency and are considered reliable (Table 4.5). The final step in the validation process indicated that three of the five subscales were making unique contributions to the overall PEB scale with results indicating that the FB and CS scales may be performing like alternate measures of similar concepts.

Section 4.5 of this chapter presented the empirical analysis of the data. Multiple linear regression analysis was conducted on all five subscales to determine the effect of clinical status and sex and other demographic characteristics on the various perceived burden areas. Regression analysis indicated that affected males perceived significantly greater levels of burden in human capital, consumption and savings, financial burden and insurance. Affected females also reported statistically significant increased perceived burden with respect to financial burden and were significant predictors of consumption and savings and insurance at 10%. Finally, those with some or completed post secondary education also perceived greater insurance burden than those with lower levels of education.

Chi-square analysis was used to determine the relationship between responses to binomial questions and clinical status/sex categories. These results indicated that affected males reported having to go on both short-term and long term-disability compared to unaffected males, affected females and unaffected females. A similar result was observed

in a question about insurance where affected males perceived paying higher premiums compared to all other clinical status/sex groups.

Chapter 5: Discussion

This study had three main empirical components; the development of a survey tool, the initial validation of the Perceived Economic Burden (PEB) of ARVC scale, and the application of the PEB scale to examine the perceived economic burden experienced by families with a known family/genetic history of ARVC caused by the p.S538L mutation in *TMEM43*. Similarly, the study aimed to determine the influence of various demographic and clinical characteristics on the perceived economic burden such as clinical status, sex, age, having children, education level, employment status income and marital status. To date, this appears to be the first quantitative study to explore the perceived economic burden in this population. Few studies exist that examine how individuals and families with serious genetic conditions alter their career, education and savings plan choices based on their genetic diagnosis. Previous preliminary qualitative research on this population by members of our research team has indicated perceived economic burden in areas such as employment abilities and choices, worry about insurance for self and children, decreased household spending, and the need for childhood employment (Etchegary et al., 2015).

5.1 Survey Response Rates and Representativeness of The Sample

The response rate for this study was 37.2%. Approximately 77% of respondents were female. Fewer males in the final sample appear to explain the lack of representativeness of the sample compared to the population in regards to sex as shown by chi-squared analysis. This observation is of particular interest as a higher response rate for males was expected due to the sex influence of the disease, affecting males more severely than females. Female respondents often dominate survey research, including

health research, and the current study was no different (Mindell et al., 2015; Moore & Tarnai, 2002). Future research efforts to recruit males would be valuable given the sex influence of ARVC. Similarly, unaffected individuals were under represented in the sample comprising 41% of the sample. It is possible that the unaffected population were less likely to respond as they did not perceive any economic burden according to their risk and felt the study was not applicable to them.

5.2 Perceived Economic Burden (PEB) Scale Construct and Validation

The first two objectives of this study were to develop, construct and validate an instrument to measure the perceived economic burden of ARVC caused by the p.S538L mutation in *TMEM43.* The initial economic impact of ARVC survey instrument was developed resulting in the subsequent construction of the PEB scale as a tool to quantitatively measure the perceived economic burden of living with a family and genetic history of ARVC. Both qualitative study findings on the economic burden experienced by ARVC families and supplemental literature discussing the economic burden experienced due to illness and diseases were used to develop the original 76 survey items. Utilizing available data from a the previous qualitative study on the population was particularly advantageous to this study as the content was reflective of personal experiences within the ARVC population and it contributed to the face and content validity of the scale. Gilgun (2004) supports the combination of qualitative research with literature reviews in scale construction as this method provides confidence in scale content and increases face validity of concepts that comprise scales.

This study provides preliminary evidence supporting the psychometric properties of the PEB scale. The findings from the Multitrait/Multi-Item analysis validation suggest

that the PEB scale (including each of the 5 subscales) met Likert scaling assumptions (Ware & Gandek, 1998). When applied to findings from the ARVC sample, the PEB scale had satisfactory item internal consistency, equality of item-scale correlations, and discriminant validity for most items. Scale items that did not support item-discriminant validity are retained in the current version of the scale on the basis of their contribution to content validity, their minimal impact on validity and the exploratory nature of this study. PEB scale validation findings provided evidence to support its validity, where each of the subscales contained relevant content and measured their desired properties. This validation provides preliminary confirmation that PEB scale scores are appropriate, meaningful and useful and therefore inferences and claims made from scale scores can be interpreted with a higher degree of confidence (Zumbo & Chan, 2014). Reliability testing using Chronbach's alpha coefficients for all five subscales provided good internal consistency and as a result were determined to be reliable. As such, each subscale likely gave consistent accurate results that reflected the true scale score and not random error (Ware & Gandek, 1998).

An important contribution of this study to the economic burden of disease research is it provides confirmation of the content validity of measures of economic burden. A lack of concrete quantitative measures of economic burden in the literature required that this study be exploratory, using a broad scope of subscale and item content. The pattern of correlations between subscales is relevant to the content validity of scales (Ware & Gandek, 1998). Inter-scale correlation findings demonstrate that the content of the subscales are inter-related, yet distinct, and consequently have relevant content validity.

With the exception of the FB and CS subscales, inter-scale correlation analysis found that all other subscales were making a distinct contribution to the overall PEB scale. Initially, the FB and CS items were included in the same subscale, however, for face validity they were separated as measures of distinct concepts. Additionally, the separation of these two concepts contributed to an increase in statistical significance of the regression analysis of the ARVC sample data. Despite the inter-scale correlation between the FB and CS subscales, the content of each subscale are distinct and therefore not likely to be alternate measures of similar concepts. These findings may reflect the potential relationship between perceived financial and consumption and savings burdens, an area for potential future research. It is expected that future studies with a larger sample size would provide additional validation of the PEB scale.

5.3 Predictors of Perceived Burden

The purpose of the empirical analysis of the PEB subscales focuses on identifying general trends in the measures of economic burden as opposed to specific scale item content. Empirical analysis results represent objective three of the study, of using the validated PEB scale to identify predictors of perceived economic burden. These results reflect the exploratory nature of this study and provide trends to support future research on the economic burden experienced by ARVC families, and to report similar findings reflected in the current literature. The findings from multiple regression analysis on the five subscale scores suggest differences in perceived burden observed in factors such as sex and clinical status.

The first and most evident difference was observed between affected males and females. Affected males perceived higher levels of burden with observed statistical

significance in human capital, consumption and savings, financial burden and insurance. Affected females only reported statistically significant increased perceived burden with respect to financial burden. The results do suggest, however, that affected females reported increased perceived burden for consumption and savings and insurance at a 10% statistical significance level, and therefore it is likely that with a large sample size these measures would be significant.

Despite the lack of evidence from existing literature that support the observed difference between males and females, a possible theory can be hypothesized from what is known about ARVC caused by a p.S538L mutation in *TMEM43*. Factors such as earlier symptoms, increased disease severity and shorter life expectancies in males compared to females with this subtype of ARVC (Hodgkinson et al., 2013) may contribute to their increased perceived burden in the majority of measures. This study therefore suggests that affected males experience an increased perceived burden in significantly more of the predictors of economic burden compared to affected females. Although it does appear the perceived economic burden for affected females is also increased due to ARVC.

In addition to the overarching sex differences in scale scores discussed above, a further exploration of the measures of perceived burden suggests other contributing factors as reflected in current literature. The HC scale is intended to capture the perceptions of individuals and their families regarding education and career choices as they relate to a risk for ARVC. As previously mentioned, regression analysis suggests that affected males report a greater perceived HC burden. The observed perceived HC burden in this study is supported by previous research on ARVC and other genetic conditions (Etchegary et al., 2015; Oster et al., 2013a).

ARVC caused by a p.S538L in *TMEM43* is associated with physical and safety limitations for lifestyle and employment considerations due to disease characteristics and treatment with ICDs in addition to a known reduced life expectancy. Therefore affected individuals are faced with the challenge of carefully considering their careers, and by extension the type and level of education they pursue. One of the main findings from the qualitative economic burden evaluation on this population supports considerations for future and current employment for ARVC patients, as there were limitations on the type of employment that could be safely undertaken (Etchegary et al, 2015). Teachman (2012) found that the likelihood of post-secondary enrollment increases by approximately 15% when limitation on the type of future work occurred due to disease.

Contrary to Teachman (2012), a positive genetic test for Huntington disease patients and a decreased life expectancy had a negative impact on the level of education attained, where affected patients completed less education and were 30% less likely to complete post secondary education (Oster et al., 2013a). The greater perceived economic burden reported in this study confirms that considerations of education and employment are occurring in the ARVC population, particularly for affected men. Although our study only measured whether considerations about education and career were occurring, the literature supports that decisions can both positively and negatively affect the pursuit of higher education, and likely influencing career choices. This presents an important area for the clinical management and guidance of ARVC patients in regards to education and career choices as our study findings and the literature reflect these choices occurring as a result of disease characteristics of ARVC.

No significant predictors were observed in the regression model for the labour supply and productivity (LSP) scale that measures the perceived burden with respect to employment, hours worked, wages, workforce participation and decisions about retirement. These results contradict the proportion of literature that suggests disease/illness has an impact on hours worked, wages and early retirement (Pelkowski & Berger, 2004; Yen et al., 2011). In fact, previous qualitative work suggested that ARVC patients and families reported experiences of taking time off work, lessened quality of work, or other family members returning to work/working additional hours to make up for lost income (Etchegary et al., 2015). A possible protective factor of LSP burden may be explained by findings from Etchegary et al. (2015) where participants discussed the positive impact of supportive and understanding employers.

Statistical significance was observed, however, with chi-squared analysis of some binomial LSP survey items. Affected males were more likely to report having to go on both short-term and long-term disability when compared to affected females, unaffected males and unaffected females. These results are consistent with Johansen (1999) who concluded that a significant proportion of heart disease patients report being on disability. Generally, LSP findings suggest that although employment is affected, the effect of ARVC appears to result in short/long term disability rather than a decrease in hours or wages. Again, these results demonstrate the possible effect of disease burden for affected men, where their disease and implantation of an ICD may be severe enough that affected men require extended time off work without leaving the workforce permanently. These are important psychosocial issues to be explored in genetic counseling sessions and may suggest areas for follow up supportive care and management.

The consumption and savings (CS) scale is intended to capture how people make decisions about their savings/spending habits and incurred costs associated with their risk for ARVC. Results from the multiple regression analysis suggest affected males were the single statistically significant predictor of CS scale scores being more likely to report perceived burden. These results support the notion of precautionary saving in response to future health uncertainty and a risk of poor health reflected in the literature (Japelli et al, 2007; Palumbo, 1999). Furthermore, the study results also suggest that affected male ARVC patients and their families incur costs associated with medications, travel for medical appointments and other costs as a result of their risk for ARVC, consistent with the broader literature on chronic disease management (McGillion et al., 2008; Sanmartin et al., 2014).

Out-of-pocket costs for health related expenses were an expected finding from this study as research suggests these costs are increasing for Canadians (Sanmartin et al, 2014), and patients with heart disease have reported significant out-of-pocket costs (McGillan et al, 2008). Findings from Etchegary et al. (2015) also support these findings with ARVC patients incurring costs associated with treatment and expressing concerns over financial planning. It appears that the ARVC population in Newfoundland and Labrador makes decisions that reflect anticipatory savings, while incurring medical related costs that are not covered by the publically funded health care system.

Financial burden was measured by the FB subscale capturing the effect of contributing factors to financial burden such as the need for regular monitoring, costs of medication, costs for travel and other potential costs. Both affected males and affected females reported a statistically significant increase in reported perceived financial burden.

These finding are expected as affected males also reported an increased perceived burden in their spending on health related goods and services and savings decisions that likely relate to an increase in financial burden.

Finally, the insurance (IN) scale intended to capture challenges and concerns with existing or obtaining medical or life insurance coverage as a result of a risk for ARVC. Two significant predictors of perceived IN burden were observed (i) those with an education of some or completed post-secondary education and (ii) affected males. These two groups had a higher likelihood of reporting an increasd perceived burden associated with insurance coverage. A higher level of education was identified by Bombard et al. (2011) as one of the factors that increased the likelihood of genetic discrimination in Huntington disease patients. The results from this study support these previous findings in a genetic disease population perhaps suggesting that those with higher education levels are more likely to purchase additional medical or life insurance.

A greater perceived IN burden was expected for affected men; however, an unexpected finding for the insurance scale was the non-significant predictor of affected women. This may again reflect the sex dependence of this subtype of ARVC where females experience a wider variety of disease severity, while men experience increased disease severity. These findings may be explained by previous research conducted by Bombard et al. (2009) where insurance discrimination was found to reflect disease and family histories and not necessarily the result of actual genetic testing results. Findings suggesting a concern over the ability to obtain insurance are mirrored in the study by Etchegary et al. (2015) where having enough insurance was a major worry for participants.

Sex differences were also observed in the chi-squared analysis of an item intended to capture paying a higher premium for private extended health insurance. The relationship between paying higher premiums and clinical status suggests a statistically significant difference for affected men who were more likely to report the perception of paying higher insurance premiums compared to all other clinical status/sex groups. Although it was expected that clinical status would be related to perceived insurance burden, factors such as 91% of all extended health coverage coming from employee benefits packages was expected to be a protective factor against insurance burden (Canadian Life and Health Insurance Association, 2013). Employee benefit packages were suggested to be a potential protective factor for ARVC patients as good insurance plans from employers lessened worries over insurance coverage in qualitative interviews (Etchegary et al., 2015). Current study findings may indicate that a significant proportion of affected men in the ARVC population may either not be enrolled in extended health insurance coverage or their type of employment/employer may not offer group coverage.

5.4 Study Limitations

Despite efforts to ensure increased response rates such as facilitating respondent preference in survey (electronic or hard copy) methods and follow up calls, a relatively small sample size is a limitation of this study. This is particularly reflected in the representativeness of the sample where males and unaffected individuals were under represented. Therefore the perceived economic burden might well be greater for individuals and families where the male was at risk for ARVC or unaffected individuals may experience an increased burden, at least in childhood, as qualitative findings seem to suggest. Future research with greater number of males and unaffected individuals would

be valuable. Additionally, an increase in sample size may provide statistical significance for affected females for the consumption and savings and insurance measures.

Another study limitation was the inability to perform factor analysis as a component of scale validation. Additional studies using the PEB scale to evaluate economic burden with a larger sample size would allow for factor analysis as a component of scale validation and further increase validity of the scale.

Lastly, although significant differences were identified for the majority of subscale measures for economic burden, the magnitude of these differences were not discussed in this study. Therefore, although predictors of perceived economic burden were identified, the degree to which the difference between predictors such as being an affected males remains unknown, and as such another area for further study.

Chapter 6: Conclusion and Future Recommendations

This study used findings from the existing literature to develop survey items, construct, and validate a scale (PEB scale) to measure the perceived economic burden associated with ARVC caused by the p.S358L mutation in *TMEM43*. The PEB scale was then used to explore predictors of perceived economic burden particularly clinical status and sex. This study provides important information to allow the provision of adequate holistic care, and to inform future policy decisions for programs and services offered to ARVC patients. Furthermore, it contributes to the identified gap in the wider literature on the economic burden of ARVC and other genetic conditions.

Validation of the PEB scale provided preliminary evidence of the psychometric properties of the scale allowing results to be interpreted with a greater degree of confidence. This process also confirmed the validity of the measures of economic burden selected from the literature.

We found that affected males reported an increased perceived economic burden in human capital attainment, consumption and savings, financial burden, and insurance. Affected females also reported financial burden as it related to their risk for ARVC. A study with a larger sample size is likely to report statistical significance for consumption and savings and insurance for affected females. Study findings suggest that affected males experience a significantly greater perceived burden across the measures of economic burden compared to affected females, and both unaffected groups. Although the sample size is small (10 affected males), results suggest affected males report having to go on short-and long-term disability and experience paying higher premiums for private medical insurance.

Findings on HC suggest that affected males make considerations and decisions about their education and employment related to their risk for ARVC. Affected males also reported increased perceived burdens in the form of precautionary savings in anticipation of future health events, and those associated with incurred costs for medications or travel for medical appointments as suggested in CS scale results. Financial burden (FB) was perceived by both affected males and females as a result of costs incurred related to their risk for ARVC. Those with a higher level of education and affected males experienced greater perceived burden in obtaining insurance for themselves or their families.

Our findings suggest the importance of supporting the clinical treatment of ARVC patients with counseling or guidance that extends to education and career choices based on limitations caused by their condition. Findings also suggest that despite a universal health care system in Canada, ARVC patients still experience economic burden, particularly associated with costs not covered by public health insurance. These challenges extend to insurance as affected individuals are concerned about the ability to obtain insurance and pay higher insurance premiums as a result of their risk for ARVC. Extended coverage for ARVC patients, their families and other genetic disease populations may act to reduce the experienced burden in this population. Furthermore, additional analysis and potential changes to insurance provision may be required to mitigate challenges in obtaining insurance resulting from a risk for ARVC or other genetic diseases.

Although this study is a major contribution to the gap in literature on the economic burden of ARVC and provides a foundational understanding of the perceived economic burden in this population, study limitations such as small sample size support

the need for further research in this area. Future studies can act to confirm these study findings using a larger sample size, and provide additional analysis of the degree of perceived burden experience. Analysis of ARVC disease characteristics within the affected population that might influence the level of perceived burden such as disease severity or treatment types would also be advantageous allowing for a narrower target for clinical support. Finally, the PEB instrument can be further applied to other genetic conditions and in different geographic settings to measure the perceived economic burden in a variety of populations.

References

Abegunde, D. O., & Stanciole, A. E. (2008). The economic impact of chronic diseases: how do households respond to shocks? Evidence from Russia. *Social Science & Medicine*, *66*(11), 2296-2307.

Aghdassi, E., Zhang, W., St-Pierre, Y., Clarke, A. E., Morrison, S., Peeva, V., Landolt-Marticorena, C., Su, J., Reich, H., Scholey, J., Herzenberg, A., Pope, J.E., Peschken, C., Canios, L., Wither, J., & Fortin, P. R. (2011). Healthcare cost and loss of productivity in a Canadian population of patients with and without lupus nephritis. *The Journal of Rheumatology*, *38*(4), 658-666.

Ahmad, F., Li, D., Karibe, A., Gonzalez, O., Tapscott, T., Hill, R., Weilbaecher, D., Blackie, P., Furey, M., Gardner, M., Bachninski., L., & Roberts, R. (1998). Localization of a gene responsible for arrhythmogenic right ventricular dysplasia to chromosome 3p23. *Circulation*, *98*(25), 2791-2795.

Aiken, L. S., West, S. G., & Pitts, S. C. (2003). Multiple linear regression. *Handbook of psychology*. doi: 10.1002/0471264385.wei0219

Alavinia, S. M., & Burdorf, A. (2008). Unemployment and retirement and ill-health: a cross-sectional analysis across European countries. *International Archives of Occupational and Environmental Health*, *82*(1), 39-45.

Andrén, D., & Palmer, E. (2001). The effect of sickness on earnings. *Work, Sickness, Earnings, And Early Exits From The Labor Market*, 37.

Azaouagh, A., Churzidse, S., Konorza, T., & Erbel, R. (2011). Arrhythmogenic right ventricular cardiomyopathy/dysplasia: a review and update. *Clinical Research in Cardiology*, *100*(5), 383-394.

Bartel, A., & Taubman, P. (1979). Health and labor market success: The role of various diseases. *The Review of Economics and Statistics*, *61*(1), 1-8.

Bartel, A., & Taubman, P. (1986). Some economic and demographic consequences of mental illness. *Journal of Labor Economics*, 4(2), 243-256.

Basso, C., Corrado, D., Marcus, F. I., Nava, A., & Thiene, G. (2009). Arrhythmogenic right ventricular cardiomyopathy. *The Lancet*, *373*(9671), 1289-1300

Bennett, R.L., (2010) Practical Guide to the Genetic Family History, Second Edition. New York: John Wiley & Sons.

Berger, M. C. and Leigh, J. P. (1989). Schooling, self-selection, and health. *Journal of Human Resources,* 24(3), 433–455.

Billings, P. R., Kohn, M. A., De Cuevas, M., Beckwith, J., Alper, J. S., & Natowicz, M. R. (1992). Discrimination as a consequence of genetic testing. *American Journal of Human Genetics*, *50*(3), 476.

Bloom, D. E., & Canning, D. (2000). The health and wealth of nations. *Science, 287*(5456), 1207-1209.

Bombard, Y., Veenstra, G., Friedman, J. M., Creighton, S., Currie, L., Paulsen, J. S., Bottorff, J.L., & Hayden, M. R. (2009). Perceptions of genetic discrimination among people at risk for Huntington's disease: a cross sectional survey. *British Medical Journal*, *338*, b2175.

Bound, J., Schoenbaum, M., Stinebrickner, T. R., & Waidmann, T. (1999). The dynamic effects of health on the labor force transitions of older workers. *Labour Economics*, *6*(2), 179-202.

Bound, J., Stinebrickner, T., & Waidmann, T. (2010). Health, economic resources and the work decisions of older men. *Journal of Econometrics*, *156*(1), 106-129.

Cahill, T. J., Ashrafian, H., & Watkins, H. (2013). Genetic cardiomyopathies causing heart failure. *Circulation Research*, *113*(6), 660-675.

Calkins, H., & Marcus, F. (2008). Arrhythmogenic right ventricular cardiomyopathy/dysplasia: an update. *Current Cardiology Reports*, *10*(5), 367-375.

Callander, E. J., Schofield, D. J., & Shrestha, R. N. (2013). Freedom poverty: a new tool to identify the multiple disadvantages affecting those with CVD. *International Journal of Cardiology*, *166*(2), 321-326.

Campuzano, O., Alcalde, M., Berne, P., Castro, V., Guzzo, G., Iglesias, A., & Brugada, R. (2012). Genetic testing of candidate genes in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *European Journal of Medical Genetics*, *55*(4), 225-234.

Canadian Life and Health Insurance [CLHIA]. (2015a) A guide to life insurance. Retrieved July 15, 2015 from: https://www.clhia.ca/domino/html/clhia/clhia_lp4w_lnd_webstation.nsf/resources/Consumer+Brochures/$file/Brochure_Guide_To_Life_ENG.pdf

Canadian Life and Health Insurance [CLHIA]. (2015b) Key Statistics 2015 Edition. Retrieved July 15, 2015 from: http://clhia.uberflip.com/i/563156-canadian-life-and-health-insurance-facts

Canadian Life and Health Insurance [CLHIA]. (2013). Canadian Life and Health Insurance Facts 2013 Edition. Electronic Version Received directly from CLHIA May 2, 2014.

Canadian Life and Health Insurance Association [CLHIA]. (2012). A guide to supplementary health insurance. Retrieved May 2, 2014 from: http://www.clhia.ca/domino/html/clhia/CLHIA_LP4W_LND_Webstation.nsf/resources/Consumer+Brochures/$file/Brochure_Guide_To_Health_ENG.pdf

Canadian Life and Health Insurance Association [CLHIA]. (2010). CLHIA Position Statement on Genetic Testing. Retrieved May 2, 2014 from: https://www.clhia.ca/domino/html/clhia/CLHIA_LP4W_LND_Webstation.nsf/resources/Guidelines/$file/Genetic_Testing_CLHIA_Industry_Position_2010.pdf

Canadian SADS Foundation (2011), Arrhythmogenic Right Ventricular Cardiomyopathy: An information booklet for Patients and Their Families.

Cervellati, M., & Sunde, U. (2005). Human capital formation, life expectancy, and the process of development. *American Economic Review*, 1653-1672.

Charles, K. K. (1999). Sickness in the family: Health shocks and spousal labor supply. *Ann Arbor, MI: Gerald R. Ford School of Public Policy, University of Michigan*.

Chirikos, T. N., & Nestel, G. (1985). Further evidence on the economic effects of poor health. *The Review of Economics and Statistics*, 61-69.

Coile, C. C. (2004). Health shocks and couples labor supply decisions (No. w10810). National Bureau of Economic Research. Working paper 10810. Retrieved from http://academics.wellesley.edu/Economics/Coile/w10810.pdf

Conard, M. W., Heidenreich, P., Rumsfeld, J. S., Weintraub, W. S., & Spertus, J. (2006). Patient-reported economic burden and the health status of heart failure patients. *Journal of Cardiac Failure*, *12*(5), 369-374.

Contoyannis, P., & Rice, N. (2001). The impact of health on wages: evidence from the British Household Panel Survey. *Empirical Economics*, *26*(4), 599-622.

Corrado, D., Basso, C., Rizzoli, G., Schiavon, M., & Thiene, G. (2003). Does sports activity enhance the risk of sudden death in adolescents and young adults? *Journal of the American College of Cardiology*, *42*(11), 1959-1963.

Corrado, D., Fontaine, G., Marcus, F. I., McKenna, W. J., Nava, A., Thiene, G., & Wichter, T. (2000). Arrhythmogenic right ventricular dysplasia/cardiomyopathy need for an international registry. *Circulation*, *101*(11), e101-e106.

Deniz, H. B., Ward, A., Jaime Caro, J., Alvarez, P., & Sadri, H. (2009). Cost-benefit analysis of primary prevention of sudden cardiac death with an implantable cardioverter defibrillator versus amiodarone in Canada. *Current Medical Research and Opinion*, *25*(3), 617-626.

Deschryvere, M. (2005). Health and retirement decisions: an update of the literature. Working Paper 932, Retrieved from http://www.econstor.eu/bitstream/10419/63852/1/395909287.pdf

Disney, R., Emmerson, C., & Wakefield, M. (2006). Ill health and retirement in Britain: A panel data-based analysis. *Journal of Health Economics*, *25*(4), 621-649.

Elliott, P. M., & Mohiddin, S. A. (2012). Almanac 2011: cardiomyopathies. *The National Society Journals Present Selected Research That has Driven Recent Advances in Clinical Cardiology. Kardio list*, *7*(1-2), 14-23.

Erwin, C., Williams, J. K., Juhl, A. R., Mengeling, M., Mills, J. A., Bombard, Y., Hayden, M. R., Quaid, K., Shoulson, I., Taylor, S., & Paulsen, J. S. (2010). Perception, experience, and response to genetic discrimination in Huntington disease: The international RESPOND‐HD study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *153*(5), 1081-1093.

Etchegary, H., Enright, G., Audas, R., Pullman, D., Young, T-L., Hodgkinson, K. (2015). Perceived economic burden associated with an inherited cardiac condition: a qualitative inquiry with families affected by arrhythmogenic right ventricular cardiomyopathy caused by a TMEM43 p.S358L disease causing mutation. *Genetics in Medicine.* doi:10.1038/gim.2015.132.

Freedman, V. A. and Martin, L. (1999). The role of education in explaining and forecasting trends in functional limitations among older Americans. *Demography,* 36(4): 461–473.

Gallo, A. M., Hadley, E. K., Angst, D. B., Knafl, K. A., & Smith, C. A. (2008). Parents' concerns about issues related to their children's genetic conditions. *Journal for Specialists in Pediatric Nursing*, *13*(1), 4-14.

Gannon, B., & Nolan, B. (2003). *Disability and labour market participation*. Equality Authority. HRB Working Paper. Retrieved from: http://www2.eur.nl/ecuity/public_papers/ECuity3wp8Gannon.pdf

Gemayel, C., Pelliccia, A., Thompson, P. (2001) Arrythmogenic Right Ventricular Cardiomyopathy. *Journal of the American College of Cardiology, 38*(7), 1773-1781.

Gilgun, J. F. (2004). Qualitative methods and the development of clinical assessment tools. *Qualitative Health Research*, *14*(7), 1008-1019.

Goldenberg, I., Moss, A. J., Maron, B. J., Dick, A. W., & Zareba, W. (2005). Cost‐Effectiveness of Implanted Defibrillators in Young People with Inherited Cardiac Arrhythmias. *Annals of Noninvasive Electrocardiology*, *10*(s4), 67-83.

Gordon, R. H., & Blinder, A. S. (1980). Market wages, reservation wages, and retirement decisions. *Journal of Public Economics*, *14*(2), 277-308.

Government of Newfoundland and Labrador (2014). Programs Funded through the Department of Health and Community Services. Retrieved May 24, 2014 from: http://www.health.gov.nl.ca/health/personsdisabilities/fundingprograms_hcs.html#phsp

Griffiths AJF, Miller JH, Suzuki DT, et al (2000). An Introduction to Genetic Analysis. 7th edition. New York: W. H. Freeman;. Penetrance and expressivity. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK22090/

Grossman, M. (1972). On the concept of health capital and the demand for health. *The Journal of Political Economy*, *80*(2), 223.

Grover, S. A., Ho, V., Lavoie, F., Coupal, L., Zowall, H., & Pilote, L. (2003). The importance of indirect costs in primary cardiovascular disease prevention: can we save lives and money with statins. *Archives of Internal Medicine*, *163*(3), 333-339.

Guiraudon, G. M., Klein, G. J., Gulamhusein, S. S., Painvin, G. A., Del Campo, C., Gonzales, J. C., & Ko, P. T. (1983). Total disconnection of the right ventricular free wall: surgical treatment of right ventricular tachycardia associated with right ventricular dysplasia. *Circulation*, *67*(2), 463-470.

Hamilton, R. M. (2009). Arrhythmogenic right ventricular cardiomyopathy. *Pacing and Clinical Electrophysiology*, *32*(s2), S44-S51.

Hansen, J. (2000). The effect of work absence on wages and wage gaps in Sweden. *Journal of Population Economics*, *13*(1), 45-55.

Health Canada. (2012a). Canada's Health Care System: Additional (Supplementary) services. Retrieved May 2, 2014 from: http://www.hc-sc.gc.ca/hcs-sss/pubs/system-regime/2011-hcs-sss/index-eng.php#a11

Health Canada. (2012b). Canada's Health Care System: The federal government. Retrieved May 2, 2014 from: http://www.hc-sc.gc.ca/hcs-sss/pubs/system-regime/2011-hcs-sss/index-eng.php#a5

Heart and Stoke Foundation of Canada. (2011a) Antiarrhythmics. Retrieved on April 29, 2014 from: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3484147/k.174A/Heart_disease__Antiarrhythmics.htm

Heart and Stroke Foundation of Canada. (2011b) Beta-blockers. Retrieved on April 29, 2014 from: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3484113/k.7B27/Heart_disease__Betablockers.htm

Heart and Stroke Foundation of Canada. (2012) Heart Transplant Surgery. Retrieved April 29, 2014 from: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3831903/k.30F/Heart_disease__Heart_transplant_surgery.htm

Heart and Stroke Foundation of Canada. (2013a) Implantable Cardioverter Defibrillator. Retrieved April 29, 2014 from: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3831917/k.8279/Heart_disease__Implantable_cardioverter_defibrillator_ICD.htm

Heart and Stroke Foundation of Canada. (2013b) What is heart failure? Retrieved on April 28, 2014 from: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3484065/k.C530/Heart_disease__Heart_failure.htm

Hodgkinson, K. A., Connors, S. P., Merner, N., Haywood, A., Young, T. L., McKenna, W. J., Gallagher, B., Curtis, F., Bassett, A.S., & Parfrey, P. S. (2013). The natural history of a genetic subtype of arrhythmogenic right ventricular cardiomyopathy caused by a p. S358L mutation in TMEM43. *Clinical Genetics*, *83*(4), 321-331.

Hodgkinson, K. A., Parfrey, P. S., Bassett, A. S., Kupprion, C., Drenckhahn, J., Norman, M. W., & Connors, S. P. (2005). The impact of implantable cardioverter-defibrillator therapy on survival in autosomal-dominant arrhythmogenic right ventricular cardiomyopathy (ARVD5). *Journal of the American College of Cardiology*, *45*(3), 400-408.

Hurley, J., & Guindon, G. H., (2008). Private Health Insurance in Canada. *Centre for Health Economics and Policy Analysis (CHEPA) McMaster University (Working Paper 08-04)* Retrieved May 5, 2014 from*: http://chepa.org/docs/working-papers/chepa-wp-08-04-.pdf*

Jappelli, T., Pistaferri, L., & Weber, G. (2007). Health care quality, economic inequality, and precautionary saving. *Health Economics*, *16*(4), 327-346.

Jeon, Y. H., Essue, B., Jan, S., Wells, R., & Whitworth, J. A. (2009). Economic hardship associated with managing chronic illness: a qualitative inquiry. *BMC Health Services Research*, *9*(1), 182.

Jiménez-Martín, S., Labeaga, J. M., & Martinez-Granado, M. (1999). Health status and retirement decisions for older European couples. Working Paper 99-82. Retrieved from: http://orff.uc3m.es/bitstream/handle/10016/6170/we998230.PDF?sequence=1

Johansen, H. (1999). Living with heart disease-the working-age population. *Health reports/Statistics Canada, Canadian Centre for Health Information Rapports sur la sante/Statistique Canada, Centre Canadien d'information sur la sante*, *10*(4), 33-45.

Jönsson, B. (1996). Measurement of health outcome and associated costs in cardiovascular disease. *European Heart Journal*, *17*(suppl A), 2-7.

Kemler, M. A., & Furnée, C. A. (2002). The impact of chronic pain on life in the household. *Journal of Pain and Symptom Management*, *23*(5), 433-441.

Laizzo, P.A., (2009). Handbook of Cardiac Anatomy, Physiology and Devices. New York, NY: Springer.

Lillard, L. A., & Weiss, Y. (1997). Uncertain health and survival: Effects on end-of-life consumption. *Journal of Business & Economic Statistics*, *15*(2), 254-268.

Lindholm, C., Burström, B., & Diderichsen, F. (2002). Class differences in the social consequences of illness. *Journal of Epidemiology and Community Health*, *56*(3), 188-192.

Longo, C. J., Fitch, M., Deber, R. B., & Williams, A. P. (2006). Financial and family burden associated with cancer treatment in Ontario, Canada. *Supportive Care in Cancer*, *14*(11), 1077-1085.

Luft, H. S. (1975). The impact of poor health on earnings. *The Review of Economics and Statistics*, *57*(1), 43-57.

Marcus, F. I., Edson, S., & Towbin, J. A. (2013). Genetics of Arrhythmogenic Right Ventricular Cardiomyopathy A Practical Guide for Physicians. *Journal of the American College of Cardiology*, *61*(19), 1945-1948.

Marcus, F. I., Fontaine, G. H., Guiraudon, G., Frank, R., Laurenceau, J. L., Malergue, C., & Grosgogeat, Y. (1982). Right ventricular dysplasia: a report of 24 adult cases. *Circulation*, *65*(2), 384-398.

Marcus, F. I., McKenna, W. J., Sherrill, D., Basso, C., Bauce, B., Bluemke, D. A., Calkins, H., Corrado, D., Cox, M.G.P.J., Daubert, J.P., Fontaine, G., Gear, K., Hauer, R., Nava, A., Picard., M.H., Protonotarios, N., Saffitz, J.E., Sanborn, D.N.Y., Steinberg, J.S., Tandri, H., Thienne, G., Towbin, J., Tsatsopoulou, A., Wichter, T., & Zareba, W. (2010). Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia Proposed Modification of the Task Force Criteria. *European Heart Journal*, *31*(7), 806-814.

McGillion, M., Croxford, R., Watt-Watson, J., LeFort, S., Stevens, B., & Coyte, P. (2008). Cost of illness for chronic stable angina patients enrolled in a self-management education trial. *Canadian Journal of Cardiology*, *24*(10), 759-764.

McKenna, W. J., Thiene, G., Nava, A., Fontaliran, F., Blomstrom-Lundqvist, C., Fontaine, G., & Camerini, F. (1994). Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *British Heart Journal*, *71*(3), 215.

Menses, K., Azuero, A., Hassey, L., McNees, P., Pisu, M. (2012). Does economic burden influence quality of life in breast cancer survivors? *Gynecologic Oncology.* 123(3), 437-443.

Merner, N. D., Hodgkinson, K. A., Haywood, A. F., Connors, S., French, V. M., Drenckhahn, J. D., Kupprion, C., Ramadanova, K., Thierfelder, L., McKenna, W., Gallagher, B., Morris-Larkin, L., Bassett, A., Parfrey, P.S., & Young, T. L. (2008). Arrhythmogenic Right Ventricular Cardiomyopathy Type 5 Is a Fully Penetrant, Lethal Arrhythmic Disorder Caused by a Missense Mutation in the TMEM43 Gene. *The American Journal of Human Genetics*, *82*(4), 809-821.

Miah, M. S., & Wilcox-Gök, V. (2007). Do the sick retire early? Chronic illness, asset accumulation and early retirement. *Applied Economics*, *39*(15), 1921-1936.

Milting, H., Klauke, B., Christensen, A. H., Müsebeck, J., Walhorn, V., Grannemann, S., Münnich, T., Saric, T., Rasmussen, T.B., Jensen, H.K., Mogensen, J., Baecker, C., Romaker, E., Laser, K.T., Knyphausen, E., Kassner, A., Gummert, J., Judge, D.P., Connors, S., Hodgkinson, K., Young, T.L., Zwaag, P.A., Tintelen, P., & Anselmetti, D. (2014). The TMEM43 Newfoundland mutation p. S358L causing ARVC-5 was imported from Europe and increases the stiffness of the cell nucleus. *European Heart Journal*, doi: 10.1093/eurheartj/ehu077

Mindell, J. S., Giampaoli, S., Goesswald, A., Kamtsiuris, P., Mann, C., Männistö, S., Morgan, K., Shelton, N., Verschuren, M., & Tolonen, H. (2015). Sample selection, recruitment and participation rates in health examination surveys in Europe–experience from seven national surveys. *BMC Medical Research Methodology*, *15*(1), 1.

Moore, D., Tarnai, J. (2002) Evaluating nonresponse error in mail surveys. *Survey Nonresponse,* Wiley & Sons, New York, NY, 197-211.

Murray, B. (2012) Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy: a review of molecular and clinical literature. *Journal of Genetic Counseling,* (21), 494-504.

Norman, G. (2010). Likert scales, levels of measurement and the “laws” of statistics. *Advances in Health Sciences Education*, *15*(5), 625-632.

Oster, E., Shoulson, I., Dorsey, E.R. (2013a). Limited Life expectancy, Human Capital and Health Investments. *American Economic Review*, 103(5), 1977-2002.

Oster, E., Shoulson, I., Dorsey, E.R. (2013b). Optimal Expectation and Limited Medical Testing: Evidence from Huntington Disease. *American Economic Review,* 103(2), 804-830.

Pallant, J. (2010). *SPSS survival manual: A step by step guide to data analysis using SPSS* (4th ed.). Maidenhead: Open University Press/McGraw-Hill.

Palumbo, M. G. (1999). Uncertain medical expenses and precautionary saving near the end of the life cycle. *The Review of Economic Studies*, *66*(2), 395-421.

Paris, V., Devaux M., & Wei, L., (2010). Health Systems Institutional Characteristics: A Survey of 29 OECD Countries, *OECD Health Working Papers*, No. 50, OECD Publishing. Retrieved from http://dx.doi.org/10.1787/5kmfxfq9qbnr-en

Pedhazur, E. J. (1997). Multiple regression in behavioral research: Explanation and prediction. Toronto, ON: Harcourt Brace College Publishers

Pelkowski, J. M., & Berger, M. C. (2004). The impact of health on employment, wages, and hours worked over the life cycle. *The Quarterly Review of Economics and Finance*, *44*(1), 102-121.

Perri, T. J. (1984). Health status and schooling decisions of young men. *Economics of Education Review,* 3(3): 207–213.

Pattenden, J. F., Roberts, H., & Lewin, R. J. P. (2007). Living with heart failure; patient and carer perspectives. *European Journal of Cardiovascular Nursing*, *6*(4), 273-279.

Pirzada, A., Connors, S., Williams, A., Collier, A., Curtis, F., Gallagher, B., Young T., Hodgkinson, K. (2015). Diagnostic dilemmas and the power of genetics: a case report. Canadian Cardiovascular Congress, October 2015, Toronto.

Pit, S. W., Shrestha, R., Schofield, D., & Passey, M. (2010). Health problems and retirement due to ill-health among Australian retirees aged 45–64 years. *Health Policy*, *94*(2), 175-181.

Pullman, D., & Lemmens, T. (2010). Keeping the GINA in the bottle: assessing the current need for genetic non-discrimination legislation in Canada. *Open Medicine*, *4*(2), e95.

Radwin, L. E., Washko, M., Suchy, K. A., & Tyman, K. (2005, January). Development and pilot testing of four desired health outcomes scales. *Oncology Nursing Forum,* 32(1), 92-96.

Ranzi, T. L., D'Errico, A., & Costa, G. (2013). Association between chronic morbidity and early retirement in Italy. *International Archives of Occupational and Environmental Health*, *86*(3), 295-303.

Romero, J., Mejia-Lopez, E., Manrique, C., & Lucariello, R. (2013). Arrhythmogenic right ventricular cardiomyopathy (ARVC/D): a systematic literature review. *Clinical Medicine Insights. Cardiology*, *7*, 97-114. doi:10.4137/CMC.S10940.

Ruger, J. P., Jamison, D. T., Bloom, D. E., & Canning, D. (2011). Chapter 15: Health and the economy. *Global health: diseases, programs systems and policies*, 757-814. Retrieved from http:ssrn.com/abstract=1952056.

Sanmartin, C., Hennessy, D., Lu, Y., Law, M.R. (2014) Trends in out-of-pocket health care expenditures in Canada, by household income, 1997-2009. Health Reports: Statistics Canada Catalogue no.82-003-X.

Sammartino, F. J. (1987). The Effect of Health on Retirement . *Social Security Bulletin, 50*, 31.

Schofield, D. J., Shrestha, R. N., Passey, M. E., Earnest, A., & Fletcher, S. L. (2008). Chronic disease and labour force participation among older Australians. *Medical Journal of Australia*, *189*(8), 447.

Schofield, D. J., Shrestha, R. N., Percival, R., Passey, M. E., Callander, E. J., & Kelly, S. J. (2012b). The personal and national costs of early retirement because of spinal disorders: impacts on income, taxes, and government support payments. *The Spine Journal*, *12*(12), 1111-1118.

Schofield, D., Kelly, S., Shrestha, R., Passey, M., Callander, E., & Percival, R. (2012a). The long term financial impacts of CVD: Living standards in retirement. *International Journal of Cardiology*, *155*(3), 406-408.

Sen-Chowdhry S., Morgan, R., Chambers, J., McKenna, W. (2010). Arrhythmogenic Cardiomyopathy: etiology, diagnosis, and treatment. *Annual Review of Medicine,* 61, 233-253.

Shultz, T.W. (1961). Investment in human capital. *American Economic Review,* 51(1), 1–17.

Sickles, R. C., & Taubman, P. (1984). An analysis of the health and retirement status of the elderly. NBER Working Paper No. 1459. Retrieved from http://www.nber.org/papers/w1459

Siddiqui, S. (1997). The impact of health on retirement behavior: empirical evidence from West Germany. *Health economics*, *6*(4), 425-438.

Smith, J. P. (1999). Healthy bodies and thick wallets: the dual relation between health and economic status. *The Journal of Economic Perspectives: A Journal of the American Economic Association*, *13*(2), 144.

Smith, W. (2011). Guidelines for the diagnosis and management of arrhythmogenic right ventricular cardiomyopathy. *Heart, Lung and Circulation*, *20*(12), 757-760.

Stevens, J. (1996). Applied multivariate statistics for the social sciences (3rd ed). Boston, MT: Houghton Mifflin.

Stuckler, D., & Siegel, K. (Eds.). (2011). *Sick societies: responding to the global challenge of chronic disease*. New York, NY: Oxford University Press.

Suhrcke, M., McKee, M., Stuckler, D., Sauto Arce, R., Tsolova, S., & Mortensen, J. (2006). The contribution of health to the economy in the European Union. *Public Health*, *120*(11), 994-1001.

Tabib, A., Loire, R., Chalabreysse, L., Meyronnet, D., Miras, A., Malicier, D., Thivolet, F., Chevalier, P., & Bouvagnet, P. (2003). Circumstances of death and gross and microscopic observations in a series of 200 cases of sudden death associated with arrhythmogenic right ventricular cardiomyopathy and/or dysplasia. *Circulation*, *108*(24), 3000-3005.

Teachman, J. (2012). Health Limitations and Post-Secondary School Enrollment. *Population Research and Policy Review*, *31*(1), 85-96.

Teare, M. D. (Ed.). (2011). *Genetic epidemiology*. Springer: New York, NY: Humana Press.

U.S Department of Health and Human Services. (2008) *Genetic Information Nondiscrimination Act (GINA)*. Retrieved from http://www.gpo.gov/fdsys/pkg/PLAW-110publ233/pdf/PLAW-110publ233.pdf

Van de Mheen, H., Stronks, K., Schrijvers, C. T., & Mackenbach, J. P. (1999). The influence of adult ill health on occupational class mobility and mobility out of and into employment in the Netherlands. *Social Science & Medicine*, *49*(4), 509-518.

Watkins, K. E., Way, C. Y., Gregory, D. M., LeDrew, H. M., Ludlow, V. C., Esplen, M. J., Dowden J. J., Cox, J. E., Fitzgerald, G.W.N., & Parfrey, P. S. (2013). Development and preliminary testing of the psychosocial adjustment to hereditary diseases scale. *BMC Psychology*, *1*(1), 7.

Ware, J. E., & Gandek, B. (1998). Methods for testing data quality, scaling assumptions, and reliability: the IQOLA Project approach. *Journal of Clinical Epidemiology*, *51*(11), 945-952.

Wichter, P. D. D. T., Paul, T. M., Eckardt, L., Gerdes, P., Kirchhof, P., Böcker, D., & Breithardt, G. (2005). Arrhythmogenic Right Ventricular Cardiomyopathy. *Herz Kardiovaskuläre Erkrankungen*, *30*(2), 91-101.

World Health Organization [WHO]. (2009). WHO guide to identifying the economic consequences of disease and injury. Retrieved from http://www.who.int/choice/publications/d_economic_impact_guide.pdf

Yen, L., McRae, I., Jeon, Y. H., Essue, B., & Herath, P. (2011). The impact of chronic illness on workforce participation and the need for assistance with household tasks and personal care by older Australians. *Health & Social Care in the Community*, *19*(5), 485-494.

Zumbo, B.D., & Chan, E. K. H. (2014). *Validity and Validation in Social, Behavioural, and Health Sciences, Social indicators Research Series 54.* Switzerland: Springer

Appendices

Appendix A: ARVC Task Force Diagnostic Criteria (Mckenna et al., 1994; Marcus et al., 2010)

1994 Task Force Criteria	2010 Task Force Criteria
1. Global and/or regional dysfunction and structural alterations	
Major -Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment -Localized RV aneurisms (akinetic or dyskinetic areas with diastolic bulging) -Severe degmental dilation of the RV	By 2D Echo: -Regional RV akinesia, dyskinesia, or aneurysm *and* 1 of the following (end diastole): • -PLAX RVOT ≥ 32mm (corrected for body size [PLAX/BSA] ≥ 19 mm/m^2) • -PLAX RVOT ≥ 36mm (corrected for body size [PLAX/BSA] ≥ 21 mm/m^2) • *or* fractional area change ≤ 33% By MRI: - Regional RV akinesia, or dyskinesia or dyssynchronous RV contraction *and* 1 of the following: • -Ratio or RV end-diastolic volume to BSA ≥110mL/m^2 (male) or ≥ 100mL/m^2 (female) • *or* RV ejection fraction ≤ 40% By RV angiography: -Regional RV akinesia, dyskinesia or aneurysm
Minor - Mild global RV dilatation and/or ejection fraction reduction with normal LV -Mild segmental dilation of the RV -Regional RV hypokinesia	By 2D echo: -Regional RV akinesia or dyskinesia *and* 1 of the following (end diastole): • -PLAX RVOT ≥29mm to < 32mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m^2) • -PLAX RVOT ≥ 32 to <36mm (corrected for body size [PLAX/BSA] ≥18 to < 21 mm/m^2) • *or* fractional area change > 33% to ≤ 40% By MRI: - Regional RV akinesia or dyskinesia or dyssynchronous RV contraction - *and* 1 of the following: • Ratio of RV end-diastolic volume to BSA≥ 100 to < 110 mL/m^2 (male) or ≥90 to 100 mL/m^2 (female) • *or* RV ejection fraction >40% to ≤ 45%

2. Tissue characterization of walls	
Major - Fibrofatty replacement of the myocardium on endomyocardial biopsy	-Residual mycocytes < 60% by morphometric analysis (or < 50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with our without fatty replacement of tissue on endomyocardial biopsy
Minor	-Residual mycocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with our without fatty replacement of tissue on endomyocardial biopsy
3. Repolarization Abnormalities	
Major	- Inverted T waves in right precordial leads (V_2 and V_3) (people age > 12years, in the absence of right-bundle-branch- block
Minor - Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals > 14 years of age (in the absence of complete right bundle-branch-block QRS ≥ 120 ms)	- Inverted T waves leads V_1 and V_2 in individuals > 14 years of age (in the absence of complete right bundle-branch-block) or in V_4, V_5, or V_6. - Inverted T waves leads V_1 V_2, V_3, and V_4 in individuals > 14 years of age in the presence of complete right bundle-branch-block
4. Depolarization/conduction Abnormalities	
Major - Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V_1 to V_3)	- Late potentials (SAECG)
Minor - Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordical leads (V_1 to V_3)	- Late potentials by SAECG in ≥ 1 of 3 parameters in the absence of QRS duration of ≥ 110 ms on the standard ECG - Filtered QRS duration (fQRS) ≥ 114 ms -Duration of terminal QRD <40 μV (low-amplitude signal duration) ≥ 38 ms - Root-mean-square voltage terminal 40 ms ≤ 20 μV - Terminal activation duration of QRS ≥ 55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V_1, V_2, or V_3, in the absence of complete right bundle-branch block
5. Arrhythmias	

Major	-Left bundle-branch block-type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise) -Frequent ventricular extrasystoles (>1000 per 24 hours) (Holter)
Minor - Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III and aVF and positive lead aVL)	- Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III and aVF and negative in lead aVL) or of unknown axis. - >500 ventricular extrasystoles per 2 hours (Holter)
6. Family History	
Major - Family disease confirmed at necropsy or surgery	- Family history of premature sudden death (<35 years of age) due to suspected ARVC/D) - Familial History (clinical diagnosis based on present criteria)
Minor - ARVC/D confirmed in a first-degree relative who meets current Task Force criteria - ARVC/D confirmed pathology at autopsy or surgery in a first-degree relative - Identification of a pathogenic mutation categorized as associated or probably associated with ARVC/D in the patient under evaluation	- History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force Criteria - Premature sudden death (< 35 years of age) due to suspected ARVC/D in a first-degree relative - ARVC/D confirmed pathologically or by the current Task Force criteria in second-degree relative

Appendix B: *Canada Health Act* Principles (Health Canada, 2012b)

Public Administration:

The provincial and territorial plans must be administered and operated on a non-profit basis by a public authority accountable to the provincial or territorial government.

Comprehensiveness:

The provincial and territorial plans must insure all medically necessary services provided by hospitals, medical practitioners and dentists working within a hospital setting.

Universality:

The provincial and territorial plans must entitle all insured persons to health insurance coverage on uniform terms and conditions.

Accessibility:

The provincial and territorial plans must provide all insured persons reasonable access to medically necessary hospital and physician services without financial or other barriers.

Portability:

The provincial and territorial plans must cover all insured persons when they move to another province or territory within Canada and when they travel abroad. The provinces and territories have some limits on coverage for services provided outside Canada, and may require prior approval for non-emergency services delivered outside their jurisdiction.

Appendix C: Original Study Documents

C1: Study Consent Form

Consent to Take Part in Research

TITLE: Understanding the psychosocial and economic effects of arrhythmogenic right ventricular cardiomyopathy (ARVC) on families in Newfoundland and Labrador

INVESTIGATOR(S): MSc Candidates: Glenn Enright, Erin Baker
Research Supervisors: Dr. Rick Audas, Dr. Holly Etchegary, Dr. Kathy Hodgkinson, Dr. Daryl Pullman.

SPONSOR: Atlantic Canada Opportunities Agency: Atlantic Innovation Fund

You have been invited to take part in a research study. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. You can decide not to take part in the study. If you decide to take part, you are free to leave at any time. This will not affect your usual health care.

Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study.

Please read this carefully. Take as much time as you like. If you like, take it home to think about for a while. Mark anything you do not understand, or want explained better. After you have read it, please ask questions about anything that is not clear.

The researchers will:

- discuss the study with you
- answer your questions
- keep confidential any information which could identify you personally
- be available during the study to deal with problems and answer questions

1. Introduction/Background:

Cardiomyopathies are diseases that lead to a weakening of the heart muscle. They are genetic diseases that may lead to sudden cardiac death. One such disease is known as arrhythmogenic right ventricular cardiomyopathy or ARVC. There are many families in Newfoundland (NL) with this condition. We are interested in the effect this condition has

on families, including the physical, mental, emotional and economic impacts. We hope that by describing psychosocial and economic impacts, we can improve the care we provide to at risk families.

2. Purpose of study:

We want to explore the effects of living in a family at risk for sudden cardiac death due to ARVC, an inherited heart condition common in NL. If we can better understand how this genetic disorder affects people, this should help us improve the care to high risk families.

3. Description of the study procedures:

You will be invited to take part in completing two surveys lasting about 1 hour total. The surveys can be completed wherever you feel most comfortable and will be sent to you in the mail, by email or delivered in person. Once you have completed the surveys we would kindly ask you to return them in the self-addressed postage paid envelopes or by email. There are no right or wrong answers to the questions. We are only interested in your thoughts. The surveys will ask questions about your your family's history of heart disease, your thoughts about living at risk for this condition, and the impact the disease has had on your life and your family's life. Your name will never be reported in any papers or reports written from the surveys.

4. Length of time:

You will be expected to fill out two surveys at a place of your convenience. In total, both surveys will take about one hour to one hour and a half.

5. Possible risks and discomforts:

In general, we do not foresee any risks with this study. However, sometimes it can be hard to talk about genetic diseases in the family, especially those that can cause young death. If you wish, a genetic counsellor will talk about these issues with you. If there are still any issues you wish to talk about, referrals can be made for further follow-up.

6. Benefits:

It is not known whether this study will benefit you.

7. Liability statement:

Signing this form gives us your consent to be in this study. It tells us that you understand the information about the research study. When you sign this form, you do not give up your legal rights. Researchers or agencies involved in this research study still have their legal and professional responsibilities.

8. What about my privacy and confidentiality?

Protecting your privacy is an important part of this study. Every effort to protect your privacy will be made. However it cannot be guaranteed. For example we may be required by law to allow access to research records.

When you sign this consent form you give us permission to

- Collect information from you
- Share information with the people conducting the study
- Share information with the people responsible for protecting your safety

Use of your study information

The research team will collect and use only the information they need for this research study.

This information will include your

- date and place of birth
- sex
- family history
- medical conditions
- medications
- the results of tests and procedures you had before and during the study
- information from study surveys

Your name and contact information will be kept secure by the research team in Newfoundland and Labrador. It will not be shared with others without your permission. Your name will not appear in any report or article published as a result of this study.

Information collected for this study will be kept for twenty years. If you do not wish for the data to be held for this long please select "no" in the correct box below. If you select no, your data will be destroyed following this study.

If you decide to withdraw from the study, the information collected up to that time will continue to be used by the research team. It may not be removed. This information will only be used for the purposes of this study.

Information collected and used by the research team will be stored by Memorial University. Dr. Kathy Hodgkinson, the Provincial Medical Genetics program and the cardiac care unit are responsible for keeping it secure.

Your access to records
You may ask the study researchers to see the information that has been collected about you.

9. Questions or problems:

If you have any questions about taking part in this study, you can meet with the investigators who are in charge of the study at this institution. They are: Dr. Kathy Hodgkinson or Glenn Enright

Dr. Kathy Hodgkinson, 777-6819 Glenn Enright, 699-8741

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
Health Research Ethics Authority
709-777-6974 or by email at info@hrea.ca

***Please return the completed signature page and surveys in the self-addressed postage paid envelope included in this package, and keep the rest of this document for your records. ***

Signature Page

Study title: Understanding the psychosocial and economic effect of arrythmogenic right ventricular cardiomyopathy (ARVC) on families in Newfoundland and Labrador

Name(s) of principal investigators: Glenn Enright
To be filled out and signed by the participant:

	Please check as appropriate:	
I have read the consent.	Yes { }	No { }
I have had the opportunity to ask questions/to discuss this study	Yes { }	No { }
I have received satisfactory answers to all of my questions.	Yes { }	No { }
I have received enough information about the study.	Yes { }	No { }
I have spoken to Dr. Kathy Hodgkinson or Glenn Enright and she/he has answered my questions	Yes { }	No { }
I understand that I am free to withdraw from the study	Yes { }	No { }

- at any time
- without having to give a reason
- without affecting my health care

I understand that it is my choice to be in the study and that I may not benefit.Yes }No { }
I understand how my privacy is protected and my records kept confidential Yes { } No { }

I agree that my data collected for this study be kept for 20 years.	Yes { }	No { }
I agree to take part in this study.	Yes { }	No { }
I agree to be contacted for future research studies.	Yes { }	No { }

_____ _____ _____
Signature of participant Name printed Year Month Day

_____ _____ _____
Signature of person authorized as Name printed Year Month Day

*Substitute decision maker, if applicable*_____

<u>To be signed by the investigator or person obtaining consent</u>

I have explained this study to the best of my ability. I invited questions and gave answers. I believe that the participant fully understands what is involved in being in the study, any potential risks of the study and that he or she has freely chosen to be in the study.

_____ _____
_____
Signature of investigator Name printed Year Month Day

Telephone number: _____

Signature Page for Parent/Guardian

Study title: Understanding the psychosocial and economic effect of arrythmogenic right ventricular cardiomyopathy (ARVC) on families in Newfoundland and Labrador

Name of principal investigator: Glenn Enright

To be filled out and signed by the parent/guardian:

Please check as appropriate:

I have read the consent.Yes { } No { }
I have had the opportunity to ask questions/to discuss this study. Yes { } No { }
I have received satisfactory answers to all of my questions. Yes { } No { }
I have received enough information about the study. Yes { } No { }
I have spoken to, Dr. Kathy Hodgkinson or Glenn Enright and he/she has answered my questions Yes { } No { }
I understand that I am free to withdraw my child/ward from the study Yes { } No { }

- at any time
- without having to give a reason
- without affecting future care

I understand that it is my choice for child/ward to be in the study and that he/she may not benefit Yes { } No { }
I understand how my child/ward's privacy is protected and records kept confidential Yes { } No { }
I agree that my child's/ward's data collected in this study be kept for 20 years. Yes { }No { }
I agree to be contacted for future research studies. Yes { } No { }
I consent for my child/ward _____to take part in this study. Print Name

_____	_____	_____
Signature of parent/guardian	Name printed	Year Month Day

_____	_____	_____
Signature of person conducting the consent discussion	Name printed	Year Month Day

To be signed by the investigator:

have explained this study to the best of my ability. I invited questions and gave answers. I believe that the parent/guardian fully understands what is involved in being in the study, any potential risks of the study and that he or she has freely chosen for the child/ward to be in the study.

_____ _____ _____

Signature of investigator Name Printed Year Month Day

To be signed by the minor participant

Study title: Understanding the psychosocial and economic effect of arrythmogenic right ventricular cardiomyopathy (ARVC) on families in Newfoundland and Labrador

Name of principal investigator: Glenn Enright

Assent of minor participant:

I understand the purpose of this research
I understand that it is my decision to take part in this study. I can stop taking part if I choose.
I understand that taking part in this research may not help me.
I agree that I will take part in this study

Signature of minor participant Year Month Day

Name printed Age

C2: Original Survey and Demographic Sheet

Economic Impact of ARVC Scale

The Economic impact scale has 8 sections with a total of 76 questions.

Each section has several statements that we would like you to rate from **1 (Strongly disagree)** to **5 (Strongly agree)** or indicate **Y (Yes)** or **N (No).**

Please circle the best answer for each.

There is also an opportunity for you to provide any other details you think are important on the final page.

Thank you

Section 1: Education
The first section of this survey relates to education choices. Using the scale given, you are asked to rate your agreement with each statement as it reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree
N/A – Not applicable to me

1. Identification of the gene change that causes ARVC in my family has influenced my education choices.	1	2	3	4	5	
2. My past education choices were influenced by my risk for ARVC.	1	2	3	4	5	
3. Knowing my risk for ARVC, I wish I had made different choices about my education.	1	2	3	4	5	
4. My decision to pursue education in the future is affected by my risk for ARVC.	1	2	3	4	5	N/A
5. I encourage other family members to consider their risk for ARVC when making decisions about their education.	1	2	3	4	5	
6. Knowing their risk for ARVC has affected the education choices of other family members.	1	2	3	4	5	
7. Education choices are important to my family knowing the risk for ARVC.	1	2	3	4	5	

Section 2: Career

The second section of this survey relates to career choices. Using the scale given, you are asked to rate your agreement with each statement as it reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree
N/A – Not applicable to me

1. Identification of the gene change that causes ARVC in my family has influenced my career choices.	1	2	3	4	5	
2. My past career choices were influenced by my risk for ARVC.	1	2	3	4	5	
3. Knowing my risk for ARVC, I wish I had made different choices about my career.	1	2	3	4	5	
4. My decision to pursue certain careers in the future is affected by my risk for ARVC.	1	2	3	4	5	N/A
5. I encourage other family members to consider their risk for ARVC when making decisions about their career.	1	2	3	4	5	
6. Knowing their risk for ARVC has affected the career choices of other family members.	1	2	3	4	5	
7. Medical benefits are an important factor when making career choices as a result of my family's risk for ARVC.	1	2	3	4	5	
8. Career choices are important to my family knowing the risk for ARVC.	1	2	3	4	5	

Section 3: Indirect Costs
The third section of questions relates to personal indirect costs. Using the scale given, you are asked to rate your agreement with each statement as it reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree
Y – Yes
N – No

1. The presence of the gene that causes ARVC in my family has affected my employment.	1 2 3 4 5
2. Knowing my risk for ARVC has caused me to work **less** than I did before finding out my risk.	1 2 3 4 5
3. My work has been disrupted because of time off for medical appointments related to my risk for ARVC.	1 2 3 4 5
4. My work has been disrupted because of time off for other family members' medical appointments related to their risk for ARVC.	1 2 3 4 5
5. Knowing my risk for ARVC has caused me to work **more** than I did before finding out my risk.	1 2 3 4 5
6. I have had to change the type of work that I do at my job because of my risk for ARVC.	1 2 3 4 5
7. I have had to change careers/professions because of my risk for ARVC.	1 2 3 4 5
8. My decision of when I retire has changed because of my risk for ARVC.	1 2 3 4 5
9. My work has been disrupted because of time off to care for a family member, because of their risk for ARVC.	1 2 3 4 5
10. I have had to work less because of another family member's risk for ARVC.	1 2 3 4 5

11. I have had to work more because of another family member's risk for ARVC.	1 2 3 4 5
12. I have changed careers/professions because of another family member's risk for ARVC.	1 2 3 4 5
13. I am unable to work because of my risk for ARVC.	Y N
14. I have had to go on short-term disability because of my risk of ARVC.	Y N
15. I have had to go on long-term disability because of my risk of ARVC.	Y N
16. I am unable to work because of another family member's risk for ARVC.	Y N

Section 4: Indirect Costs – Other Family Members
The fourth section of questions relates to indirect costs to other family members. Using the scale given, you are asked to rate your agreement with each statement as it reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree
Y – Yes
N – No

1. The presence of the gene that causes ARVC in my family has affected another family members' employment.	1 2 3 4 5
2. Knowing my risk for ARVC has caused another family member to work **less** than they did before I found out my risk.	1 2 3 4 5
3. Another family member's work has been disrupted because of time off for medical appointments related to my risk for ARVC.	1 2 3 4 5
4. Another family member has had to take time off work to care for me because of my risk for ARVC.	1 2 3 4 5
5. Another family member has had to work **more** because of my risk for ARVC.	1 2 3 4 5
6. Another family member has had to change careers/professions because of my risk for ARVC.	1 2 3 4 5
7. Another family member has changed their decision of when to retire because of my risk for ARVC.	1 2 3 4 5
8. Another family member is unable to work because of my risk for ARVC.	Y N

Section 5: Income
The fifth set of questions relates to income. Using the scale given, you are asked to rate your agreement with each statement as it reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree

1. The presence of the gene that causes ARVC in my family has affected my income.	1 2 3 4 5
2. My income has changed because of my risk for ARVC.	1 2 3 4 5
3. My income is less because of my risk for ARVC.	1 2 3 4 5
4. My income has changed because of another family member's risk for ARVC.	1 2 3 4 5
5. My income is less because of another family member's risk for ARVC.	1 2 3 4 5
6. The presence of the gene that causes ARVC in my family has affected another family member's income.	1 2 3 4 5
7. Another family member's income has changed because of my risk for ARVC.	1 2 3 4 5
8. Another family member's income is less because of my risk for ARVC.	1 2 3 4 5
9. Another family member's income is more because of my risk for ARVC.	1 2 3 4 5
10. The presence of the gene that causes ARVC in my family has affected my family's total income.	1 2 3 4 5
11. Changes to my family's income because of the presence of the gene that causes ARVC in my family has been a financial burden.	1 2 3 4 5

Section 6: Direct Costs

The sixth section of questions relates to direct costs. Using the scale given, you are asked to rate your agreement with each statement as it reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree

1. The risk for ARVC in my family has been a financial burden.	1 2 3 4 5
2. The need for regular monitoring for cardiac problems related to ARVC has been a financial burden on my family.	1 2 3 4 5
3. My family has incurred costs because of the need for medications related to ARVC.	1 2 3 4 5
4. The cost of medication related to ARVC has been a financial burden on our family.	1 2 3 4 5
5. My family has incurred costs associated with travel for medical appointments (planned or unplanned) related to ARVC.	1 2 3 4 5
6. My family has had to travel out of province for medical appointments/services related to ARVC.	1 2 3 4 5
7. Costs associated with travel for medical appointments (planned or unplanned) related to ARVC have been a financial burden on my family.	1 2 3 4 5
8. My family has incurred other costs associated with the ARVC gene.	1 2 3 4 5
9. The other costs incurred by my family associated with the ARVC gene have been a financial burden.	1 2 3 4 5

Section 7: Insurance
The seventh section of questions relates to insurance. Using the scale given, you are asked to rate how well each statement reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree
Y– Yes
N– No
N/A – Not Applicable to me

1. The government's Medicare plan covers costs associated with medical services related to my risk of ARVC.	1 2 3 4 5
2. It is difficult for any member of my family (including myself) to buy medical insurance as a result of their risk for ARVC.	1 2 3 4 5 N/A
3. My current medical insurance does not cover costs associated with the ARVC condition that are not already covered by the Government's Medicare plan.	1 2 3 4 5 N/A
4. I am concerned about the future ability of my family members to receive medical insurance as a result of their risk for ARVC.	1 2 3 4 5
5. It is difficult for any member of my family (including myself) to purchase life insurance as a result of our risk for ARVC.	1 2 3 4 5 N/A
6. Insurance is important to my family knowing the risk for ARVC.	1 2 3 4 5
7. I have been denied medical insurance because of my risk for ARVC.	Y N
8. I have paid a higher premium for medical insurance because of my risk for ARVC.	Y N

Section 8: Finances/Spending
The eighth section of questions relates to finances and spending. Using the scale given, you are asked to rate how well each statement reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree

1. I am concerned about the economic/financial future of my family as a result of my risk for ARVC.	1 2 3 4 5
2. I am more aware of my spending habits as a result of my risk for ARVC.	1 2 3 4 5
3. I have changed my spending habits because of my risk for ARVC.	1 2 3 4 5
4. I do more financial planning (saving) because of my risk for ARVC.	1 2 3 4 5
5. I am more aware of my spending habits because of another family member's risk for ARVC.	1 2 3 4 5
6. I am concerned about the economic/financial future of my family as a result of another family members' risk for ARVC.	1 2 3 4 5
7. I have changed my spending habits because of another family member's risk for ARVC.	1 2 3 4 5
8. I do more financial planning (saving) because of another family member's risk for ARVC.	1 2 3 4 5
9. Finances are important to my family knowing the risk for ARVC.	1 2 3 4 5

Please tell us anything else you think is important for you or your family's economics in living with ARVC.

February 4, 2014

ARVC Demographic Information Sheet

We would like to collect some information about you. It will help us compare survey answers among different groups of people. As with all of the information you give us, these responses will be kept confidential.

1. What is your current marital status?

   ☐ Single, never married
   ☐ Married or living with a partner
   ☐ Divorced or separated
   ☐ Widowed

2. How many children do you have? If none, enter zero _____

3. What is the highest level of education you have *completed*?

   ☐ Some high school but no diploma
   ☐ High school diploma
   ☐ Trade school or non-university post-secondary program
   ☐ Some university
   ☐ Bachelor's Degree
   ☐ Graduate Degree
   ☐ Other, please specify _____

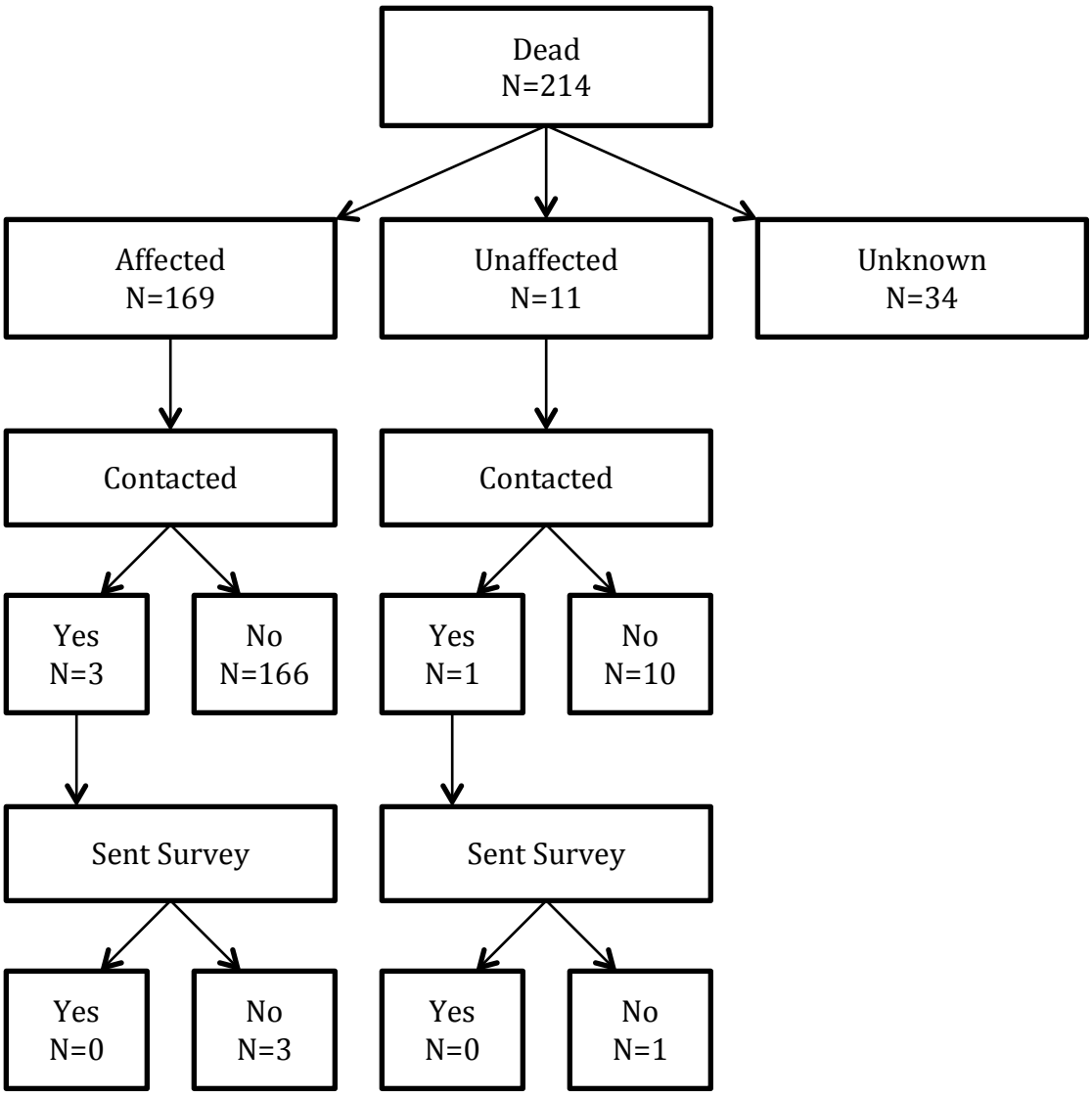
4. What is your current employment status?

   ☐ Employed Full-Time
   ☐ Employed Part – Time
   ☐ Student
   ☐ Retired
   ☐ Unemployed

5. What is your annual household income?

   ☐ Less than $25,000
   ☐ $26,000 – $50,000
   ☐ $51,000 – $75,000
   ☐ $75,000 – $100,000
   ☐ More than $100,000

Appendix D: Deceased Flowchart



Appendix E: Ethics Approval and Amendments

Health Research Ethics Authority

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

October 15, 2013

Mr. Glenn Enright
C/o Dr Rick Audas
Community Health Division
Room 1407
Health Sciences Centre

Dear Mr. Enright:

Reference # 13.096

RE: **Understanding the psychosocial and economic effects of arrgythmogenic right ventricular cardiomyopathy (ARVC) on families in Newfoundland and Labrador**

This will acknowledge receipt of your correspondence.

This correspondence has been reviewed by the Chair under the direction of the Board. ***Full board approval*** of this research study is granted for one year effective **October 3, 2013.**

This is to confirm that the Health Research Ethics Board reviewed and approved or acknowledged the following documents (as indicated):

- Application, approved
- Letter from child psychologist, acknowledged
- Economic Impact ARVC Scale (Youth Version), approved
- Hereditary Diseases and Genetic Testing (HD-GT) Scale (ARVC Youth Version), approved
- Psychosocial Adjustment to Hereditary Diseases (PAHD) Scale (ARVC Youth Version), approved
- Revised consent form, dated August 26, 2013, approved

MARK THE DATE

This approval will lapse on October 3, 2014. **It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HREB office prior to the renewal date; you may not receive a reminder, therefore the ultimate responsibility is with you as the Principle Investigator.** *The information provided in this form must be* ***current to the time of submission*** *and submitted to HREB* ***not less than 30 nor more than 45 days*** *of the anniversary of your approval date.* The Ethics Renewal form can be downloaded from the HREB website http://www.hrea.ca.

email: info@hrea.ca Phone: 777-8949 FAX: 777-8776

The Health Research Ethics Board advises THAT IF YOU DO NOT return the completed Ethics Renewal form prior to date of renewal:

- *Your ethics approval will lapse*
- *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

It is **your responsibility to seek the necessary approval from the Regional Health Authority or other organization as appropriate.**

Modifications of the protocol/consent are not permitted without prior approval from the Health Research Ethics Board. Implementing changes in the protocol/consent without HREB approval may result in the approval of your research study being revoked, necessitating cessation of all related research activity. Request for modification to the protocol/consent must be outlined on an amendment form (available on the HREB website) and submitted to the HREB for review.

This research ethics board (the HREB) has reviewed and approved the research protocol and documentation as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Health Research Ethics Board currently operates according to *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*; ***ICH Guidance E6: Good Clinical Practice*** **and applicable laws and regulations. The membership of this research ethics board is constituted in compliance with the membership requirements for research ethics boards as defined by** ***Health Canada Food and Drug Regulations Division 5; Part C.***

Notwithstanding the approval of the HREB, the primary responsibility for the ethical conduct of the investigation remains with you.

We wish you every success with your study.

Sincerely,

Dr Fern Brunger, PhD (Chair Non-Clinical Trials)
Ms. Patricia Grainger, (Vice-Chair Non-Clinical Trials)
Health Research Ethics Board

For Office Use only: October 17, 2013

Health Research Ethics Board
777-6974 (Phone)
777-8776 (Fax)

RECEIVED NOV 13 2013

Version June 2013

Request for Amendment to an Approved Application

HREB #: 13.096	**Current Date**: November 12th 2013

Title of study: Include protocol number, if any.

Understanding the economic and psychosocial impact of Arrythmogenic Right Ventricular Cardiomyopathy (ARVC) on families in Newfoundland and Labrador.	
Amendment Date: November 12th 2013	**Version #** (if applicable):

Are these changes editorial and/or administrative?	Yes	**No**
Will there be any increase in risk, discomfort or inconvenience to the participants?	Yes (Specify below)	**No**
Are there changes to inclusion or exclusion criteria?	Yes (Specify below)	**No**
Is a modification to the consent form required?	**Yes** (Append form)	No

Summarize the significant changes being requested. It is not necessary to itemize editorial, administrative and similar changes.

1.The economic survey has been updated from six sections with 43 questions to eight sections with 76 questions (Youth 67 questions) and now uses a different scale. There has been no change to the general topics covered in the survey questions.
2. Participants will be given the option to receive the study documents by email. The invitation process will not change as a member of the research team with a long standing relationship (Kathy Hodgkinson or Fiona Curtis) with potential participants will make the initial contact. After the initial invitation, the research team will confirm contact information and the study documents will be distributed using mail, email or in person chosen by the participants. The consent form has been amended to include email as a distribution option for survey documents.

What is the rationale for the amendment(s)?

1.Additional professionals with clinical experience involving ARVC patients and the research team reviewed the economic survey and new questions were identified. These additional questions aim to better meet the study objectives particularly the impact of ARVC on families in addition to individuals at risk.
2. It has come to the attention of the research team that some potential participants would prefer email communication as their means to participate. Allowing participants to choose how they receive the study documents should increase convenience for participants and improve the response rate.

Other pertinent information – List ALL documents, including version dates, to be reviewed:

Final_Economic Survey ARVC_Nov 11 2013
Final_ Youth Economic Survey ARVC_Nov 11 2013
Final _Quantitative phase consent form November 12, 2013

Glenn Enright — Printed Name of Principal Investigator
Signature of Principal Investigator
2013/11/12 — Date

HREB #: 13.096	Amendment Date: NOV 12, 2013	Version:

Health Research Ethics Board
777-6974 (Phone)
777-8776 (Fax)

This Health Research Ethics Board (the HREB) has reviewed the amendment as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified study site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Health Research Ethics Board currently operates according to Tri-Council Policy Statement (TCPS2) and applicable laws and regulations. The membership of this research ethics board complies with the membership requirements for research ethics boards defined in TCPS2.

***Full Board** Review and Approval granted at* N/A *Meeting*

Signature Chair (Dr. Fern Brunger) *Date*

Signature Vice-Chair (Patricia Grainger) *Date*

OR

***Reported** to Full Committee at* NOV 28, 2013 *Meeting*

Approved by:

Signature Chair (Dr. Fern Brunger) APPROVED NOV 15 2013 *Date*

Signature Vice-Chair (Patricia Grainger) *Date*

*Attach additional documentation if necessary

Health Research Ethics Board
777-6974 (Phone)
777-8776 (Fax)

Version June 2013

Request for Amendment to an Approved Application

HREB #: 13.096	Current Date: February 4th 2014

Title of study: Include protocol number, if any.

Understanding the economic and psychosocial impact of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) on families in Newfoundland and Labrador.	
Amendment Date: February 4th 2014	**Version #** (if applicable):

Are these changes editorial and/or administrative?	Yes	No X
Will there be any increase in risk, discomfort or inconvenience to the participants?	Yes (Specify below)	No X
Are there changes to inclusion or exclusion criteria?	Yes (Specify below)	No X
Is a modification to the consent form required?	Yes (Append form)	No X

Summarize the significant changes being requested. It is not necessary to itemize editorial, administrative and similar changes.

1. We request the addition of a brief demographic section comprised of five additional questions including marital status, number of children, highest level of education completed, employment status, and annual household income. This section will be appended to one of the current surveys.

What is the rationale for the amendment(s)?

1. In order to properly reflect the literature the collection of additional demographic variables is required. These variables will also aid in achieving the study objectives. Originally, demographic information was going to be accessed through the pre-existing SPSS dataset however it has been determined that there is not sufficient demographic information contained within the dataset to reflect the literature and answer all study objectives.

Other pertinent information – List ALL documents, including version dates, to be reviewed:

1. ARVC Demographic Sheet February 4th 2014

Glenn Enright _____ _____ Feb 4 2014
Printed Name of Principal Investigator **Signature of Principal Investigator** **Date**

HREB #: 13.096	Amendment Date: Feb 4, 2014	Version:

RECEIVED Feb 05 2014

Health Research Ethics Board
777-6974 (Phone)
777-8776 (Fax)

This Health Research Ethics Board (the HREB) has reviewed the amendment as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified study site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Health Research Ethics Board currently operates according to Tri-Council Policy Statement (TCPS2) and applicable laws and regulations. The membership of this research ethics board complies with the membership requirements for research ethics boards defined in TCPS2.

***Full Board** Review and Approval granted at* N/A *Meeting*

Signature Chair (Dr. Fern Brunger) *Date*

Signature Vice-Chair (Patricia Grainger) *Date*

OR

***Reported** to Full Committee at* February 20, 2014 *Meeting*

Approved by:

Signature Chair (Dr. Fern Brunger) *Date*

Signature Vice-Chair (Patricia Grainger) *Date*

APPROVED FEB 05 2014

*Attach additional documentation if necessary

Health Research Ethics Board
777-6974 (Phone)
777-8776 (Fax)

RECEIVED FEB 13 2014

Request for Amendment to an Approved Application

HREB #: 13.096	**Current Date**: February 12th 2014

Title of study: Include protocol number, if any.

Understanding the economic and psychosocial impact of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) on families in Newfoundland and Labrador.	
Amendment Date: February 12th 2014	**Version #** (if applicable):

Are these changes editorial and/or administrative?	Yes	No X
Will there be any increase in risk, discomfort or inconvenience to the participants?	Yes (Specify below)	No X
Are there changes to inclusion or exclusion criteria?	Yes (Specify below)	No X
Is a modification to the consent form required?	Yes (Append form)	No X

Summarize the significant changes being requested. It is not necessary to itemize editorial, administrative and similar changes.

1. We request the addition of Dr. Charlene Simmonds as an approved member of our research team to make initial contact with potential participants by phone on behalf of Dr. Kathy Hodgkinson & Ms. Fiona Curtis.

What is the rationale for the amendment(s)?

1. Ms. Fiona Curtis will be leaving on maternity leave and therefore will not be able to contact potential participants.

Other pertinent information – List ALL documents, including version dates, to be reviewed:

Glenn Enright _____ _____ Feb 12 2014
Printed Name of Principal Investigator **Signature of Principal Investigator** **Date**

HREB #: 13.096	Amendment Date: Feb 12, 2014	Version:

Health Research Ethics Board
777-6974 (Phone)
777-8776 (Fax)

This Health Research Ethics Board (the HREB) has reviewed the amendment as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified study site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Health Research Ethics Board currently operates according to Tri-Council Policy Statement (TCPS2) and applicable laws and regulations. The membership of this research ethics board complies with the membership requirements for research ethics boards defined in TCPS2.

***Full Board** Review and Approval granted at* N/A *Meeting*

Signature Chair (Dr. Fern Brunger) *Date*

Signature Vice-Chair (Patricia Grainger) *Date*

OR

Reported to Full Committee at February 20, 2014 ***Meeting***

Approved by:

Signature Chair (Dr. Fern Brunger) *Date*

Signature Vice-Chair (Patricia Grainger) *Date*

*Attach additional documentation if necessary

Appendix F: Scale Validation Tables

Table F1: Assignment of original survey items into hypothesized subscales.

	Hypothesized Subscale					Non Scale Items		Assigned Subscale Item Name
Survey Item	**HC**	**LSP**	**CS**	**FB**	**IN**	**Exc**	**Binomial**	
Edu1	X							HC1
Edu2	X							HC2
Edu3	X							HC3
Edu4	X							HC4
Edu5	X							HC5
Edu6	X							HC6
Edu7						X		N/A
Car1	X							HC7
Car2	X							HC8
Car3	X							HC9
Car4	X							HC10
Car5	X							HC11
Car6	X							HC12
Car7						X		N/A
Car8						X		N/A
Ind1		X						LSP1
Ind2		X						LSP2
Ind3		X						LSP3
Ind4		X						LSP4
Ind5		X						LSP5
Ind6		X						LSP6
Ind7		X						LSP7
Ind8		X						LSP8
Ind9		X						LSP9
Ind10		X						LSP10
Ind11		X						LSP11
Ind12		X						LSP12
Ind13							X	N/A
Ind14							X	N/A
Ind15							X	N/A
Ind16							X	N/A
Indof1		X						LSP13
Indof2		X						LSP14

	Hypothesized Subscale					Non Scale Items		Assigned Subscale Item Name
Survey Item	**HC**	**LSP**	**CS**	**FB**	**IN**	**Exc**	**Binomial**	
Indof3		X						LSP15
Indof4		X						LSP16
Indof5		X						LSP17
Indof6		X						LSP18
Indof7		X						LSP19
Indof8							X	N/A
Incm1		X						LSP20
Incm2		X						LSP21
Incm3		X						LSP22
Incm4		X						LSP23
Incm5		X						LSP24
Incm6		X						LSP25
Incm7		X						LSP26
Incm8		X						LSP27
Incm9		X						LSP28
Incm10		X						LSP29
Incm11				X				FB8
Dir1				X				FB1
Dir2				X				FB2
Dir3			X					CS1
Dir4				X				FB3
Dir5			X					CS2
Dir6						X		N/A
Dir7				X				FB4
Dir8			X					CS3
Dir9				X				FB5
Insur1						X		N/A
Insur2					X			IN1
Insur3					X			IN2
Insur4					X			IN3
Insur5					X			IN4
Insur6						X		N/A
Insur7							X	N/A
Insur8							X	N/A
Fin1				X				FB6
Fin2			X					CS4

	Hypothesized Subscale					Non Scale Items		Assigned Subscale Item Name
Survey Item	**HC**	**LSP**	**CS**	**FB**	**IN**	**Exc**	**Binomial**	
Fin3			X					CS5
Fin4			X					CS6
Fin5			X					CS7
Fin6				X				FB7
Fin7			X					CS8
Fin8			X					CS9
Fin9						X		N/A

Table F2: Survey item descriptives

Item	Mean	SD	Missing (%)	Min	Max	Frequency of response values*					
						1	2	3	4	5	N/A§
Edu1	1.86	1.11	13.6	1	5	30	12	10	3	2	18
Edu2	1.81	1.03	12.1	1	5	30	14	11	1	2	
Edu3	2.35	1.41	6.1	1	5	24	14	10	6	8	
Edu4	2.22	1.42	4.5	1	5	19	12	6	1	7	
Edu5	2.95	1.54	0.0	1	5	19	8	10	15	14	
Edu6	2.55	1.40	0.0	1	5	21	13	17	5	10	
Edu7	2.94	1.48	0.0	1	5	17	9	14	13	13	
Car1	2.20	1.30	10.6	1	5	22	19	8	4	6	
Car2	1.88	1.04	12.1	1	5	25	22	7	1	3	
Car3	2.50	1.46	9.1	1	5	19	19	4	9	9	
Car4	2.39	1.41	1.5	1	5	13	15	3	4	6	24
Car5	3.03	1.42	1.5	1	5	14	10	13	16	12	
Car6	2.56	1.49	3.0	1	5	20	17	11	3	13	
Car7	3.50	1.56	0.0	1	5	14	3	11	12	26	
Car8	3.20	1.51	0.0	1	5	13	12	8	15	18	
Ind1	2.39	1.40	7.6	1	5	20	21	4	8	8	
Ind2	2.08	1.26	6.1	1	5	24	25	3	4	6	
Ind3	2.71	1.46	6.1	1	5	17	16	7	12	10	
Ind4	2.41	1.33	6.1	1	5	19	19	9	9	6	
Ind5	1.66	0.97	6.1	1	5	36	17	4	4	1	
Ind6	2.26	1.40	7.6	1	5	24	19	3	8	7	
Ind7	1.81	1.04	10.6	1	5	28	21	6	1	3	
Ind8	2.56	1.53	6.1	1	5	20	19	3	8	12	
Ind9	2.11	1.28	4.5	1	5	27	18	7	6	5	
Ind10	1.85	1.04	6.1	1	5	28	23	5	4	2	
Ind11	1.55	0.74	6.1	1	5	34	24	3	0	1	
Ind12	1.48	0.75	12.1	1	5	36	18	3	0	1	
Ind13	1.94	0.24	1.5	1	2	4	61				
Ind14	1.92	0.27	3.0	1	2	5	59				
Ind15	1.97	0.18	3.0	1	2	2	62				
Ind16	1.97	0.17	1.5	1	2	2	63				
Indof1	3.08	1.65	3.0	1	5	17	11	7	8	21	
Indof2	1.87	1.18	6.1	1	5	31	20	3	4	4	
Indof3	2.44	1.46	4.5	1	5	24	14	5	13	7	
Indof4	2.10	1.38	6.1	1	5	28	20	1	6	7	
Indof5	1.63	0.91	6.1	1	5	34	22	3	1	2	
Indof6	1.56	0.85	7.6	1	5	35	22	2	0	2	
Indof7	1.73	0.98	6.1	1	5	32	21	5	2	2	
Indof8	2.00	0.00	3.0	2	2	0	64				

Item	Mean	SD	Missing (%)	Min	Max	Frequency of response values*					
						1	2	3	4	5	N/A§
Incm1	2.19	1.43	4.5	1	5	27	20	2	5	9	
Incm2	2.06	1.33	6.1	1	5	27	22	2	4	7	
Incm3	2.14	1.40	4.5	1	5	27	21	3	3	9	
Incm4	1.67	1.06	4.5	1	5	37	19	1	3	3	
Incm5	1.73	1.12	4.5	1	5	36	18	3	2	4	
Incm6	2.44	1.49	4.5	1	5	24	14	8	7	10	
Incm7	1.66	0.97	4.5	1	5	36	18	4	4	1	
Incm8	1.59	0.87	4.5	1	5	36	21	4	0	2	
Incm9	1.58	0.87	6.1	1	5	36	21	2	1	2	
Incm10	2.14	1.38	4.5	1	5	29	16	4	8	6	
Incm11	2.02	1.28	4.5	1	5	29	19	6	3	6	
Dir1	1.98	1.24	3.0	1	5	29	21	6	2	6	
Dir2	2.06	1.14	3.0	1	5	24	24	7	6	3	
Dir3	2.41	1.46	4.5	1	5	24	15	6	10	8	
Dir4	2.08	1.20	3.0	1	5	26	19	12	2	5	
Dir5	3.03	1.52	3.0	1	5	16	11	5	19	13	
Dir6	2.42	1.52	3.0	1	5	25	17	2	10	10	
Dir7	2.64	1.40	3.0	1	5	17	18	9	11	9	
Dir8	2.48	1.43	3.0	1	5	22	16	6	13	7	
Dir9	2.31	1.39	3.0	1	5	24	18	8	6	8	
Insur1	3.61	1.16	7.6	1	5	6	4	9	31	11	17
Insur2	3.63	1.37	4.5	1	5	4	7	9	8	18	
Insur3	2.70	1.25	4.5	1	5	7	16	9	7	5	19
Insur4	3.69	1.31	7.6	1	5	7	3	13	17	21	
Insur5	3.94	1.27	4.5	1	5	4	2	12	8	25	12
Insur6	4.11	1.18	6.1	1	5	3	4	9	13	33	
Insur7	1.73	0.45	4.5	1	2	17	46				
Insur8	1.82	0.39	6.1	1	2	11	51				
Fin1	2.78	1.48	4.5	1	5	17	14	9	12	11	
Fin2	2.52	1.37	4.5	1	5	20	14	11	12	6	
Fin3	2.43	1.38	4.5	1	5	21	17	9	9	7	
Fin4	2.44	1.38	4.5	1	5	23	13	7	16	4	
Fin5	2.11	1.27	4.5	1	5	27	17	9	5	5	
Fin6	2.38	1.44	4.5	1	5	24	15	9	6	9	
Fin7	2.10	1.20	4.5	1	5	26	17	12	4	4	
Fin8	2.17	1.31	6.1	1	5	26	16	8	7	5	
Fin9	3.33	1.46	3.0	1	5	15	2	7	27	13	

* Response values indicate level of agreement, 1 (strongly disagree) through 5 (strongly agree) for likert scoring items, and, 1 (yes) to 2 (no) for binomial items.

§ Only items that were identified as possibly not applicable to some participants included a N/A response option

Table F3: Multitrait/MultiItem Correlation Matrix for Scale Level Assumption Analysis

Item Name	Mean	SD	Pearson Item-Scale Correlations				
			HC	LSP	CS	FB	IN
Scale = HC (Human Capital)							
HC1	1.86	1.11	0.66	0.40	0.45	0.39	0.30
HC2	1.81	1.03	0.78	0.37	0.31	0.29	0.22
HC3	2.35	1.42	0.71	0.34	0.34	0.32	0.36
HC4	2.22	1.43	0.81	0.38	0.42	0.46	0.30
HC5	2.95	1.54	0.83	0.52	0.49	0.48	0.42
HC6	2.55	1.41	0.78	0.46	0.43	0.36	0.47
HC7	2.20	1.30	0.84	0.55	0.49	0.57	0.46
HC8	1.88	1.04	0.68	0.43	0.31	0.41	0.36
HC9	2.50	1.46	0.78	0.44	0.37	0.40	0.46
HC10	2.39	1.41	0.83	0.52	0.57	0.60	0.42
HC11	3.03	1.42	0.79	0.52	0.44	0.44	0.40
HC12	2.56	1.49	0.76	0.44	0.38	0.34	0.43
Scale = LSP (Labour Supply and Productivity)							
LSP1	2.39	1.41	0.59	0.66	0.44	0.51	0.36
LSP2	2.08	1.26	0.63	0.67	0.55	0.56	0.41
LSP3	2.71	1.46	0.50	0.54	0.34	0.37	0.44
LSP4	2.42	1.33	0.41	0.58	0.49	0.49	0.33
LSP5	1.66	0.97	0.18	0.42	0.38	0.40	0.01
LSP6	2.26	1.40	0.64	0.60	0.49	0.48	0.47
LSP7	1.81	1.04	0.57	0.53	0.40	0.43	0.29
LSP8	2.56	1.53	0.66	0.69	0.49	0.51	0.46
LSP9	2.11	1.28	0.41	0.65	0.51	0.55	0.30
LSP10	1.85	1.04	0.32	0.64	0.50	0.52	0.22
LSP11	1.55	0.74	0.22	0.49	0.30	0.31	0.14
LSP12	1.48	0.75	0.18	0.41	0.25	0.24	0.11
LSP13	3.08	1.65	0.24	0.52	0.31	0.36	0.41
LSP14	1.87	1.18	0.26	0.63	0.39	0.40	0.24
LSP15	2.44	1.46	0.31	0.57	0.33	0.32	0.36
LSP16	2.10	1.38	0.26	0.62	0.31	0.34	0.43
LSP17	1.63	0.91	0.10	0.70	0.24	0.31	0.18
LSP18	1.56	0.85	0.11	0.63	0.18	0.25	0.14
LSP19	1.73	0.98	0.22	0.74	0.27	0.34	0.24
LSP20	2.19	1.44	0.45	0.73	0.44	0.46	0.30

Item Name	Mean	SD	Pearson Item-Scale Correlations				
			HC	LSP	CS	FB	IN
LSP21	2.06	1.33	0.48	0.77	0.51	0.56	0.35
LSP22	2.14	1.40	0.51	0.77	0.49	0.52	0.39
LSP23	1.67	1.06	0.21	0.67	0.45	0.51	0.07
LSP24	1.73	1.12	0.22	0.66	0.51	0.60	0.10
LSP25	2.44	1.49	0.25	0.47	0.26	0.32	0.11
LSP26	1.67	0.97	0.29	0.71	0.45	0.54	0.18
LSP27	1.59	0.87	0.35	0.67	0.40	0.51	0.15
LSP28	1.58	0.90	0.25	0.65	0.36	0.42	0.15
LSP29	2.14	1.38	0.49	0.77	0.51	0.55	0.24
Scale =CS (Consumption and Savings)							
CS1	2.41	1.46	0.32	0.54	0.73	0.68	0.30
CS2	3.03	1.52	0.16	0.24	0.60	0.57	0.34
CS3	2.48	1.43	0.28	0.42	0.65	0.72	0.27
CS4	2.52	1.37	0.61	0.58	0.85	0.74	0.37
CS5	2.43	1.38	0.61	0.60	0.81	0.73	0.35
CS6	2.44	1.38	0.59	0.59	0.72	0.58	0.37
CS7	2.11	1.27	0.41	0.49	0.81	0.73	0.14
CS8	2.10	1.20	0.36	0.43	0.82	0.75	0.14
CS8	2.18	1.31	0.39	0.44	0.76	0.69	0.22
Scale = FB (Financial Burden)							
FB1	1.98	1.24	0.53	0.74	0.76	0.86	0.25
FB2	2.06	1.14	0.30	0.49	0.71	0.82	0.15
FB3	2.08	1.20	0.42	0.63	0.73	0.76	0.30
FB4	2.64	1.41	0.08	0.30	0.64	0.70	0.25
FB5	2.31	1.39	0.23	0.45	0.68	0.78	0.17
FB6	2.78	1.48	0.72	0.61	0.77	0.77	0.47
FB7	2.38	1.44	0.48	0.41	0.72	0.72	0.25
FB8	2.02	1.28	0.50	0.81	0.75	0.85	0.27
Scale = IN (Insurance)							
IN1	3.63	1.37	0.48	0.48	0.36	0.32	0.85
IN2	2.70	1.25	0.00	-0.06	0.01	-0.03	0.56
IN3	3.69	1.31	0.57	0.56	0.44	0.43	0.80
IN4	3.94	1.27	0.48	0.44	0.41	0.45	0.81

Table F4: Item Discriminant Validity Tests

Item Name	HC	LSP	CS	FB	IN
Scale = HC (Human Capital)					
HC1	**	2.00	1.00	2.00	2.00
HC2	**	2.00	2.00	2.00	2.00
HC3	**	2.00	2.00	2.00	2.00
HC4	**	2.00	2.00	2.00	2.00
HC5	**	2.00	2.00	2.00	2.00
HC6	**	2.00	2.00	2.00	2.00
HC7	**	2.00	2.00	2.00	2.00
HC8	**	1.00	2.00	2.00	2.00
HC9	**	2.00	2.00	2.00	2.00
HC10	**	2.00	1.00	1.00	2.00
HC11	**	2.00	2.00	2.00	2.00
HC12	**	2.00	2.00	2.00	2.00
Scale = LSP (Labour Supply and Productivity)					
LSP1	1.00	**	1.00	1.00	2.00
LSP2	1.00	**	1.00	1.00	2.00
LSP3	1.00	**	1.00	1.00	1.00
LSP4	1.00	**	1.00	1.00	2.00
LSP5	1.00	**	1.00	1.00	2.00
LSP6	-1.00	**	1.00	1.00	1.00
LSP7	-1.00	**	1.00	1.00	1.00
LSP8	1.00	**	1.00	1.00	1.00
LSP9	1.00	**	1.00	1.00	2.00
LSP10	2.00	**	1.00	1.00	2.00
LSP11	2.00	**	1.00	1.00	2.00
LSP12	1.00	**	1.00	1.00	2.00
LSP13	2.00	**	1.00	1.00	1.00
LSP14	2.00	**	1.00	1.00	2.00
LSP15	2.00	**	1.00	2.00	1.00
LSP16	2.00	**	2.00	2.00	1.00
LSP17	2.00	**	2.00	2.00	2.00
LSP18	2.00	**	2.00	2.00	2.00
LSP19	2.00	**	2.00	2.00	2.00
LSP20	2.00	**	2.00	2.00	2.00
LSP21	2.00	**	2.00	1.00	2.00

Item Name	HC	LSP	CS	FB	IN
LSP22	2.00	**	2.00	2.00	2.00
LSP23	2.00	**	1.00	1.00	2.00
LSP24	2.00	**	1.00	1.00	2.00
LSP25	1.00	**	1.00	1.00	2.00
LSP26	2.00	**	2.00	1.00	2.00
LSP27	2.00	**	2.00	1.00	2.00
LSP28	2.00	**	2.00	1.00	2.00
LSP29	2.00	**	2.00	1.00	2.00
Scale =CS (Consumption and Savings)					
CS1	2.00	1.00	**	1.00	2.00
CS2	2.00	2.00	**	1.00	2.00
CS3	2.00	1.00	**	-1.00	2.00
CS4	1.00	2.00	**	1.00	2.00
CS5	1.00	1.00	**	1.00	2.00
CS6	1.00	1.00	**	1.00	2.00
CS7	2.00	2.00	**	1.00	2.00
CS8	2.00	2.00	**	1.00	2.00
CS8	2.00	2.00	**	1.00	2.00
Scale = FB (Financial Burden)					
FB1	2.00	1.00	1.00	**	2.00
FB2	2.00	2.00	1.00	**	2.00
FB3	2.00	1.00	1.00	**	2.00
FB4	2.00	2.00	1.00	**	2.00
FB5	2.00	2.00	1.00	**	2.00
FB6	1.00	1.00	1.00	**	2.00
FB7	1.00	2.00	1.00	**	2.00
FB8	2.00	1.00	1.00	**	2.00
Scale = IN (Insurance)					
IN1	2.00	2.00	2.00	2.00	**
IN2	2.00	2.00	2.00	2.00	**
IN3	1.00	1.00	2.00	2.00	**
IN4	2.00	2.00	2.00	2.00	**

Appendix G: SPSS® Normality Probability Plot of Regression Standardized Residuals and Scatterplot output for Regression Analyses.

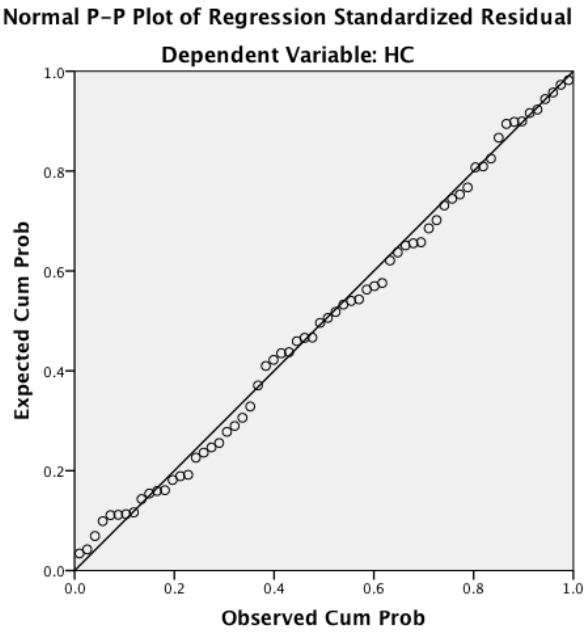


Figure G1: SPSS® Normal probability plot for HC scale regression analysis.

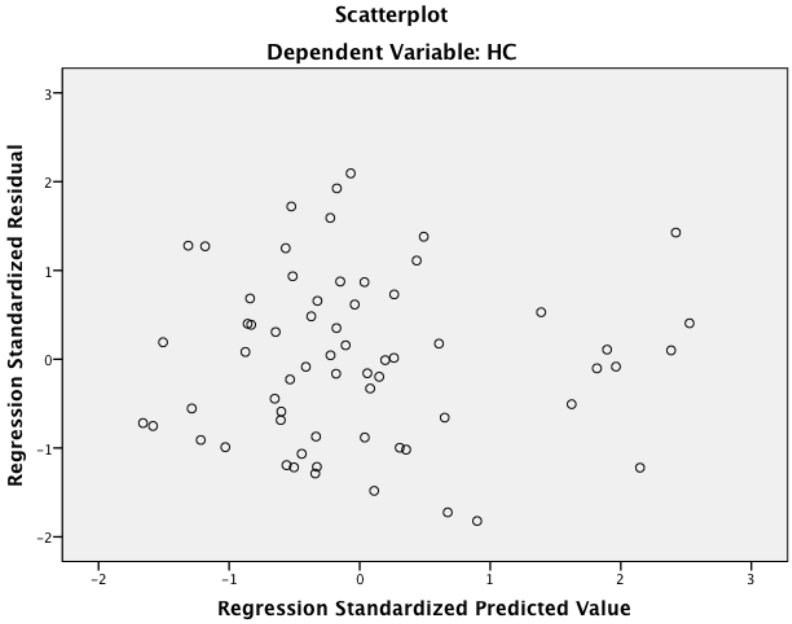


Figure G2: SPSS® Scatterplot for HC scale regression analysis

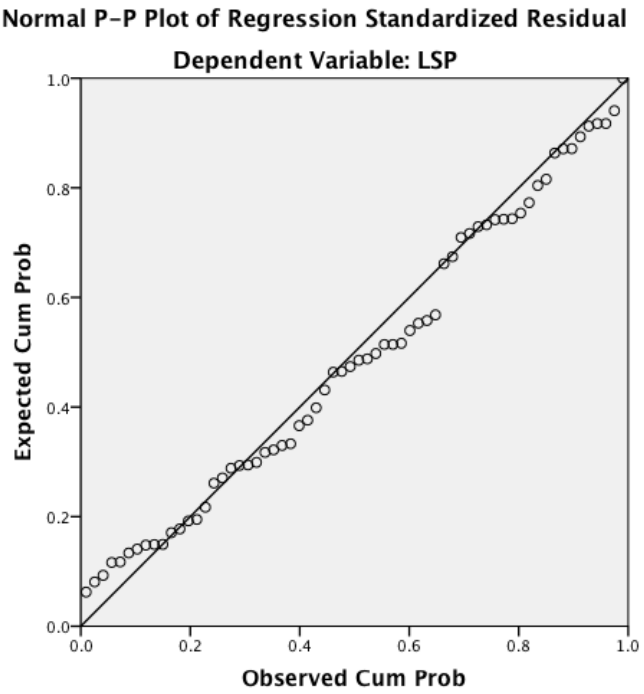


Figure G3: SPSS® Normal probability plot for LSP scale regression analysis.

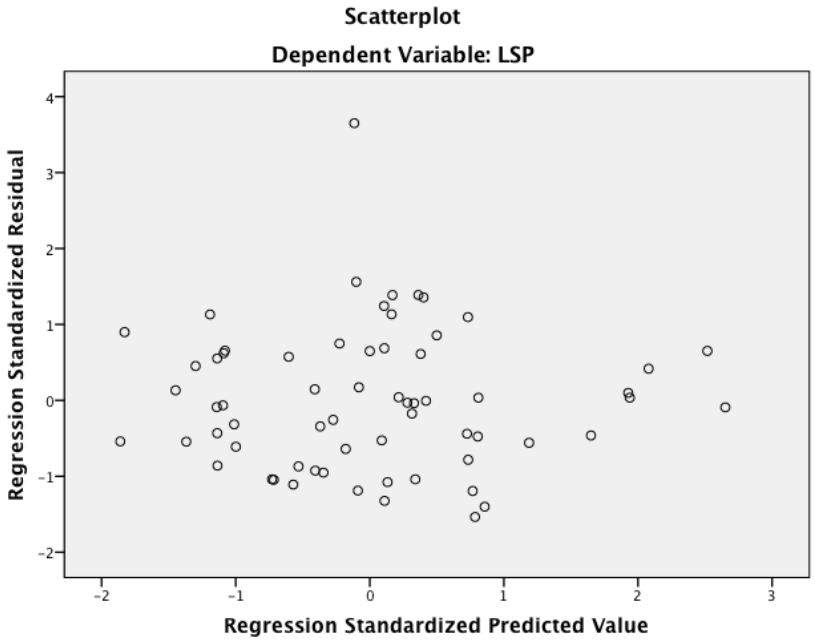


Figure G4: SPSS® Scatterplot for LSP scale regression analysis

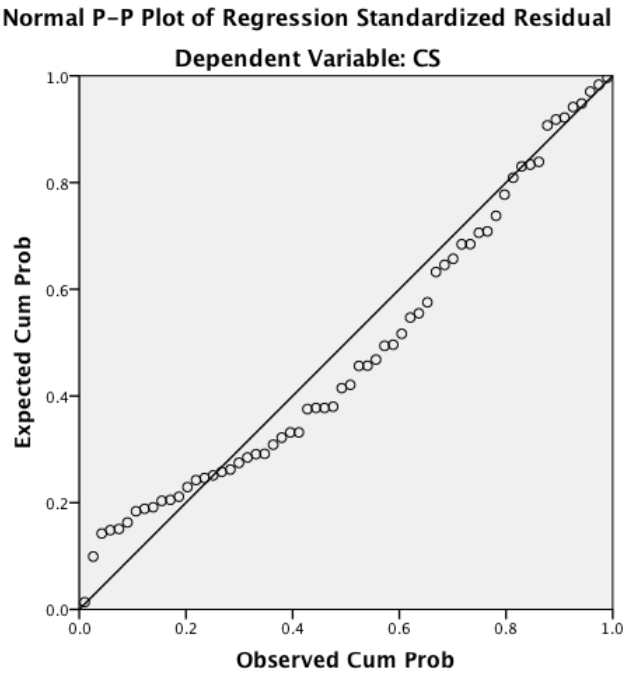


Figure G5: SPSS® Normal probability plot for CS scale regression analysis.

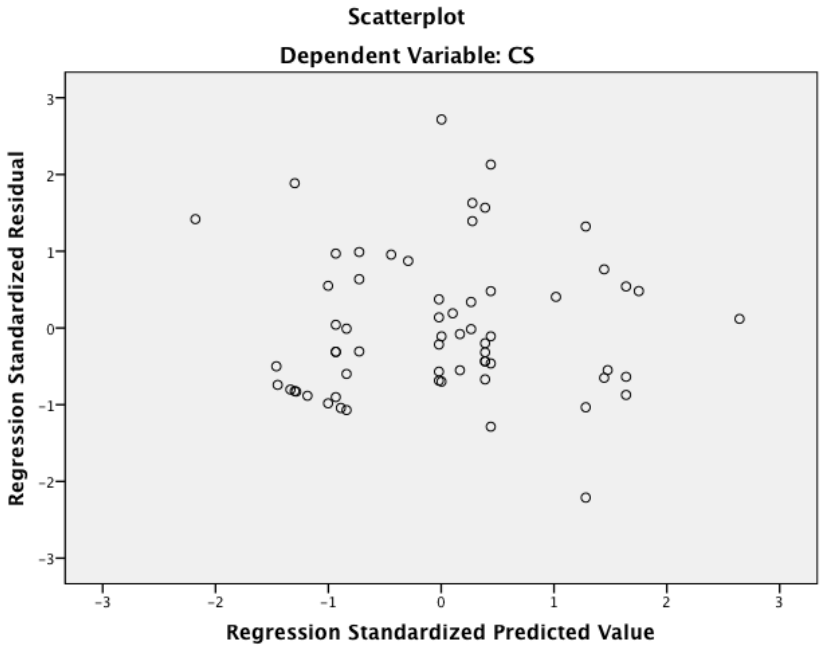


Figure G6: SPSS® Scatterplot for CS scale regression analysis

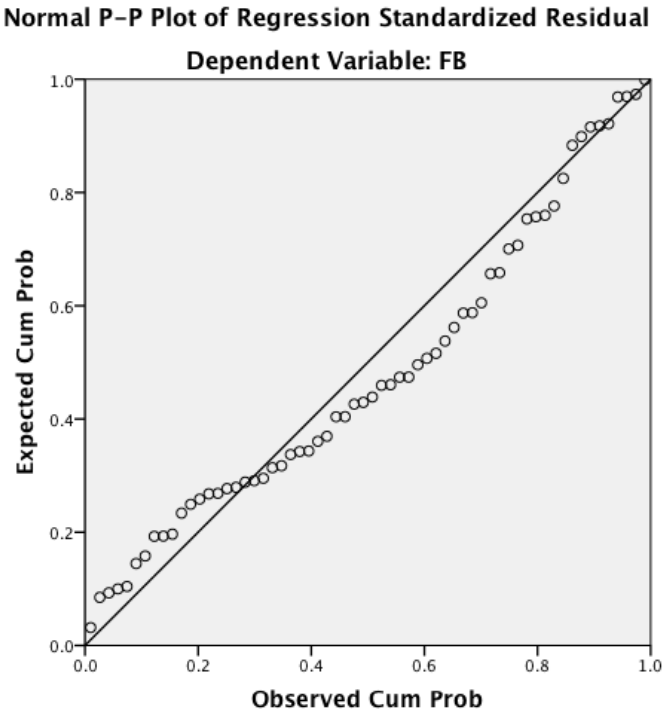


Figure G7: SPSS® Normal probability plot for FB scale regression analysis.

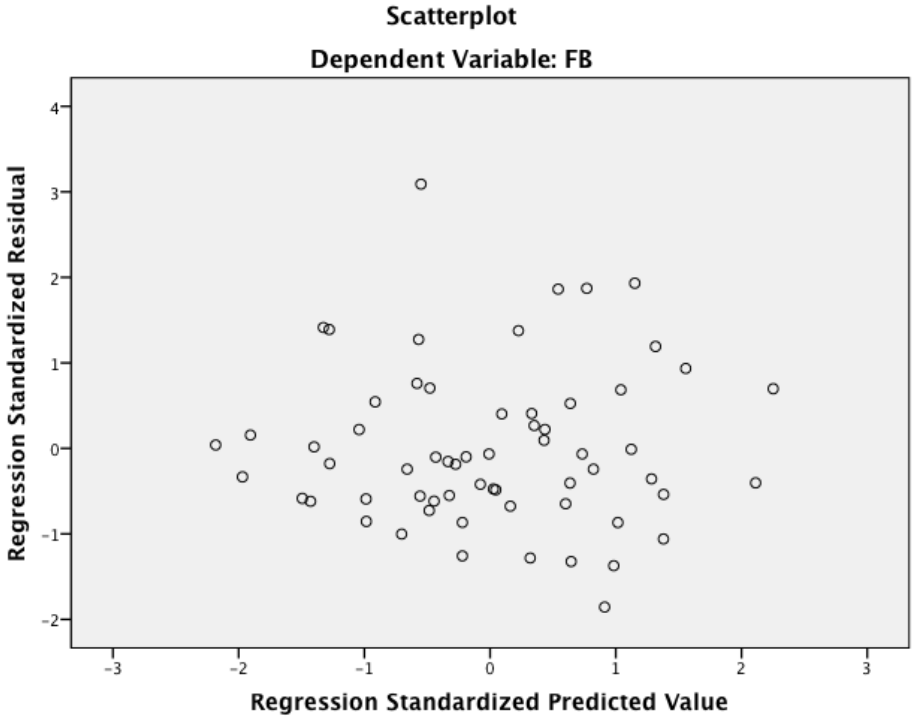


Figure G8: SPSS® Scatterplot for FB scale regression analysis

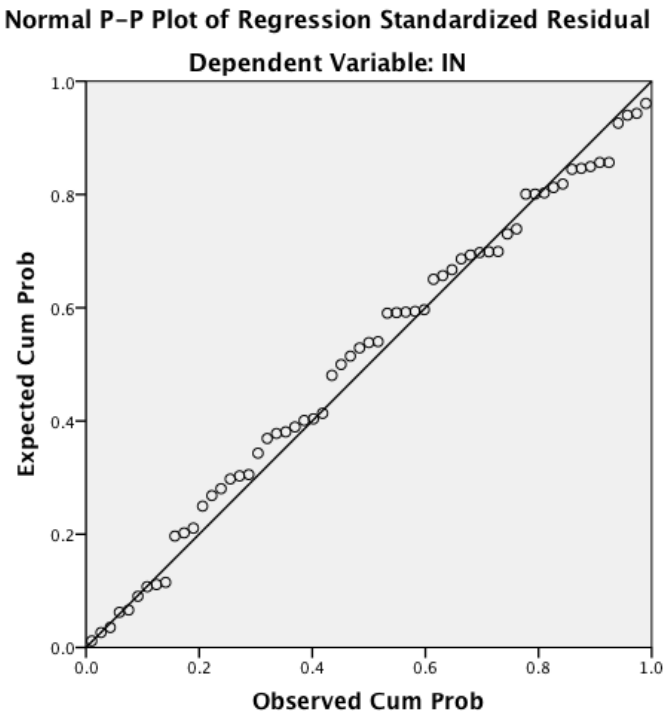


Figure G9: SPSS® Normal probability plot for IN scale regression analysis.

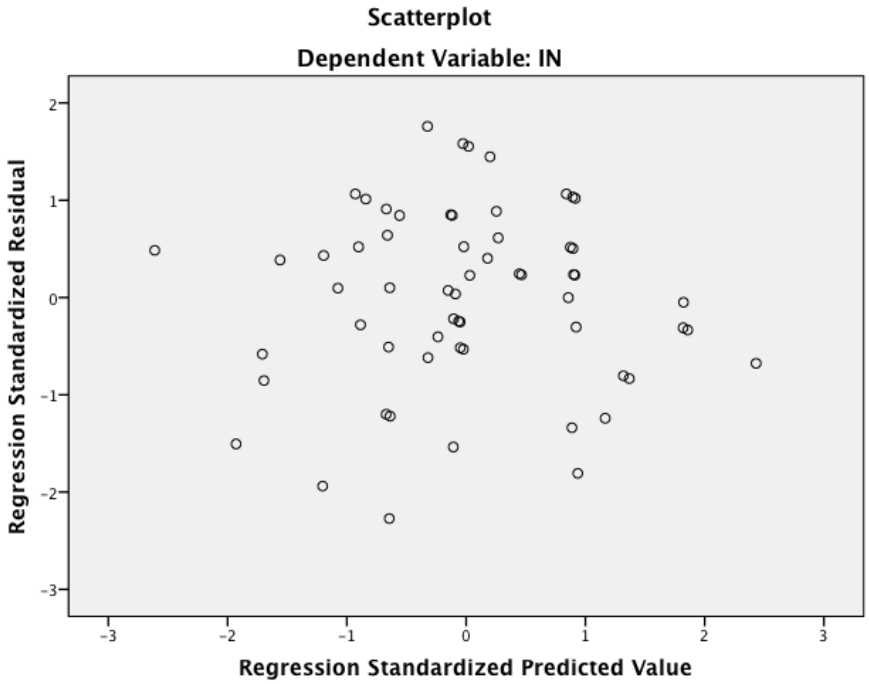


Figure G10: SPSS® Scatterplot for IN scale regression analysis

Appendix H: Validated PEB Scale Survey

Perceived Economic Burden (PEB) of ARVC Scale

The validated Perceived Economic Burden scale has 5 sections with a total of 62 questions.

Each section has several statements that we would like you to rate from **1 (Strongly disagree)** to **5 (Strongly agree).**

Please circle the best answer for each.

Thank you

Section 1: Human Capital Attainment
The first section of this survey relates to education and career choices. Using the scale given, you are asked to rate your agreement with each statement as it reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree
N/A – Not applicable to me

1. Identification of the gene change that causes ARVC in my family has influenced my education choices.	1 2 3 4 5
2. My past education choices were influenced by my risk for ARVC.	1 2 3 4 5
3. Knowing my risk for ARVC, I wish I had made different choices about my education.	1 2 3 4 5
4. My decision to pursue education in the future is affected by my risk for ARVC.	1 2 3 4 5 N/A
5. I encourage other family members to consider their risk for ARVC when making decisions about their education.	1 2 3 4 5
6. Knowing their risk for ARVC has affected the education choices of other family members.	1 2 3 4 5
7. Identification of the gene change that causes ARVC in my family has influenced my career choices.	1 2 3 4 5
8. My past career choices were influenced by my risk for ARVC.	
9. Knowing my risk for ARVC, I wish I had made different choices about my career.	1 2 3 4 5
10. My decision to pursue certain careers in the future is affected by my risk for ARVC.	1 2 3 4 5
11. I encourage other family members to consider their risk for ARVC when making decisions about their career.	1 2 3 4 5 N/A
12. Knowing their risk for ARVC has affected the career choices of other family members.	1 2 3 4 5

Section 2: Labour Supply And Productivity
The second section of this survey relates to your/your family experiences with work. Using the scale given, you are asked to rate your agreement with each statement as it reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree
N/A – Not applicable to me

1. The presence of the gene that causes ARVC in my family has affected my employment.	1 2 3 4 5
2. Knowing my risk for ARVC has caused me to work **less** than I did before finding out my risk.	1 2 3 4 5
3. My work has been disrupted because of time off for medical appointments related to my risk for ARVC.	1 2 3 4 5
4. My work has been disrupted because of time off for other family members' medical appointments related to their risk for ARVC.	1 2 3 4 5
5. Knowing my risk for ARVC has caused me to work **more** than I did before finding out my risk.	1 2 3 4 5
6. I have had to change the type of work that I do at my job because of my risk for ARVC.	1 2 3 4 5
7. I have had to change careers/professions because of my risk for ARVC.	1 2 3 4 5
8. My decision of when I retire has changed because of my risk for ARVC.	1 2 3 4 5
9. My work has been disrupted because of time off to care for a family member, because of their risk for ARVC.	1 2 3 4 5
10. I have had to work less because of another family member's risk for ARVC.	1 2 3 4 5
11. I have had to work more because of another family member's risk for ARVC.	1 2 3 4 5
12. I have changed careers/professions because of another family member's risk for ARVC.	1 2 3 4 5
13. The presence of the gene that causes ARVC in my family has affected another family members' employment.	1 2 3 4 5

14. Knowing my risk for ARVC has caused another family member to work **less** than they did before I found out my risk.	1 2 3 4 5
15. Another family member's work has been disrupted because of time off for medical appointments related to my risk for ARVC.	1 2 3 4 5
16. Another family member has had to take time off work to care for me because of my risk for ARVC.	1 2 3 4 5
17. Another family member has had to work **more** because of my risk for ARVC.	1 2 3 4 5
18. Another family member has had to change careers/professions because of my risk for ARVC.	1 2 3 4 5
19. Another family member has changed their decision of when to retire because of my risk for ARVC.	1 2 3 4 5
20. The presence of the gene that causes ARVC in my family has affected my income.	1 2 3 4 5
21. My income has changed because of my risk for ARVC.	1 2 3 4 5
22. My income is less because of my risk for ARVC.	1 2 3 4 5
23. My income has changed because of another family member's risk for ARVC.	1 2 3 4 5
24. My income is less because of another family member's risk for ARVC.	1 2 3 4 5
25. The presence of the gene that causes ARVC in my family has affected another family member's income.	1 2 3 4 5
26. Another family member's income has changed because of my risk for ARVC.	1 2 3 4 5
27. Another family member's income is less because of my risk for ARVC.	1 2 3 4 5
28. Another family member's income is more because of my risk for ARVC.	1 2 3 4 5
29. The presence of the gene that causes ARVC in my family has affected my family's total income.	1 2 3 4 5

Section 3: Consumption and Savings
The third section of questions relates to personal direct costs and financial decisions. Using the scale given, you are asked to rate your agreement with each statement as it reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree
Y – Yes
N – No

1. My family has incurred costs because of the need for medications related to ARVC	1 2 3 4 5
2. My family has incurred costs associated with travel for medical appointments (planned or unplanned) related to ARVC.	1 2 3 4 5
3. My family has incurred other costs associated with the ARVC gene.	1 2 3 4 5
4. I am more aware of my spending habits as a result of my risk for ARVC.	1 2 3 4 5
5. I have changed my spending habits because of my risk for ARVC.	1 2 3 4 5
6. I do more financial planning (saving) because of my risk for ARVC.	1 2 3 4 5
7. I am more aware of my spending habits because of another family member's risk for ARVC.	1 2 3 4 5
8. I have changed my spending habits because of another family member's risk for ARVC.	1 2 3 4 5
9. I do more financial planning (saving) because of another family member's risk for ARVC.	1 2 3 4 5

Section 4: Financial Burden
The fourth section of questions relates to financial burden. Using the scale given, you are asked to rate your agreement with each statement as it reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree
Y – Yes
N – No

1. The risk for ARVC in my family has been a financial burden.	1 2 3 4 5
2. The need for regular monitoring for cardiac problems related to ARVC has been a financial burden on my family.	1 2 3 4 5
3. The cost of medication related to ARVC has been a financial burden on our family.	1 2 3 4 5
4. Costs associated with travel for medical appointments (planned or unplanned) related to ARVC have been a financial burden on my family.	1 2 3 4 5
5. The other costs incurred by my family associated with the ARVC gene have been a financial burden.	1 2 3 4 5
6. I am concerned about the economic/financial future of my family as a result of my risk for ARVC.	1 2 3 4 5
7. My family has had to travel out of province for medical appointments/services related to ARVC.	1 2 3 4 5
8. Changes to my family's income because of the presence of the gene that causes ARVC in my family has been a financial burden.	1 2 3 4 5

Section 5: Insurance
The seventh section of questions relates to insurance. Using the scale given, you are asked to rate how well each statement reflects your situation.

1 – Strongly disagree
2 – Disagree
3 – Neither agree nor disagree
4 – Agree
5 – Strongly agree
Y– Yes
N– No
N/A – Not Applicable to me

1. It is difficult for any member of my family (including myself) to buy medical insurance as a result of their risk for ARVC.	1 2 3 4 5 N/A
2. My current medical insurance does not cover costs associated with the ARVC condition that are not already covered by the Government's Medicare plan.	1 2 3 4 5 N/A
3. I am concerned about the future ability of my family members to receive medical insurance as a result of their risk for ARVC.	1 2 3 4 5
4. It is difficult for any member of my family (including myself) to purchase life insurance as a result of our risk for ARVC.	1 2 3 4 5 N/A