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# Immunoglobulin Therapy and Primary Immunodeficient Patients' Health-Related Quality of Life and Well-Being

Niedre Heckman  
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# Walden University

College of Health Sciences

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Walden University  
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Abstract

Immunoglobulin Therapy and Primary Immunodeficient Patients' Health-Related Quality  
of Life and Well-Being

by

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

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## Abstract

Individuals born with primary immune deficiency diseases (PIDD) have a dysfunctional immune system, and many are treated by lifelong injections of immunoglobulin therapy. Studies have shown that these patients have low health-related quality of life (HRQOL) and well-being (WB) and that these outcomes might be improved by the availability of therapy innovated according to preferences for fewer needle sticks or a shorter infusion time. Regulators at the U.S. Food and Drug Administration (FDA) have approved therapies innovated per these preferences. However, there is limited data demonstrating how these innovations impact HRQOL and WB. Using the biopsychosocial model, the purpose of this cross sectional quantitative study was to evaluate whether patients with PIDD using therapies innovated for fewer needle sticks or a shorter infusion time had a higher mean HRQOL and WB compared to those who were not. The study included 153 patients who completed the Patient Reported Outcomes Measurement Information System (PROMIS)-29 survey. The dependent variables were HRQOL and WB measured by PROMIS-29, and the independent variables were the medical product innovations. Independent samples *t* tests results showed mean PROMIS-29 scores were not statistically different ( $p > .05$ ). This suggests patients were optimized according to their treatment preference. A subgroup of patients who had taken the PROMIS-29 survey more than once concurrent with switching to a therapy aligned with patient preferences showed improved HRQOL and WB. These findings have implications for positive social change in that seeking the patient's voice to inform medical product innovation and FDA regulatory decision-making has potential to improve biopsychosocial outcomes.

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## Dedication

First and foremost, I dedicate this dissertation to my parents, Ralph Preston and Lovie Marie Pope, who, even with their personal brilliance and wisdom, still also admired, championed, and cherished me. They would be proud beyond measure, and that makes my heart smile.

I also dedicate this dissertation to the wonderful people who have helped me accomplish opportunities and experiences leading up to this occasion: Dr. Vasu Dev, my undergraduate research advisor, who introduced me to the world of academic research and secured my first publication, and Dr. Richard Allen Heckman, my late husband, who showed me firsthand the life of a scholar.

My career has been integral to my academic pursuits, and I dedicate this dissertation to two outstanding coworkers: my supervisor Dr. Yu-An Chang, who taught me how to do thorough research and prepare findings for publication in peer-reviewed journals, and my supervisor W. Bryan Silvey, who showed interest in my academic inclination and secured a sponsorship to support my doctoral work.

Finally, I dedicate this dissertation to those who provided moral support throughout this long journey: my dear sister, Rochelle C. (Pope) Owens; my love, Lamont McNamara; my second mom, Marge Davis, and my lifelong friend who made me aware when we were young children that I wanted to make my mark doing what I would come to know as public health, Francisco Guerrero.

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## Chapter 1: Introduction to the Study

### **Introduction**

Primary immune deficiency disease (PIDD) comprises a group of more than 230 different rare genetic disorders where immune system cells, antibodies, and complement proteins are missing, defective, or present in insufficient amounts (Chapel et al., 2014). Persons with an immune system deficiency have greater susceptibility to common and unusual infections which are chronic, more severe, of longer duration, and are more difficult to treat with standard medical care, compared to individuals with an intact immune system (Chapel et al., 2014; Costa-Carvalho et al., 2014; Heath, Lehman, Saunders, & Craig, 2016). Examples of the effects of immune system deficiency include bone, gastrointestinal, mucous membrane, and respiratory infections; abscesses of the brain, liver, or lungs; autoimmune diseases (due to an improperly functioning immune system) leading to anemia, arthritis, or asthma; abnormal gland development; heart defects; and increased cancer risk (American Academy of Asthma, Allergy, and Immunology, 2016; Costa-Carvalho et al., 2014).

In the United States, researchers estimate prevalence of PIDD to be 1 in 2000 children, 1 in 1200 individuals, and 1 in 600 households (Jiang, Torgerson, & Ayars, 2015; Melamed, Testori, & Spirer, 2012). The rarity of PIDD raises public health concerns and merits study because delayed diagnosis often results in life-threatening illnesses and in high costs from greater use of health care services, such as emergency room visits and hospital admittance prior to the individual receiving effective treatment (Chapel et al., 2014; Resnick, Bhatt, Sidi, & Cunningham-Rundles, 2013). Haddad,

Barnes, and Kafal (2012) cited survey results that revealed an average 9-year delay from presentation of symptoms to diagnosis. Haddad et al. also commented on low PIDD awareness in the medical community as a possible cause for the delay in diagnosis. Menzin, Sussman, Munsell, and Zbrozek (2014) determined the mean PIDD infection-related medical costs, over a seven month period in 2010, to be U.S. \$11,925 per patient. The overall mean cost per patient included the following individual patient costs: an emergency visit (\$899), an outpatient visit (\$1,460), and an inpatient hospital visit (\$38,574; Menzin et al., 2014). Jiang, Torgerson, and Ayars (2015) found a 1.7% increased risk of death with each year of delayed diagnosis, and a 4.5% increased risk of death with each increase in chronological age at diagnosis.

Although there is no treatment for PIDD that can repair the immune system to normal function, lifelong (after diagnosis) immunoglobulin antibody replacement therapy is an option for many patients. Medical product manufacturers have developed immunoglobulin replacement therapies for PIDD treatment and have made these therapies available to patients through their medical practitioners, subsequent to approval by the Food and Drug Administration (FDA; FDA, 2015b). Thus, medical practitioners are prescribing lifelong regular infusions of immunoglobulins (also referred to as immune globulins or antibodies) for PIDD treatment (Menzin, Sussman, Munsell, & Zbrozek, 2014). Moreover, medical product manufacturers have conducted clinical trials demonstrating the safety and efficacy of immunoglobulin replacement therapy based on biomedical endpoints such as blood levels of immunoglobulin (Melamed et al., 2012).

The FDA has subsequently approved a number of these medical products for immunoglobulin replacement therapy (Schroeder & Dougherty, 2012).

Though immunoglobulin replacement therapies are available, the biomedical and the psychosocial burdens that patients face daily, and for an extended duration of time with chronic diseases such as PIDD, are a serious global public health concern (Heath et al., 2016; Hirsch, Walker, Chang, & Lyness, 2012). Examples of some of the burdens that patients with PIDD face include decreased health-related quality of life (HRQOL) due to anxiety and depression around fear of infection, missed days of school or work, inability to work; and feelings of isolation due to the inability to function socially with friends and family and as a member of society (Bienvenu et al., 2016). Menzin et al. (2014) cited a Jeffrey Modell Centers Network survey which showed that the average patient with PIDD has 70 emergency room visits, 19 hospitalizations, and 34 missed days of school or work in the year preceding diagnosis. These numbers underscore the public health issue for patients with PIDD.

Although immunoglobulin replacement therapy (IGRT) mitigates some of the biomedical and psychosocial burdens of PIDD caused by recurrent infections (Melamed et al., 2012), the life-long therapy regimen creates other biomedical and psychosocial burdens. Examples of life-long therapy burdens include systemic and localized reactions to therapy; travel to an infusion clinic and wait time at the clinic; and frequency, duration, and route of therapy administration (Dashti-Khavidaki et al., 2009; Haddad, Barnes, & Kafal, 2012). Because immunoglobulin replacement therapy is administered

intravascularly, needles are involved; thus, needle sticks are also a burden (Espanol, Prevot, Drabwell, Sondhi, & Olding, 2014).

To address these issues, researchers, medical products manufacturers, and the FDA are currently seeking more patient input regarding treatment preferences and treatment psychosocial outcomes, such as HRQOL and well-being. Patient treatment preferences have informed innovations in therapies developed by medical product manufacturers, which are now FDA-approved and commercially available. Examples of innovative therapies include treatments which enable patients to self-administer medication in their home instead of intravenous infusions administered in a clinical setting by a medical practitioner (Jiang et al., 2015). Additionally, in 2014 the FDA approved a therapy that patients can self-administer with fewer needle sticks and in a shorter time per infusion (Espanol et al., 2014; Garduff & Nicoloy, 2006; Ponsford et al., 2015; Wasserman, 2014).

Individuals researching treatment regimens indicated for patients with PIDD might also elect to use validated survey instruments as a tool for assessing patient psychosocial outcomes (such as HRQOL and well-being). Researchers have studied HRQOL and well-being in patients with PIDD focusing on location of therapy administration, route of administration, and patient preferences related to therapy frequency, duration, and number of needle sticks, using standard validated survey instruments such as the EuroQOL five-dimension questionnaire (EQ-5D) and the Short Form Health Survey (SF-36; Espanol et al., 2014; Jiang et al., 2015; Tabolli et al., 2014; Vultaggio et al., 2015). Researchers with the National Institutes of Health (NIH)



developed the Patient-Reported Outcomes Measurement Information System (PROMIS) survey instruments to gather HRQOL and well-being information and to measure health outcomes from the patient's perspective about chronic diseases globally (NIH, 2017). In addition, the Immune Deficiency Foundation (IDF), an advocacy organization for patients with PIDD, is partnering with the NIH to administer the abbreviated PROMIS (called PROMIS-29) survey instrument to individuals from IDF's patient registry (C. Scalchunes, personal communication, October 20, 2016). In this study I present the first findings of HRQOL and well-being of patients with PIDD as measured by the PROMIS-29 survey instrument.

The goal of this study was to evaluate whether medical product innovations based on patient treatment preferences for number of needle sticks and infusion time improve HRQOL and well-being, as measured by the PROMIS-29 instrument. The implications of this study for positive social change include providing additional evidence supporting the gathering and use of patient preferences in medical product development and regulatory decision-making. Findings may encourage researchers, manufacturers, and regulators to shift from a purely biomedical (or clinical) focus to a psychosocial (or public health) one whereby they consider the psychosocial impact of therapy innovation. Incorporating this type of focus and considering patient preferences for treatment may result in improved HRQOL and well-being for patients with PIDD.

### **Background**

Patients have access to medical products because there exists a supply chain from medical product manufacturers, through regulatory authority (i.e. FDA) review and

approval, to recognition of the medical product by insurance companies and distribution to pharmacies, and culminating with a physician's prescription (FDA, 2015b).

Researchers, manufacturers, regulatory authorities, and medical practitioners seek patient feedback (or patient-reported outcomes) according to their role within the medical products supply chain. For instance, medical product manufacturers might want to understand treatment satisfaction and patient preferences for treatment as they innovate medical products designed to reduce the burden chronic disease poses to the patient on a daily basis; regulatory authorities might be interested in HRQOL reports to establish a risk to benefit profile as they review a medical product application; and medical practitioners might seek to evaluate patient reports of health status and adherence to regimen as they talk with the patient regarding an optimal treatment plan (Willke, Burke, & Erickson, 2004). Willke, Burke, and Erickson (2004) reviewed drug medical product labeling between the years 1997-2002 to determine the extent to which patient-reported outcomes were used for medical product manufacturers' drug innovation and for regulatory review and approval by FDA. Willke et al. (2004) found patient-reported outcomes were reported in 30% (64 of 215) of the labels reviewed, behind clinical endpoints (62%) and laboratory endpoints (50%). According to their review, the medical products innovated and approved using patient-reported outcomes were used to treat inflammation, conjunctivitis; and disorders of the central nervous, gastrointestinal, respiratory, eye, and urologic systems (Willke et al., 2004).

The theoretical framework for this dissertation stems from the concept that medical products are innovated not only to alleviate the clinical presentation of disease,

but also to help patients manage their lives while also managing a disease state which cannot be cured. In this study, I focused on two aspects of PIDD management which the literature suggested patients expressed a desire to improve: (a) reduction in the number of needle sticks and (b) shorter infusion time, but where there is currently limited data showing whether these medical product innovations result in better outcomes in terms of HRQOL and well-being; hence there is a gap in knowledge.

Biomedical evidence that a medical product works and has benefits to the patient which outweigh the risks is demonstrated through clinical trials. The literature is replete with studies showing that immunoglobulin replacement therapy boosts the immune system of patients with PIDD. The goal of this study, and the reason why the study was needed, was to bring medical product innovation into the public health discipline by seeking to generate evidence that a medical product works and also has benefits of improved patient HRQOL and well-being because psychosocial parameters of patient preference for treatment were considered by medical product manufacturers in their development of the medical product.

To make this dissertation more relatable to the reader who is less familiar with rare diseases such as PIDD, I used this section to make an analogy of PIDD (a rare disease) to Type 2 diabetes (a common disease). Like PIDD, individuals with Type 2 diabetes have a condition where the primary defect (in the case of diabetes, cells cannot uptake insulin) impacts other body systems and leads to comorbidities. Additionally, the disease states are comparable in that neither can be cured, but with management, medical treatment enables the patient to live for decades. Thus, management of routine life

activities while always in a chronic disease state comes to the forefront in terms of impact to HRQOL and well-being. Presented below is a direct-to-consumer advertisement for a new drug treatment for Type 2 diabetes. The biomedical statement in the promotion reads: “Trulicity, along with diet and exercise, may help lower your blood sugar and A1C.” (How Trulicity can help, 2017, para 1).

The promotion goes on in the biomedical framework to comment on a clinical trial to demonstrate lower blood sugar and A1C levels: “In a study, the higher dose helped 78% of people and the lower dose helped 66% of people get to the A1C goal of below 7%.” (How Trulicity can help 2017, para 1). Next, the patient is informed about the innovation of Trulicity, and how the innovation might cater to patient preferences for treatment with this statement:

Trulicity is designed to be taken once a week, which may help you fit it into your busy life. You can take Trulicity any time of day, with or without meals. Just pick which day of the week will be your Trulicity Day and remember to keep taking it that day, every week. (How Trulicity can help, 2017, para 4)

The promotion is silent regarding impact on HRQOL and well-being. However, Fisher, Tang, and Polonsky (2017) introduced their paper by commenting on the advent of medical products innovated for achieving glycemic control and the associated interest among, for example, researchers, FDA, and patients regarding measures of quality of life and well-being. The authors pointed out that glycemic control is generally a primary measure but that patients and other stakeholders consider equally important the secondary or tertiary measures of quality of life (Fisher, Tang, & Polonsky, 2017).

Likewise, the literature and direct-to-consumer advertising demonstrate that medical product innovations in the treatment of PIDD still meet clinical criteria of boosting the immune system, while also offering patients flexibility to live their life; for example, to self-administer therapy wherever they might be physically located and at a time of their choosing.

The gap in knowledge this study aimed to fill is whether there were any differences in HRQOL and well-being between patients with PIDD who use medical products innovated for fewer needles sticks or for shorter infusion times versus those who do not. Since patient preferences contributed to medical products manufacturers' innovation of new medical products, this study was needed to understand whether the resultant innovated medical products improved HRQOL and well-being, as measured by PROMIS-29, for patients with PIDD.

### **Problem Statement**

The problem I addressed is the gap in the literature concerning whether medical products innovated per patient preferences for fewer needles sticks and shorter infusion times resulted in improved HRQOL and well-being, as measured by PROMIS-29, for patients with PIDD. Factors associated with poorer HRQOL include comorbidities, unemployment, stress, multiple infections, and PIDD diagnosis delay (Jiang et al., 2015). Factors associated with improved HRQOL include home-based therapy; treatment comfort, flexibility, convenience, and independence; shorter treatment duration and less impact/disruption to daily activities (e.g., school/work and social); and satisfactory immunoglobulin trough levels (Jiang et al., 2015; Vultaggio et al., 2015).

Additional to evaluating patients' treatment preferences, researchers also evaluated patients' satisfaction with treatment. Espanol, Prevot, Drabwell, Sondhi, and Olding (2014) found that the majority of patients with PIDD (76%, n = 300) were pleased with their current treatment; however, those receiving SCIG (83%) were more pleased compared to those receiving IVIG (69%). Additionally, Espanol et al. (2014) compared SCIG with IVIG in terms of impact on HRQOL measures of anxiety, depression, mobility, routine activity performance, pain, and self-care. The researchers' analysis revealed there was no difference in HRQOL (71.8% and 71.9%, respectively) as measured by the EQ-5D (Espanol et al., 2014). Deshpande, Rajan, Sudeepthi, and Nazir (2011) noted that assessing patient-reported outcomes is an important component to understanding patient compliance with treatment, improvements to medical products, and better patient outcomes such as quality of life related to medical treatment. Based on my review, the literature has not yet been expanded to present the changes in HRQOL and well-being as dependent variables to recent medical product innovations allowing for fewer needle sticks and offering shorter infusion duration using the PROMIS-29 instrument in a population of patients with PIDD.

### **Purpose of the Study**

The purpose of this quantitative study was to compare the mean differences in HRQOL and well-being as measured by PROMIS-29 for patients with PIDD who used medical product manufacturers' innovative medical products designed to require (a) fewer needle sticks or (b) shorter infusion time to patients who did not use such products. The dependent variables were PROMIS-29 instrument measures of anxiety and

depression as proxies of HRQOL and participation in social roles/activities as a proxy of well-being (HealthyPeople.gov, 2017). My overarching purpose is to help patients who have a chronic disease state which cannot be cured and can only be managed via a regular treatment routine to have optimal HRQOL and well-being. The results of this research have the potential to add to the body of scientific knowledge and provide support for patient-reported outcomes of HRQOL and well-being as valid inputs in medical product development and FDA regulatory decision-making.

### **Research Questions and Hypotheses**

Research Question 1: Is there a difference in the well-being proxy PROMIS score for “Ability to Participate in Social Roles/Activities” between patients with PIDD who report using medical products innovated to offer therapeutic dosing with one needle stick every 3 or 4 weeks compared to those who report using medical products innovated to offer therapeutic dosing with more than one needle stick every 3 or 4 weeks?

$H_0$ 1: The mean differences are not statistically significant.

$H_a$ 1: The mean differences are statistically significant.

The independent variable was needle sticks, and the dependent variable was PROMIS score (Likert scale mean).

Research Question 2: Is there a difference in the HRQOL proxy PROMIS score for “Anxiety” between patients with PIDD who report using medical products innovated to offer therapeutic dosing with one needle stick every 3 or 4 weeks compared to those who report using medical products innovated to offer therapeutic dosing with more than one needle stick every 3 or 4 weeks?

$H_{02}$ : The mean differences are not statistically significant.

$H_{a2}$ : The mean differences are statistically significant.

The independent variable was needle sticks, and the dependent variable was PROMIS score (Likert scale mean).

Research Question 3: Is there a difference in the HRQOL proxy PROMIS score for “Depression” between patients with PIDD who report using medical products innovated to offer therapeutic dosing with one needle stick every 3 or 4 weeks compared to those who report using medical products innovated to offer therapeutic dosing with more than one needle stick every 3 or 4 weeks?

$H_{03}$ : The mean differences are not statistically significant.

$H_{a3}$ : The mean differences are statistically significant.

The independent variable was needle sticks, and the dependent variable was PROMIS score (Likert scale mean).

Research Question 4: Is there a difference in the well-being proxy PROMIS score for “Ability to Participate in Social Roles/Activities” between patients with PIDD who report using medical products innovated for shorter infusion time compared to those who report using medical products not innovated for shorter infusion time?

Interpretation: Because infusion time depends on patient tolerance irrespective of product innovation, for this study shorter infusion time was defined as less than or equal to 4 hours and longer infusion time was defined as greater than 4 hours (Ponsford et al., 2015).

$H_{04}$ : The mean differences are not statistically significant.



$H_{a4}$ : The mean differences are statistically significant.

The independent variable was infusion time duration, and the dependent variable was PROMIS score (Likert scale mean).

Research Question 5: Is there a difference in the HRQOL proxy PROMIS score for “Anxiety” between patients with PIDD who report using medical products innovated for shorter infusion time compared to those who report using medical products not innovated for shorter infusion time?

Interpretation: Because infusion time depends on patient tolerance irrespective of product innovation, for this study shorter infusion time was defined as less than or equal to 4 hours and longer infusion time was defined as greater than 4 hours (Ponsford, et al., 2015).

$H_{05}$ : The mean differences are not statistically significant.

$H_{a5}$ : The mean differences are statistically significant.

The independent variable was infusion time duration, and the dependent variable was PROMIS score (Likert scale mean).

Research Question 6: Is there a difference in the HRQOL proxy PROMIS score for “Depression” between patients with PIDD who report using medical products innovated for shorter infusion time compared to those who report using medical products not innovated for shorter infusion time?

Interpretation: Because infusion time depends on patient tolerance irrespective of product innovation, for this study shorter infusion time was defined as less than or equal

to 4 hours and longer infusion time was defined as greater than 4 hours (Ponsford, et al., 2015).

$H_0$ : The mean differences are not statistically significant.

$H_a$ : The mean differences are statistically significant.

The independent variable was infusion time duration, and dependent variable was PROMIS score (Likert scale mean).

### **Theoretical Framework**

The theoretical framework used for this dissertation was George Engel's (1977) biopsychosocial model, which is found within medical sociology and derived from the understanding among sociologists and physicians, that there is an interplay between biology, culture, social determinants of health, and the environment which influence whether, and how, people become ill (also the duration, intensity, and type of illness manifestation) from a given cause. George Engel (1977) introduced the biopsychosocial model as a counter to the biomedical approach toward the practice of medicine. Engel posited that the biomedical model was inadequate as it reduced the patient to his or her body parts and biochemical elements. However, Engel argued, the patient is a whole being with senses and experiences. Thus, the patient is a composite of biological, psychological, and social systems and sub-systems, none of which exists in isolation from the others.

Physicians use the biopsychosocial model as a model for patient interaction, and as a framework for how the physician can view the patient and provide care (Engel, 1977; Engel, 1980; Haveilka, Lcuanin, & Lcuanin, 2009). Medical product manufacturers and

regulatory authorities can use this framework in a way that they can observe the patient who will use the medical products once approved. In medical sociology, illness is described in the broader term encompassing sickness caused by microorganisms or physiologic malfunction (e. g. flu, diabetes, or HIV/AIDS) and illness related to daily living (e. g. depression, stress, or fatigue) (Cockerham, 1981). Albrecht and Devlieger (1999) postulated via the disability paradox framework that people with debilitating illness can experience an excellent quality of life. I used the disability paradox framework as a basis for including a well-being measure in this study (Albrecht & Devlieger, 1999; Fellinghauer, Reinhardt, Stucki & Bickenbach, 2012). My use of the biopsychosocial model can help determine if consideration of patients' perspectives, incorporated into drug development, results in better outcomes in terms of HRQOL and well-being.

### **Nature of the Study**

I used quantitative methodology to analyze patient registry data from the United States Immunodeficiency Network (USIDNET) to understand mean changes in HRQOL and well-being as measured by the NIH sponsored PROMIS-29 instrument. The objective for this study was to measure differences in HRQOL scores and well-being of patients with PIDD based on patient preferences for treatment; namely, number of needle sticks and infusion time using the biopsychosocial model framework to explain the relationship between the independent and dependent variables.

## Definitions

*Ability to participate in social roles/ activities:* The ability to participate in social roles/activities bank of PROMIS questions focuses on feelings of well-being or thriving as individuals participate in their typical societal roles and social relationships (Bode, Hahn, DeVellis, & Cella, 2013).

*Anxiety:* The anxiety bank of PROMIS questions focuses on feelings of fear, dread, and nervousness which might be accompanied by cardiovascular system response and dizziness (Schalet et al., 2016)

*Depression:* The depression bank of PROMIS questions focuses on feelings of sadness, guilt, low self-worth, loneliness, and disinterest in life (“Depression: A Brief Guide,” 2017).

*Food and Drug Administration:* As related to this dissertation, FDA is a governmental agency under the Department of Health and Human Services charged with protecting public health by ensuring the availability of safe, effective, and innovative medical products and advancing public health through provision of science-based, publicly available information (FDA, 2015c).

*Health-related quality of life (HRQOL/ HRQL):* The subjective measure of patient perceptions of their physical, social, and emotional functioning with one or more chronic diseases (Elliott & Richardson, 2014).

*Patient-centered:* An approach which encompasses the biopsychosocial theoretical framework in that it is inclusive of patients or their proxies (e.g., a caregiver, parent, or advocate; Kalra, 2014). This approach involves considering patients’ and/or

proxy members' opinions and contributions to decision-making in all aspects of care, from medical product development through regulatory approval to type of treatment prescribed by a medical practitioner and pharmacy provider (Kalra, 2014).

*Patient-reported outcomes (PRO):* A self-assessed measure of health status which is independent of a clinical analysis or medical professional evaluation (Nicassio et al., 2011).

*Perceived health:* An individual's subjective assessment of his or her biological, cultural, social, and psychological functioning which can be used as an indicator of patient satisfaction with his or her health and with medical treatments (Seeborg et al., 2015)

*Primary immune deficiency disease (primary immune deficiency disorder):* A group of rare genetic diseases in which components of the immune system are missing or defective, resulting in a tendency to have unusual infections which are more severe and last longer than in individuals with an intact immune system (IDF, 2016).

*Route of administration:* The pathway by which medication is introduced to the body. Injection routes of administrations discussed here include intramuscular (IM), intravenous (IV), and subcutaneous (SC). Injection routes of administration of immune globulin (IG) for PIDD are described using the terms IMIG, IVIG, and SCIG (Kobrynski, 2012).

*Well-being:* A measure of how people are coping in a positive way and also thriving with chronic disease (Barile et al., 2013).

### **Assumptions**

I made two assumptions for this study. The first assumption was that the USIDNET patient registry from which I obtained study data is representative of the general PIDD population in the United States and of the PIDD patient population whose treatment preferences informed drug innovation. The second assumption was that the PROMIS-29 measures are relevant for the PIDD population.

### **Scope and Delimitations**

Firstly, not all medical products are specified for pediatric patients. Therefore, the study plan was to include patients who were 16 years old and older at the time they took the survey. I used a liberal definition of adulthood to select the age 16 years and older. The rationale stemmed from concerns regarding sample size due to the rareness of PIDD, and that each state defines its criterion of adulthood for various purposes. For this study, age 16 represented the two states (New York and North Carolina) where criminal offenders would be tried in an adult court (National Conference of State Legislatures, 2017). Secondly, there are several categories of PIDD. This study captured all the categories under the general heading PIDD and I did not segment according to PIDD subtype.

### **Limitations**

Blome and Augustin (2015) presented views of the types of biases which exist when measuring changes in HRQOL prospectively and retrospectively. The research proposed here is a retrospective study where researchers collect data only after an intervention. Respondents can take the survey semiannually. Retrospective studies are

subject to recall bias, where the respondent either recalls their past situation as being either better or worse than their current situation, based on how they feel when taking the assessment or a respondent reconstructs their response based on current feelings and assumptions about their past status (Blome & Augustine, 2015). A second category of bias relates to how subjects respond to survey questions. The tendency to answer in agreement, answer in disagreement, disregard questions deemed as not applicable to the subject's situation, answer randomly, answer at the extremes, or answer in a manner the subject deems is more socially acceptable creates bias (Blome & Augustine, 2015). Blome and Augustine (2015) suggested a retrospective study even with the listed biases could be beneficial when one wants to understand patient views on treatment benefits.

Fayers, Langston, and Robertson (2007) described response error in measurements of quality of life (QOL). The authors posited that QOL bias is introduced regarding the frame of reference the subject uses when responding to the survey instrument (Fayers, Langston, & Robertson, 2007). The frame of reference could be a comparison to: self, prior to illness; self, the previous time point in a longitudinal study; other patients with the same disease; patients with a different disease; and healthy subjects. At each interval of measurement, the frame of reference can shift. Upon testing for mean differences in subjects' expressed frame of reference against QOL scores, there were statistically significant differences according to frame of reference (Fayers et al., 2007).

Lastly, the sample size was expected to be small due to the rareness of PIDD, and randomization was not possible. Limitations were addressed via statistical analytical

methods additional to t-tests as warranted by the data. Additionally, limitations are acknowledged in the methodology and conclusion chapters.

### **Significance of the Study**

Information gained from this study could help the primary immunodeficiency community understand changes (hopefully improvements) in HRQOL and well-being parameters resulting from using different medical product innovations enabling flexibility. For example, patient perspectives can inform drug development and even the regulatory process for drug approval. Once the drug is developed and on the market, which of the patient perspectives (specifically related to social parameters measured with instruments measuring HRQOL and well-being parameters) changed because of using a given drug? Such knowledge could be useful for refining drug development protocol and regulatory policy in the future.

### **Summary**

In this chapter, I presented information about PIDD, the role of medical product manufactures as it relates to HRQOL and well-being, the relevance of PIDD to public health, and a theoretical lens through which PIDD can be viewed. In the next chapter, I establish the basis for the study by reviewing existing literature and identifying gaps in the literature. Some of the areas reviewed include the biopsychosocial model theoretical framework, and key variables I used in my study.



## Chapter 2: Literature Review

### **Introduction**

Medical products manufacturers have innovated therapies for patients with PIDD based on patient preferences for fewer needle sticks and a shorter infusion time with the goal of improving these patients' HRQOL and well-being (Espanol et al., 2014; Kobrynski, 2012; Ponsford et al., 2015). Since 2015, the IDF through USIDNET has been collecting HRQOL and well-being data on patients with PIDD through the PROMIS-29 survey instrument. There is limited data showing whether therapies innovated for fewer needle sticks and shorter infusion time have an impact on HRQOL and well-being as measured by PROMIS-29. The purpose of this quantitative study was to determine the mean differences in HRQOL and well-being using PROMIS-29 scores of patients with PIDD who are using medical product manufacturers' innovative medical products allowing for (a) fewer needle sticks and (b) shorter infusion time compared to those who were not.

This literature review begins with the search strategy I used for locating literature. I then present the biopsychosocial model theoretical framework and supporting studies. Next, I present an extensive literature review of key variables and concepts. Lastly, I conclude with the gap found in the literature which my study aimed to fill, and with a summary of the chapter.

### **Literature Search Strategy**

Although the tone of the literature review is neutral and is based on the positivist tradition of biomedical research (see Wilson, 2000), it suggests the need to expand

beyond physiological parameters of biomedical research to include psychosocial parameters, along with patient experience (Mead & Bower, 2000). The literature review was conceptual in nature, to demonstrate the ongoing paradigm shift of incorporating patient views in modern biomedical research (see Wilson, 2000). I used the following questions to guide my literature search:

- In patients with the same disease state and undergoing a standard protocol of treatment for it, why do some have better biomedical (e.g., controlled disease state as evidenced by laboratory blood chemistry measures) and psychosocial (e.g., self-reported days of feeling well/sick) outcomes than others?
- What are the factors associated with better or worse outcomes?
- How have researchers analyzed the relationship between social factors and medical outcomes?
- What have researchers done to address medical outcomes related to social factors?
- What research methods have been used in the past to determine associations between social parameters and medical outcomes?

The literature search began on June 30, 2014. My strategy included assessing key words in the Walden University Library Health Sciences Research databases. The databases searched included MEDLINE with Full Text, CINAHL Plus with Full Text, ProQuest Nursing & Allied Health Source, PubMed, and Science Direct. Additionally, a Thoreau multidatabase search was conducted. The keywords used were *chronic illness* or *chronic disease*, *well-being*, AND *genetic disorders*; *well-being* AND *primary immune*; *burden of*

*disease AND subcutaneous AND intravenous; bio-psychosocial model; treatment preferences AND subcutaneous AND intravenous; patient-focused; patient-centered; patient-reported outcomes; and PIDD.*

Then, I narrowed the search to include primarily peer-reviewed articles published in the years between 2008 and 2017, unless a seminal piece of literature added context to the review. Because the medical product innovations being studied do not all have pediatric indications, I excluded articles which focused solely on children. The focus of the dissertation was a rare genetic medical condition (PIDD) which, with treatment, is manageable for years and decades like a chronic disease (see Chapel et al., 2014). Thus, I excluded literature which focused on terminal illnesses. Because PIDD stems from a biological cause, I also excluded literature focusing on psychological disorders.

I consulted timely nonscholarly works such as transcripts of the FDA's patient-centered drug development program as an endeavor to add clarity on patient perspectives (Coplan, Noel, Levitan, Ferguson, & Mussen, 2011). FDA's patient-centered drug development program encompassed a series of public meetings, each focused on a different medical condition. Patients with a given disease spoke about their life with the condition. Caregivers and individuals representing advocacy organizations spoke about their life as a caregiver or advocate of someone with the condition. Participants shared their experiences with medical treatments utilized. Participants also discussed their perspectives about clinical trials, and future treatment options (FDA, 2015a). I reviewed transcripts from public meetings held inclusive of the years 2011-2016 for the rare and genetic diseases which involved a treatment regimen administered via the subcutaneous

or intravenous routes (FDA, 2017). From the transcripts of polling questions and discussion points, I honed the idea of including well-being measures into the present study. I also consulted the websites of advocacy organizations, such as International Patient Organization for Primary Immunodeficiencies (IPOPI) and Immune Deficiencies Foundation (IDF), and articles referenced on their websites to elucidate variables for consideration in the present study. Lastly, I consulted websites such as Clinical Trials.gov, NIH, FDA, and National Organization for Rare Disorders (NORD).

### **Theoretical Foundation**

The theoretical foundation used in this study was the biopsychosocial model. According to the tenets of this model, health and illness are not merely biological. Instead, health and illness involve the whole individual. Thus, the contributions to health and illness include biological, psychological, and social parameters (Engel, 1980). This holistic framework includes biological (i.e., organs, organ systems, biochemistry, vital signs, and physical presentation); psychological (i.e., attitude, behaviors, emotions, and preferences); and social (i.e., where and with whom one navigates through daily life at home, at school, at work, at places of worship, relationships, participation) elements (Engel, 1980). I designed my study to use the biopsychosocial model to relate the biomedical variables of medical product innovation with the psychosocial variables of HRQOL and well-being.

Immunoglobulin replacement therapies developed by medical product manufacturers for PIDD are only approved by FDA once they are demonstrated via clinical trials with biomedical endpoints to be safe and effective (Melamed et al., 2012).

The biomedical endpoints include biological measures such as IG blood levels and the metabolism process, monitoring site of injection and systemic reactions, and measuring and assessing changes in infection rate (Dashti-Kavidaki et al., 2009; Melamed et al., 2012). Patients, caregivers, and advocates express their desire for improved treatments. They serve as agents stimulating medical product manufacturers to support research aimed at soliciting and evaluating patient feedback regarding satisfaction with current treatment, and preferences for improvements in treatment offerings (Doward, Gnanasakthy, & Baker, 2010). FDA regulators seek to inform their regulatory decision-making using biomedical endpoints from clinical trials and input from patient-reported outcomes collected during clinical trials (U.S. Department of Health and Human Services, 2009). A search of the literature revealed studies on the PIDD population measuring patient-reported outcomes (see Table 1).

Table 1

*Review of Patient-Reported Outcomes Studies on Primary Immune Deficiency Disease*

Reference	Objective and population	Variables	Patient-reported outcomes by measurement instrument	Results
Biennu et al. (2016)	<p>Patient treatment satisfaction and quality of life.</p> <p>Prospective, observational cohort study of 116 PIDD patients receiving immune globulin replacement therapy (IGRT) took place in France for 12 months.</p>	<p>Demographic</p> <p>Lifestyle</p> <p>Occupation</p> <p>Comorbidities</p> <p>Infections</p> <p>History of PIDD</p> <p>History of IGRT</p> <p>IGRT route/ place of administration</p> <p>IG serum level</p> <p>Patient satisfaction</p> <p>Quality of Life</p>	<p>Life Quality Index (LQI) factors I, II, III</p> <p>Treatment satisfaction with IG replacement therapy</p> <p>Treatment interference</p> <p>Therapy-related problems</p> <p>Therapy Settings</p> <p>Short Form-36 (SF-36), v2</p> <p>Quality of Life</p>	<p>Satisfaction with home-based treatment interference was higher for SCIG than for IVIG.</p> <p>Satisfaction with IVIG treatment interference was higher in a hospital setting than in a home setting.</p> <p>There was no difference between route of administration and place of administration on patients' satisfaction with therapy-related problems.</p> <p>Satisfaction with therapy setting was optimal for home-based SCIG.</p> <p>QOL related to route and place of administration revealed no statistically significant differences.</p>

*(table continues)*

Reference	Objective and population	Variables	Patient-reported outcomes by measurement instrument	Results
Espanol et al. (2014)	<p>Patient preferences regarding treatment and therapy administration.</p> <p>On-line multinational survey completed by 300 patients from 21 different countries.</p>	<p>Current treatment</p> <p>Route/ place of administration</p> <p>Dose frequency</p> <p>Treatment satisfaction</p> <p>Treatment-related adverse events</p> <p>Impact of PIDD on HRQOL</p> <p>Impact of treatment on HRQOL</p>	<p>Physical and psychosocial health measures by</p> <p>12-Item Short Form Health Survey (SF-12v2)</p> <p>HRQOL</p> <p>10-Item Short Form Health Survey (SF-10v2)</p> <p>Self-care, usual activities, pain/ discomfort, anxiety/ depression by EuroQOL five Dimensions</p>	<p>Patients preferred self-administration versus administration by a healthcare professional.</p> <p>Patients also preferred home versus hospital administration, therapy which enabled monthly versus weekly or every two weeks treatment, fewer needle sticks, and shorter infusion time.</p>
Heath, Lehman, Saunders, and Craig (2016)	<p>Depression and anxiety level experienced by patients with PIDD and how much depression and anxiety they attributed to their PIDD.</p> <p>Telephone voluntary survey was extended to PIDD patients at a university division of pulmonary, allergy, and immunology in the United States.</p>	<p>Lifestyle</p> <p>PIDD diagnosis</p> <p>PIDD treatment</p> <p>Comorbidities</p> <p>Amounts of anxiety and depression experienced and attributed to PIDD diagnosis</p>	<p>Hamilton Depression Rating Scale (HAM-D)</p> <p>Amount of depression experienced</p> <p>Amount of depression attributed to PIDD</p> <p>Hamilton Anxiety Rating Scale (HAM-A)</p> <p>Amount of anxiety experienced</p> <p>Amount of anxiety attributed to PIDD</p>	<p>Patients with PIDD had median HAM-D scores comparable to the US population.</p> <p>Patients receiving IVIG therapy in the home or in a clinic had significantly higher HAM-D scores than those receiving SCIG at home.</p> <p>Patients who had healthcare professional administered therapy had higher HAM-D scores than those who self-administered.</p> <p>Higher HAM-D scores were associated with adverse effects from IGRT.</p> <p>Patients receiving IVIG attributed higher amounts of their anxiety to their diagnosed PIDD compared with those receiving SCIG.</p>

(table continues)

Reference	Objective and population	Variables	Patient-reported outcomes by measurement instrument	Results
Jorgensen et al. (2014)	<p>HRQOL in patients with selective IgA deficiency (SIgAD) and to determine factors leading to poor HRQOL.</p> <p>Icelandic patients with SIgAD (n=33) were matched with randomly selected age and gender-matched Icelandic controls (n=96) with normal immune globulin levels.</p>	<p>Gender Age Education Employment Status</p>	<p>SF-36 Global HRQOL Self-reported HRQOL Role-physical General health Social functioning Role-emotional Mental health</p>	<p>Patients with SIgAD reported lower global HRQOL than did the control group of persons with normal immune globulin levels. The differences were not statistically significant.</p>
Mohamad, Kilambi, Luo, Iyer, & Li-McLeod (2012)	<p>To promote patient-centered care by calculating the relative importance of immune globulin treatment attributes to patients.</p> <p>Web-enabled choice-format conjoint survey was completed by 252 patients.</p>	<p>Gender Age Race Employment status PI diagnosis Route of administration</p>	<p>Self- or healthcare professional administration Frequency of administration Location of administration Number of needle sticks per treatment Treatment duration Treatment preference</p>	<p>Patients indicated preferences for monthly versus weekly administration, home setting versus doctor's office/hospital/ clinic, shorter versus longer treatment durations, and fewer needle sticks of IG treatment relative to alternative choices.</p>
Seeborg et al. (2015)	<p>Total of 1526 patients (61.2%), with PIDD from across the United States returned a self-administered questionnaire.</p>	<p>Gender Age Race Education level</p>	<p>Perceived health status</p>	<p>Patients perceived their health as excellent or very good (30%), good (31%), or fair, poor, or very poor (39%).</p>

(table continues)



Reference	Objective and population	Variables	Patient-reported outcomes by measurement instrument	Results
				Perceived health was associated with age, gender, education level, and employment status. Patients with access to IVIG therapy and specialty care were more likely to perceive their health as excellent or very good.
Tabolli et al. (2014)	HRQOL and psychological status among PIDD (specifically CVID) patients to compare immune globulin therapy administration regimens.  Six-year longitudinal cohort study followed an initial 96 patients.	Gender Age Duration of disease Comorbidities	Short Form-36 (SF-36)  General Health Questionnaire (GHQ-12) Psychological distress Depression Anxiety  PGA Disease clinical severity perception relative to other patients with the same disease	HRQOL scores were low, and were also lower than those reported by generally healthy people, and by people with other chronic diseases (except heart failure). Female gender and older age was associated with poorer quality of life.

*(table continues)*

Reference	Objective and population	Variables	Patient-reported outcomes by measurement instrument	Results
Vultaggio et al. (2015)	<p>To evaluate changes in biomedical and patient-reported parameters in response to a shift from IVIG to SCIG.</p> <p>The multicenter prospective observational study included 50 patients in Italy with PIDD who also were concurrently taking part in a PIDD medical product clinical trial monitored for 24 months.</p>	<p>Age</p> <p>PIDD diagnosis</p> <p>Treatment route of administration</p> <p>Baseline serum trough IgG levels</p> <p>Annual rate of severe bacterial infections</p> <p>Number of days off school/work</p> <p>Days of hospitalization due to infections</p> <p>Medication tolerability</p>	<p>Child Health Questionnaire-Parental Form 50 (CHQ-PF50)</p> <p>Physical functioning</p> <p>Psychosocial functioning</p> <p>Well-being</p> <p>Short Form 36</p> <p>Role-physical</p> <p>General health</p> <p>Vitality</p> <p>Social function</p> <p>Role-emotional</p> <p>Mental health</p> <p>Life Quality Index</p> <p>Impact of the IgG treatment on daily activities</p> <p>Visual Analogue Scale</p> <p>Perception of general health</p>	<p>Treatment with SCIG did not significantly improve HRQOL in patients with PIDD.</p>

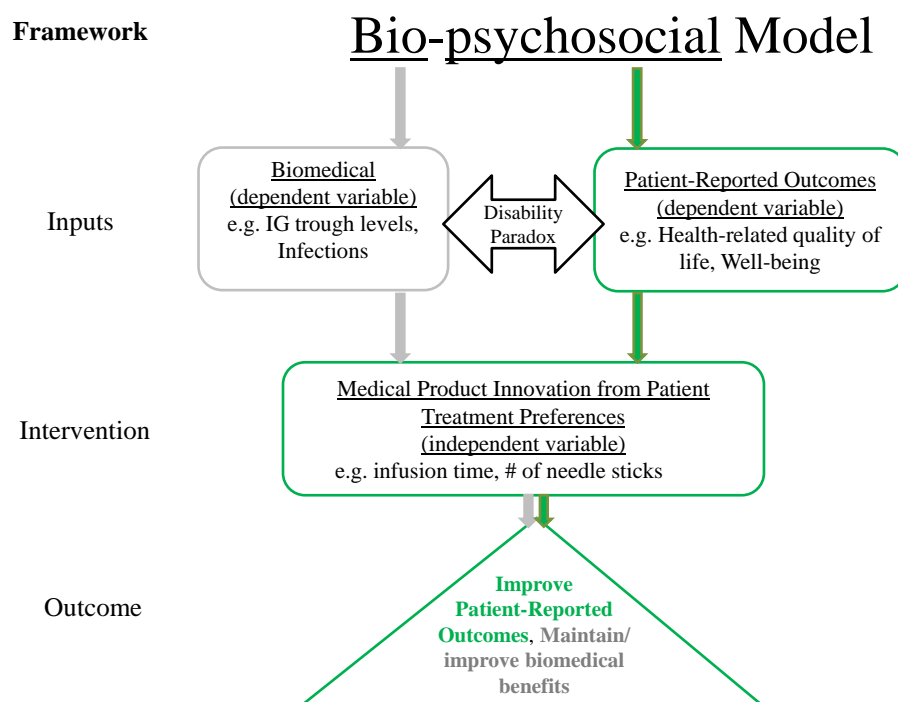
As noted in Chapter 1, I mention the disability paradox as a secondary framework to explain possible association of independent and dependent variables. The disability paradox framework is an explanation for why individuals whom an outside observer would consider to have low HRQOL based on appearance might self-assess a better HRQOL, even compared with healthy subjects (Albrecht & Devlieger, 1999; Fellinghauer et al., 2012).

### **Biopsychosocial Model**

George Engel introduced the biopsychosocial model as a counter to the biomedical approach toward the practice of medicine. Engel (1977) posited that the biomedical model was inadequate and reductionist as it reduced the patient to his or her body parts and biochemical elements. Engel posited that the patient is a whole being that senses and experiences. The patient is a composite of biological, psychological, and social systems and sub-systems, none of which exists in isolation from the others. The biopsychosocial model has been used as a model for patient-physician interaction; and as a framework for how the physician can view the patient and provide care (Engel, 1977; Engel, 1980; Haveilka et al., 2009). This framework can be used by medical product manufacturers and regulatory authorities for how they view the person who will use the medical products once approved.

**Why selected for this study?** I developed the logic model presented in Figure 1 to show how elements of the biopsychosocial model related to the variables under study in this dissertation. The biopsychosocial model includes biomedical inputs and

psychosocial inputs. Biomedical inputs include biochemical effects of the PIDD disease state and of immunoglobulin replacement therapy (e.g., immunoglobulin levels in the blood, vital signs, and infection), or how patients reported that they felt (e.g., malaise). These dependent variables are represented but greyed out in the logic model, because they are not the focus of this study. Psychosocial inputs include the patient-reported outcome dependent variables of HRQOL, and well-being. These are shown as green in the logic model and these are the focus of this study. The intervention is medical product innovation because of patient treatment preference inputs and biomedical inputs. The outcome of the intervention would hopefully be a change in patient-reported outcomes of HRQOL and well-being, for the better, along with maintained or improved clinical benefits to the patient.



*Figure 1.* Logic model.

Chronic disease defies the biomedical concept of a malfunctioning body which can be restored to function via purely medical or physiological intervention (i.e. if blood pressure is too low, position the body with head raised and feet lowered and administer a medical product which makes the blood vessels contract, and if blood pressure is too high, administer medications to lower it) because chronic disease has no cure. Chronic disease extends beyond the local physiological parameters of the body and it encroaches into life by having impact on the social (e.g. engagements, making plans, going out, and playing with children), and practical (e.g. being able to work, manage a household, self-care, and hobbies) aspects of life (Kalra, Gupta, & Unnikrishnan, 2016).

### **Literature Review of Studies Which Used the Biopsychosocial Model**

None of the PIDD articles located in the literature search specifically named the biopsychosocial model. However, the literature demonstrates that the model has been used to explain the relationships of independent and dependent variables for other chronic disease states, and in some cases for rare diseases. A summary of that literature is shown in Table 2. Elliott and Richardson (2014) studied the biopsychosocial model in persons with epilepsy. An outside observer aligned with the biomedical model might intuit that the greatest improvement to HRQOL for persons with epilepsy is to have few or no seizures. Thus, any medical products which could achieve few or no seizures, along with fewer side effects, would also improve HRQOL. However, persons with epilepsy have psychosocial manifestations of epilepsy, such as a greater tendency toward depression and anxiety which impact ability to attend to requirements of work, school, and social relationships (Elliott & Richardson, 2014). Elliott and Richardson (2014) argued that due to a biomedical focus, the psychosocial aspects of epilepsy generally remain untreated. The researchers established independent variables aligned with the biopsychosocial model; namely, biomedical (e.g. age, gender, comorbidities, and number of doctor visits); psychological (e.g. diagnosed depression and/ or anxiety, and number of visits to mental health professionals); social (e.g. educational attainment, annual income, marital status, and community belonging). The dependent variables were self-rating of health and mental health status, and satisfaction with life. Both the independent and dependent variables were organized from the Canadian Community Health Survey. The researcher performed correlational analysis on these secondary data and found that, compared to the

biomedical model, the biopsychosocial model explained more of the variance in QOL, where Whole Set Correlation  $R^2 = 24.8\%$  for the biomedical model and  $55.0\%$  for the biopsychosocial model, respectively. Additionally, the researchers evaluated biomedical, psychological, and social elements individually and found that the psychological element (Partial Set Correlation (PSC)  $R^2 = 30.4\%$ ), and the social element (PSC  $R^2 = 26.8\%$ ) explained more of the variance in QOL than the biomedical element alone (PSC  $R^2 = 14.3\%$ ). Thus, the authors concluded that the biomedical element such as controlling seizures is important; however, it is not the only element contributing to HRQOL. Further, the authors called for a patient-centered approach which also brings psychological and social practitioners into holistic treatment regimens for individuals with epilepsy. Kalra, Gupta, and Unnikrishnan (2016) argued the value of the biopsychosocial model in terms of availability of insulin preparations available to patients. When the biomedical requirements of, say, blood glucose and hemoglobin A1c are met, the patient and their physician could select an insulin therapy regimen which fits into that individual patient's psychological preferences (such as injection frequency and timing, meal frequency and size, ability to self-inject, and glucose monitoring), and social preferences (such as lifestyle, infusion location which provides privacy, and work schedule). The authors noted that soliciting and implementing patient, caregiver, and advocate treatment preferences along with biomedical measures, is essential for long-term disease management (Kalra, 2014; Kalra et al., 2016).

Baranyi et al. (2013) used the biopsychosocial framework to understand social and psychological differences between patients who became depressed during interferon

alpha treatment for hepatitis C, and those who did not as a way of predicting who would develop depression; and, therefore, to develop preventive measures for such patients (see Table 2). Baranyi et al. (2013) included a social context (i.e. social support) and set out to measure changes in HRQOL, life satisfaction, and cognitive ability via validated questionnaire.



Table 2

*Use of Biopsychosocial Model in Literature and How These Studies Compare to PIDD*

Reference	Disease state	Comparison with literature on PIDD
Baranyi et al. (2013)	Hepatitis C	Used the biopsychosocial framework to understand social and psychological differences between patients who became depressed during interferon alpha treatment for hepatitis C and those who did not. Like IGRT, interferon treatment for hepatitis C is administered by subcutaneous injection. Adherence to a medical product injection regimen is necessary for viral reduction (Ward & Kugelmas, 2005).
Lasker, Sogolow, Short, and Sass (2011)	Organ transplant	Used the biopsychosocial model to select HRQOL variables and assess the demographic, biomedical, psychological, and sociological factors the researchers believed related to quality of life. Lasker et al. determined whether those variables differed before and after transplant; and also determined which variables were most important.
Verderese, Graham, Holder-McShane, Harnett, and Barton (1993)	Gaucher's disease	Measured subjective and objective symptom relief in response to enzyme replacement therapy in patients with Gaucher's Disease. Like PIDD, Gaucher's disease is a rare genetic disorder mitigated by outpatient replacement therapy administered intravenously two to four times per month.

**Criticism of the Biopsychosocial Model.** Criticisms of the biopsychosocial model include that the model does not stand on its own, but is instead an extension of the biomedical model with psychological and social factors added on; constructs are not well defined; and the model does not explain the origin of disease (Haveilka et al., 2009).

### **Primary Immune Deficiency Disease**

The prevalence of infectious diseases in the early part of the twentieth century masked PIDD. As scientific progress in medicine and public health interventions brought infectious diseases under control, medical cases of chronic diseases became more prevalent. Cases of PIDD also became observable to the medical community due to the manifestation of unusual and severe infectious diseases which could be readily treated for individuals with an intact immune system (Chapel et al., 2014; Costa-Carvalho et al., 2014). Though there are several types of treatment available for PIDD (e. g. blood stem cell transplant, antibiotics therapy, or gene therapy), the mainstay treatment is immune globulin G (IgG) replacement therapy; referred to throughout this dissertation as IGRT (Chapel et al., 2014; Dashti-Khavidaki et al., 2009). Genetic defects of the immune system results in defective cells, antibodies, and / or complement. Immunity resides in the bone marrow and in the blood. As such, the immune system is spread throughout the body. Thus, a defect in a gene coding for an immunity cell, antibody, or the complement components has implications throughout the body (Costa-Carvalho et al., 2014).

### **The Role of the Patient**

Management of PIDD is complex in that it involves a regimen of aseptic medicine transfer into IV bags and/ or syringes, injection site cleansing, and medication injection into the intravascular system. Management of PIDD is also burdensome as it involves making time to visit an infusion clinic to receive medication, or making room in the home for supplies and time in one's schedule to administer therapy (Melamed et al., 2012). However, adherence to the infusion routine is essential for warding off infection (Bienvenu et al., 2016). IDF is a patient organization providing education, advocacy, research opportunities, and outreach to and on behalf of people with primary immune deficiency disease (IDF, n. d.). IDF is a key voice in the United States through which researchers, regulatory agencies, and medical products manufacturers can understand the needs of the patients with PIDD.

### **The Role of the FDA**

The FDA, like other ministries of health around the world, protects and promotes public health via regulation provided to manufacturers of medical products. The premise is regulatory oversight will result in safe and effective medical products which will produce positive outcomes for patients. Yet, people with the same disease state and undergoing the same treatment for it have varying experiences and outcomes (Wilson and Cleary, 1995).

Through the Patient-Focused Drug Development initiative, FDA officers are examining burden of disease, treatment preferences, and ways to improve health outcomes by engaging patients, caregivers, and advocacy organizations in dialog through

a series of meetings, each covering a different disease state (Lejbkowitz, Caspi, & Miller, 2012; Muhlbacher, Juhnke, Beyer, & Garner, 2016). FDA's responsibility is to ensure that the benefits of drugs outweigh the risks, understand how patients view benefits and risks of treatments, and guide researchers, via the regulatory process, to appropriate end points to measure how well these drugs are working (FDA, 2015a).

### **The Role of the Medical Product Manufacturers**

Immune globulin G is a highly purified plasma protein. Manufacturers produce IgG by purifying plasma collected from donors. The proprietary manufacturing process each manufacturer uses includes fractionation steps, viral deactivation, excipients addition, and pH and temperature adjustments (Chapel et al., 2014). For initial approval by FDA, manufactures of IGRT are responsible for ensuring the key biomedical factors of safety (e.g. no viral transmission from the IG to patient), efficacy (e.g. reduced infections), and tolerability (e.g. few or no adverse reactions) are confirmed in humans via clinical trial (Chapel et al., 2014). After initial approval by FDA, manufacturing status, changes, safety reports, and post-marketing clinical and non-clinical commitments or requirements are each reported to FDA on various frequencies such as batch-to-batch, quarterly, and annually.

Medical products manufacturers have incorporated patient perspectives into therapy improvements with the aim of improving treatment satisfaction and quality of life, and the FDA has approved these therapies.

The first such improvement was developing therapy alternatives enabling patients to move from intravenous administration in a clinical setting to subcutaneous

administration in the home. Research showed improvements in HRQOL (Garduff & Nicoloy, 2006). The next medical product innovation, in response to patient expression, was development of therapies with reduction in the number of needle sticks and shorter infusion times while maintaining self-infusion at home (Espanol et al., (2014).

Preliminary analysis suggested that these changes to medical product innovation would result in reduced burden; therefore, improved quality of life (Ponsford et al. 2015; Wasserman, 2014).

### **Treatment Options**

The three routes of IGRT administration include needle injections into the muscle, veins, or under the skin. Intramuscular injection (IMIG) is a rarely used route of administration. In a study of patients receiving IVIG, causes of adverse reactions (e.g. fever and chills) included infection, infusion reactions, infusing too rapidly, switching medications, first infusion, and a long-time interval between injections (Dashti-Khavidaki et al., 2009). The first IGRT was delivered subcutaneously in 1952 and was thereafter delivered intramuscularly until 1980. From 1980 to the present IVIG has been prominent and as recently as 1991, SCIG has begun to make a resurgence (Haddad et al., 2012). Researchers evaluating the biomedical effects of SCIG noted systemic adverse events were reduced while the effects (e.g. burning, itching, and swelling) were localized to the site of injection (Haddad et al., 2012; Melamed et al., 2012).

### **Burden of Treatment**

Hirsch, Walker, Chang, and Lyness (2012) studied chronic diseases in adults aged 65 and older and analyzed the extent to which anxiety, as a result of the burden of

medical illness, is reduced by the presence of optimism and increased by the presence of pessimism. The researchers' hypothesis was realized by the results and this led to their suggestion to implement moderating factors such as training patients to have positive thoughts and to foster meaningful relationships, and developing clinical health interventions which shift the patient's frame of mental reference to a more optimistic viewpoint (Hirsch et al., 2012).

Verderese et al. (1993) measured subjective and objective symptom relief in response to enzyme replacement therapy in patients with Gaucher's Disease. Like PIDD, Gaucher's disease is a rare genetic disorder (where glucocerebrosidase enzyme is lacking resulting in the systemic buildup of the lipid glucocerebroside inside macrophage white blood cells and organs such as the spleen, liver, and bone marrow) which is mitigated by outpatient replacement therapy administered intravenously. After each enzyme replacement treatment, Verderese et al. (1993) recorded subjective patient perceptions on reduction of bruising (measured by increased platelet counts), chronic fatigue (measured by increased hemoglobin concentration), and gastrointestinal protrusion (measured by reduced abdomen size) and found the subjective perception of symptom relief often preceded the laboratory measurement of the corresponding parameter. Additionally, self-concept, self-esteem, self-image, and mood were reported to have improved due to patients' having more energy and reduced abdominal size, leading to more confidence in the social and relationships arena.

### **Patient-Focused Drug Development and Patient-Centered Treatments**

As described in the FDA Prescription Drug User Fee Act Patient-Focused Drug Development (2013) announcement in the Federal Register, FDA personnel initiated a series of public meetings under its Patient-Focused Drug Development initiative. Each meeting focused on a specific disease, with involved FDA staff, patients, caregivers, and advocacy organizations. The FDA personnel used mixed-methods research methodology and gathered information through questionnaires, polls, written comments, and focus group discussions regarding daily life, lived experience with the disease, the symptoms of greatest impact, current medical and non-medical treatment regimens in use, and opinions about clinical trials. Theoretically, this patient-centered approach would be an input to the regulatory guidance provided to medical product manufacturers for new and already commercialized products as well as to the regulatory decision-making used by the Agency for initial approval (FDA, 2015a).

Patient reported outcomes are increasingly solicited via surveys presented to participants in clinical studies intended to show drug safety and efficacy. However, results may not be reflective of the general population who will use the drug upon its commercialization due to the selection criteria used for clinical trial participation. Fleurence et al. (2013) argued the importance of including the patient perspective into clinical studies. The researchers used as examples Alzheimer's dementia and a comparison of two heart surgery interventions. In the former, the clinical endpoint would typically be changes representing improved cognitive ability. However, patient preference could be for improvement in capacity to function in activities of daily life. In

the latter example, the clinical endpoint could be decreased complications and increased longevity. However, patient preference was for relief of chest pain (Fleurence et al., 2013). Related to PIDD, immunoglobulin replacement therapy safety and efficacy clinical endpoints typically are measured by IgG trough levels, change in the number and types of infections, change in the number and types of infections requiring hospitalization, and site of injection issues (Dashti-Khavidaki et al., 2009). However, one of the challenges to drawing conclusions regarding patient preferences compared to the clinical endpoints measured via laboratory analysis and/ or mathematical calculation is they are inherently subjective and require interpretation and translation to objective measures. Conjoint analysis and Best-Worst Scaling (BWS) are two statistical methods for elucidating patient medical treatment preferences and moving from qualitative to quantitative. This enables medical product manufacturers to have a quantitative basis for assessing patient-reported endpoints and also developing next generation products. Additionally, such measures of patient preferences are useful to regulators in their review of new product applications and ongoing surveillance of commercial medical products (Johnson & Zhou, 2016; Morel, et al., 2016). Conjoint analysis has its origin in consumer research aimed at understanding preferences for various attributes of a product offering (Kinter, Prior, Carswell, & Bridges, 2012). In the health care setting, conjoint analysis and BWS can be used to help medical product manufacturers, and the FDA understand the relative importance of treatment attributes, and risk to benefit tradeoffs acceptable to patients and/ or caregivers (Kinter et al., 2012). Mohamed et al. (2012) utilized conjoint analysis to examine treatment preferences of 252 patients with PIDD



and 66 parents, all in the United States, regarding treatment provider (self or healthcare professional), frequency (every other week or weekly), location (home or clinic), needle sticks (four or one), and treatment duration (6 hours or 2 hours). Treatment preferences were selected based on a qualitative pre-test with a sample of nine patients and parents using open-ended interview questions. In the study, route of administration was predominately IVIG (59.9%) versus SCIG (41.1%). Both patients and parents preferred a home setting, monthly infusions, fewer needle sticks, and shorter duration. In terms of preference for treatment, both patients and parents considered least important whether the patient self-infused treatment or a healthcare provider administered the treatment. For patients, location was the most important and for parents, frequency was most important. Regarding relative importance to patients of the individual therapy attributes and trade-offs, with increased treatment frequency, fewer needle sticks and shorter duration became more important. Espanol et al. (2014) elucidated PIDD treatment preferences from 216 patients and 84 caregivers via a multinational online survey using conjoint analysis. In contrast with Mohamed et al. (2012), route of administration (e.g. IVIG, SCIG, and other) was a distinct category along with patients and caregivers (referred to as parents by Mohamed et al.) and was analyzed as such by Espanol et al. (2014). Respondents represented 21 countries on the continents of Africa, Asia, Australia (including New Zealand), Europe, North America (excluding the US), and South America. Intravenous (53%) and subcutaneous routes (45%) of administration were represented. Patients on IVIG received therapy an average of every 23 days in a clinical (75%) setting or at home (15%) while 94% of the patients on SCIG had therapy in the home an average of every

six days. Patients and caregivers were asked to respond to the following categories of preferences: (a) self-administration versus administration by a health professional; (b) monthly, every-other weekly, or weekly treatment frequency; (c) home or clinical treatment location; (d) one, two, or four needle sticks per treatment; and (e) two, four, or six-hour therapy duration. Across the IVIG and SCIG routes of administration, both patients and caregivers preferred monthly treatments, a home environment, one or two needle sticks, and two-hour therapy duration. SCIG patients and caregivers significantly preferred self-administration while the preference for IVIG among patients and caregivers was not statistically significant. Both sets of authors indicated the importance of assessing PIDD patient and caregiver preferences and representing these preferences in treatment offerings to fulfill unmet needs in terms of HRQOL. Interestingly, both studies were supported by medical product manufacturers, and this suggests an understanding that gauging patient and caregiver preferences is an important input to their decisions about next generation therapies. Hollin, Paey, and Bridges (2015) further illustrated the usefulness of quantifying patient treatment preference. This study was initiated by caregivers to children with Duchene Muscular Dystrophy. The patient advocacy organization called Parent Project Muscular Dystrophy (PPMD) engaged the Duchene Muscular Dystrophy community in gathering treatment preferences and, with FDA's blessing, modeled their approach after FDA's Patient-Focused Drug Development initiative, with the exception that PPMD used conjoint analysis and best-worst scaling (BWS) to quantitate treatment preferences. Hollin et al. (2015) compared two methods of quantitating patient preferences to demonstrate the reliability of the survey method

used to collect preferences. Their study was also intended to provide evidence the methodology can be useful for regulatory decision-making in terms of medical product and treatment risk-to-benefit and tradeoffs patients and caregivers are willing to make (Hollin, Paey, & Bridges, 2015). This study underscores the role of patients and caregivers with their advocacy organizations, medical products manufacturers, and FDA in facilitating the provision of patient-centered treatments (Hollin et al., 2015).

### **Patient-Reported Outcomes: HRQOL and Well-being**

As discussed, one of the goals for measuring patient preferences for treatment is to demonstrate treatment tradeoffs and risk-to-benefit of treatment attributes patients and caregivers are willing to make (Hollin et al., 2015). However, another goal for measuring patient preferences for treatment is to ultimately improve patient HRQOL and well-being. As with other diseases, researchers studying patients with PIDD have argued for the development of a HRQOL instrument specific to overall primary immune deficiency as well as specific variants of the disease (Quinti et al., 2016).

Studies located for this review measured HRQOL and well-being associated with patient satisfaction with current treatment for PIDD over time; changes in treatment regimen; and aspects of treatment which change perceived health. Kobrynski (2012) reviewed nine studies which compared route of administration and location of administration (home versus hospital). The studies took place in Europe (three each in Sweden and Germany, and one in Norway and Denmark) and in North America (USA and Canada), from 1995 to 2011. Seven studies examined changes in HRQOL and well-being comparing immunoglobulin delivery by the intravenous route of administration in a

clinical setting (e.g. hospital or clinic) to immunoglobulin delivery by the subcutaneous route of administration in a home setting. Generally, study results revealed treatment satisfaction with SCIG as measured via the Life Quality Index (LQI) instrument. Other improved HRQOL measures included general health perception, family activities, and general health as measured by Short Form-36 (SF-36) and Child Health Questionnaire-Parent Form 50 (CHQ-PF50). Among patients receiving IVIG, one study showed some viewed SCIG in the home as inconvenient. One study comparing SCIG in the hospital/clinic versus SCIG in the home revealed patient satisfaction and feeling of independence with home infusions of SCIG. Finally, authors of one study compared treatment regimens which could reduce home-based SCIG infusion times and found high satisfaction with rapid infusion.

Jiang et al. (2015) also reviewed the literature regarding HRQOL in patients with PIDD. The researchers focused on treatment regimen satisfaction (i.e. route and location of administration) measured via commonly used survey instruments (see Table 1). Jiang et al. also included studies which made comparisons between patients with PIDD and healthy study subjects, and studies which compared patients with PIDD to patients with other chronic diseases. Factors associated with poorer HRQOL included comorbidities, employment status, stress, multiple infections, and PIDD diagnosis delay. Other factors associated with improved HRQOL included home-based therapy; treatment comfort, flexibility, convenience, and independence; shorter treatment duration and less impact/disruption to daily activities (e.g. school/ work, and social); and satisfactory immunoglobulin trough levels (Jiang, et al., 2015; Vultaggio et al., 2015). Espanol et al.

(2014) showed the majority of patients with PIDD (76%, n=300) were pleased with their current treatment; however, those receiving SCIG (83%) were more pleased compared to those receiving IVIG (69%). Relating SCIG and IVIG treatment to HRQOL, as assessed by the EQ-5D, measures of anxiety, depression, mobility, routine activity performance, pain, and self-care revealed there was no difference in HRQOL (71.8% and 71.9%, respectively). Overall, HRQOL was found to be poorer in patients with the common variable immune deficiency form of PIDD than in the US population as measured by EQ-5D and SF-36 instruments (Espanol et al., 2014; Tabolli et al., 2014). In contrast, assessment of HRQOL by SF-36 in PIDD patients with a deficiency of immune globulin A (n=32) compared with age and gender matched controls (n=63) revealed no statistically significant difference (Jorgensen et al., 2013). Likewise, a study focused specifically on HRQOL, anxiety and depression in patients with PIDD (n=33) as measured by HAM-D and HAM-A found that levels were similar to the general US population.

The synthesis of the abovementioned studies reveals that HRQOL has been measured as a dependent variable according to patient preference for treatment, such as route of administration (intravenous versus subcutaneous), place of administration (clinical setting versus home environment), and infusion duration using a standard SCIG route versus a newly innovated enzyme-facilitated SCIG route. The HRQOL measures were assessed using various commonly used instruments. Additionally, the literature revealed sources of variables leading to higher or lower HRQOL scores with moderating or confounding variables. The literature has not yet been expanded to present the

changes in HRQOL and well-being as dependent variables to recent medical product innovations allowing for fewer needle sticks and offering shorter infusion duration using the PROMIS-29 instrument in a population of patients with PIDD. This is the area where my dissertation can begin to close this gap.

### **PROMIS Instrument**

The PROMIS instrument is a set of standardized and validated questionnaire items used for measuring QOL. Developed under the National Institutes of Health's Roadmap Initiative, PROMIS can be utilized across a number of chronic disease states, including for genetic diseases (Cohen & Biesecker, 2010).

### **Summary and Conclusions**

I introduced the literary basis for this study of mean changes in HRQOL and well-being for patients with PIDD who use medical products innovated with consideration of patient preferences for treatment; specifically, the number of needle sticks and infusion time. Additionally, I presented a literary basis for use of the biopsychosocial framework to explain the relationship between the dependent and independent variables. In the following chapter, I present the research questions and further elucidate study variables and how these variables were operationalized.

## Chapter 3: Research Method

### **Introduction**

The purpose of this study was to examine whether the incorporation of patient preferences for treatment into medical product innovation results in improved HRQOL and well-being for patients with PIDD. Use of statistical tools such as conjoint analysis to quantify patient preferences for treatment provides medical products manufacturers with data for their development of next-generation products aimed at improving patient experience as measured by HRQOL and well-being scales (Mohamed et al., 2012; Morel et al., 2016). Patient preferences also inform FDA leaders in their regulatory decision-making. For example, FDA leaders consider the biomedical elements of a next-generation medical product in terms of safety and efficacy of metabolism once in the body as well as the psychosocial elements related to the daily life of patients and enhancing quality and well-being (Johnson & Zhou, 2016).

Through the literature review process, I learned the following: (a) HRQOL and well-being have been measured for patients with PIDD; (b) patients with PIDD have been queried regarding treatment preferences, and some of these preferences have been measured using standard instruments which measure HRQOL, such as SF-36; and (c) manufacturers of medical products have developed therapies to align with patient preferences for treatment. As discussed in Chapter 1, type 2 diabetes is one mainstream example where medical product manufacturers have innovated a variety of therapies in response to patient preferences for treatment in terms of dosing flexibility, dosing with or without food, and number of doses needed per week (“How Trulicity Can Help,” 2017;

Schroeder, & Dougherty, 2012). Similarly, manufacturers of medical products have innovated a variety of therapies for patients with PIDD. The gap that I observed in reviewing the literature regarding PIDD is that there has not yet been a study showing that patient treatment preferences for fewer needle sticks and shorter infusion time translated into improved HRQOL and well-being, as measured by the PROMIS-29 instrument, for patients taking medical products innovated per these preferences.

I divided this chapter into sections which cover the research design and rationale, the PIDD population studied, study design, determination of sampling size and methods for procuring a sample, and data analysis methods. Additionally, I discuss protection of human subjects, data handling, and threats to internal and external validity. The reliability and validity of the PROMIS survey instrument were discussed in Chapter 2.

### **Research Design and Rationale**

Using a cross-sectional study design, I sought to examine whether patient preferences for fewer needle sticks and shorter infusion time translated into differences in HRQOL and well-being for patients with PIDD who were using medical products innovated according to those preferences. The independent variables were needle sticks and infusion time. Based on the medical product each patient reported using at the time of data collection, I assigned patients into two categories: those who used the medical product innovated for each of the independent variables under study and those who did not (see Table 3). Thus, patients who reported using a medical product innovated to need fewer needle sticks were compared to those patients who reported using a medical product which does not entail fewer needle sticks. Likewise, patients who reported using



medical products which allow for a shorter infusion time were compared to those patients who reported using medical products which do not entail a shorter infusion time. I compared the mean PROMIS-29 scores for HRQOL (e.g., anxiety and depression) and well-being (e.g., ability to participate in social roles/activities) for each patient group.

I used PROMIS instrument measures for understanding well-being and HRQOL. The proxy measure for well-being was “Ability to Participate in Social Roles/Activities” while the proxy measures for HRQOL were “Anxiety” and “Depression”; all of these PROMIS measures were the dependent variables (Barile et al., 2013; HealthyPeople.gov, 2017). The potential confounding variables of age, gender, education level, and employment status related to HRQOL have been studied in patients with PIDD (see Seeborg et al., 2015; Tabolli et al., 2014). In this study, age, median household income, and gender were part of the secondary dataset I used and were, therefore, available for analysis.

## **Methodology**

### **Population**

The population data used for this research included all patients who had a confirmed diagnosis of PIDD and who were using IGRT. Additional inclusion criteria included patients who gave consent and completed the PROMIS-29 instrument via the USIDNET (collaboration between the NIH and the IDF) and who also had medical information on file in IDF’s patient registry. As of October 2017, the total population for inclusion consideration was 162 patients. Any patient who met the criteria for completion of the PROMIS-29 instrument was considered for the study.

## **Sampling and Sampling Procedures**

I received a written invitation from IDF to submit a query to USIDNET (see Appendix A) after I had contacted IDF regarding any QOL data they might have from patients with PIDD. The query was generated based on my response to questions from which I could select categories of information. The query template also included fields into which I could write provide additional information or make requests. My query served as the basis for establishing the study population (see Appendix B).

When selecting a sample, two of the considerations were effects size and also the alpha and beta levels. The effects size (Cohen's  $d$ ), which I obtained from the literature (see Bienvenu et al., 2016) and also from informal calculations of standard deviations of independent variables, is 0.16. This effect size is small (Cohen, 1988). Regarding alpha and beta levels, these should be selected so that the sample size is large enough to have enough power to detect a statistically significant difference and so that the null hypothesis is not falsely rejected or maintained (Banerjee, Chitnis, Jadhav, Bhawalkar, & Chaudhury, 2009). I selected an alpha of 0.05 and a beta of 0.20 to establish power equal to 80%.

I used the entire population of individuals meeting the inclusion criteria. IDF, via USIDNET, solicits additional patient participation every 6 months, in spring and fall (M. Goldsmith, personal communication, February 9, 2017). After I obtained Walden University IRB approval, I e-mailed IDF staffers and requested that they run my query again to potentially gain more participants. I also submitted a second query for patients who had not completed the PROMIS-29 survey. The purpose of this query was to draw

comparisons on attributes common between those who did and those who did not complete the PROMIS-29 survey in order to potentially generalize HRQOL and well-being results. Permission to submit a query and use resultant information is located in Appendix A.

### **Research Questions and Hypotheses**

The overarching question was whether addressing patient preferences for treatment through medical product innovation resulted in better outcomes from a psychosocial perspective, and whether any of these outcomes were also influenced by gender, median household income, or age. MacKinnon and Luecken (2008) described various types of other variables according to their relationship to the independent and/or dependent variable. The authors mentioned that mediating variables are caused by the independent variable and cause the dependent variable; and moderating variables as those which aid in understanding the circumstances for when the independent and dependent variables are related (MacKinnon & Luecken, 2008). MacKinnon and Luecken (2008) also defined a confounding variable as one which is related to both the independent and dependent variables and thus changes the relationship between the two; and covariates, which can be related to the independent and / or the dependent variable but do not change the relationship. In my study, consideration of gender, age, and median household income could explain the circumstances under which patients have a greater sense of well-being and HRQOL when using a medical product innovated according to a given patient-reported outcome. The variables might also be related to selection of medical product. Thus, gender, age, and median household income could be moderating or

confounding variables. There were two additional potential confounding variables over which I thought I might have control since data fields were available by query within the secondary data available from IDF. The first variable related to active disease present at the time the patient completed the PROMIS-29 assessment. Bienvenu et al. (2016) found that patients with active disease had lower HRQOL scores compared to those without. Thus, via the literature, active disease showed a link to my dependent variables which measure HRQOL. Results could be confounded if levels of active disease differ across my independent variable (patient preference for treatment). The second confounding variable potentially was treatment-related symptoms or adverse events associated with the route of administration (SCIG or IVIG) and influence on HRQOL (Espanol et al., 2014). Administration via the subcutaneous route tends to produce localized effects such as swelling, redness, and pain around the site(s) of needle insertion. Administration via the intravenous route tends to result in systemic effects such as fever and malaise (Kobrynski, 2012). However, both routes of administration can produce local and/or systemic effects. When I compared dependent variables for HRQOL for infusion time, results might have been confounded by treatment-related symptoms and/or adverse events because the SCIG group was directly compared to the IVIG group. The groups were not homogenous across the two routes of administration. However, in practice, patients move across the routes of administration according to their individual needs, preferences, and doctors' recommendation (Espanol, et al., 2014, Kobrynski, 2012). For those patients who moved across therapies and routes of administration, I used the medical product the patients were using at the time they took the PROMIS-29 survey.

Table 3 shows the link between patient preferences for treatment and medical product innovation that were assessed.

Table 3

*Operationalization of Variables*

Patient preference for treatment, with literature reference	Medical Product Innovation Comparison Groups <sup>a</sup>	
Fewer needle sticks	IVIG	10% SCIG
Kobrynski (2012, p. 285)	Enzyme-facilitated IG	20% SCIG
Shorter infusion time	20% SCIG	IVIG
Espanol et al., (2014, p. 622)	Enzyme-facilitated IG	
Melamed et al., (2012, p. 453)		
Ponsford et al., (2015, p. 305-307)		

<sup>a</sup>The mean for each dependent variable was compared.

### **Data Analysis Plan**

The statistical methods originally planned for addressing the research questions included two-tailed t-tests for independent samples, and possibly correlation and regression analyses (logistic regression for categorical variables, and multiple regression for quantitative variables), and ANCOVA in order to test the difference between means (see Table 3) while controlling for age, gender and median household income. The assumptions were that the data are homogenous and normally distributed; thus, these attributes could be tested using parametric statistics.

Research Question 1: Is there a difference in the well-being proxy PROMIS score for “Ability to Participate in Social Roles/Activities” between patients with PIDD who

report using medical products innovated to offer therapeutic dosing with one needle stick every 3 or 4 weeks compared to those who report using medical products innovated to offer therapeutic dosing with more than one needle stick every 3 or 4 weeks?

$H_01$ : The mean differences are not statistically significant.

$H_a1$ : The mean differences are statistically significant.

The independent variable was needle sticks, and the dependent variable was PROMIS score (Likert scale mean).

Research Question 2: Is there a difference in the HRQOL proxy PROMIS score for “Anxiety” between patients with PIDD who report using medical products innovated to offer therapeutic dosing with one needle stick every 3 or 4 weeks compared to those who report using medical products innovated to offer therapeutic dosing with more than one needle stick every 3 or 4 weeks?

$H_02$ : The mean differences are not statistically significant.

$H_a2$ : The mean differences are statistically significant.

The independent variable was needle sticks, and the dependent variable was PROMIS score (Likert scale mean).

Research Question 3: Is there a difference in the HRQOL proxy PROMIS score for “Depression” between patients with PIDD who report using medical products innovated to offer therapeutic dosing with one needle stick every 3 or 4 weeks compared to those who report using medical products innovated to offer therapeutic dosing with more than one needle stick every 3 or 4 weeks?

$H_03$ : The mean differences are not statistically significant.

$H_{a3}$ : The mean differences are statistically significant.

The independent variable was needle sticks, and the dependent variable was PROMIS score (Likert scale mean).

Research Question 4: Is there a difference in the well-being proxy PROMIS score for “Ability to Participate in Social Roles/Activities” between patients with PIDD who report using medical products innovated for shorter infusion time compared to those who report using medical products not innovated for shorter infusion time?

Interpretation: Because infusion time depends on patient tolerance irrespective of product innovation, for this study shorter infusion time was defined as less than or equal to 4 hours and longer infusion time was defined as greater than 4 hours (Ponsford et al., 2015).

$H_{04}$ : The mean differences are not statistically significant.

$H_{a4}$ : The mean differences are statistically significant.

The independent variable was infusion time duration, and the dependent variable was PROMIS score (Likert scale mean).

Research Question 5: Is there a difference in the HRQOL proxy PROMIS score for “Anxiety” between patients with PIDD who report using medical products innovated for shorter infusion time compared to those who report using medical products not innovated for shorter infusion time?

Interpretation: Because infusion time depends on patient tolerance irrespective of product innovation, for this study shorter infusion time was defined as less than or equal

to 4 hours and longer infusion time was defined as greater than 4 hours (Ponsford, et al., 2015).

$H_{05}$ : The mean differences are not statistically significant.

$H_{a5}$ : The mean differences are statistically significant.

The independent variable was infusion time duration, and the dependent variable was PROMIS score (Likert scale mean).

Research Question 6: Is there a difference in the HRQOL proxy PROMIS score for “Depression” between patients with PIDD who report using medical products innovated for shorter infusion time compared to those who report using medical products not innovated for shorter infusion time?

Interpretation: Because infusion time depends on patient tolerance irrespective of product innovation, for this study shorter infusion time was defined as less than or equal to 4 hours and longer infusion time was defined as greater than 4 hours (Ponsford, et al., 2015).

$H_{06}$ : The mean differences are not statistically significant.

$H_{a6}$ : The mean differences are statistically significant.

The independent variable was infusion time duration, and dependent variable was PROMIS score (Likert scale mean).



Table 4

*List of Variables*

Variable	Description	Variable Type	Code
<b>Independent</b>			
Needle sticks	Medical product promotional or label claim for the number of injection sites per dosing frequency	Categorical	0 = 1 needle stick per 3-4 weeks 1 = 2 or more needle sticks per 3-4 weeks
Infusion Duration	Medical product promotional or label claim for time per infusion	Categorical	0 = infusion time less than or equal to 4 hours 1 = infusion time greater than 4 hours
<b>Dependent</b>			
PROMIS-29: Anxiety	A domain in the PROMIS-29 validated instrument in this study used as a proxy for HRQOL	Continuous	XX
PROMIS-29: Depression	A domain in the PROMIS-29 validated instrument in this study used as a proxy for HRQOL	Continuous	XX
PROMIS-29: Ability to participate in social roles/ activities	A domain in the PROMIS-29 validated instrument in this study used as a proxy for well-being	Continuous	XX
<b>Moderating</b>			
Age	Patient reported age in years	Continuous	XX
Gender	Patient reported gender	Dichotomous	0 = male 1 = female
Median household income	Median income in US dollars for the zip code reported by the patient	Continuous	XX

### **Instrumentation**

PROMIS-29 is a general instrument intended for persons aged 18 years and older. The instrument asks four questions from each of seven domains (ability to participate in social roles and activities, anxiety, depression, fatigue, pain interference, physical function, sleep disturbance) and one question on a pain intensity scale. Except for physical function, the domains have a time element and ask for a response based on the past seven days. For each question within a domain, the participant can select a value from 1-4. Thus, the lowest score in any singular domain is 4, and the highest score is 20 from the responses, and based on a t-score (PROMIS, 2011).

For the variable anxiety, and depression, (negatively worded), a lower t-score is better than average. For the variable ability to participate in social roles: (positively worded) a lower t-score is worse than average. The average t-score is based on the U.S. population and is normalized to 50.0 (PROMIS, 2011).

### **Data Handling**

After I received IRB approval from Walden University on 28 September 2017 (approval number 09-28-17-0389089), I submitted a query for preexisting data from USIDNET through IDF. This query netted PROMIS-29 patient data from 2015 through May, 2017, and general patient registry data from April, 2008 through July, 2017. IDF provided the query results in an email containing two Excel spreadsheets. The data were downloaded onto a personal laptop, coded, and entered into SPSS. Data files were stored on a personal password protected One Share cloud drive, and the original email was stored in Outlook.

### **Protection of Human Subjects**

Data obtained for this study were obtained from USIDNET already de-identified.

### **Dissemination of Findings**

Study findings will be presented to Walden University to support partial fulfillment of academic requirement for a doctorate in public health. Although not requested, findings might be disseminated to IDF and their patient, caregiver, and advocate membership. The results of this study could be presented for publication in peer-reviewed journals such as Journal of Clinical Immunology, BMC Public Health, or Health Affairs.

### **Threats to Internal Validity**

Threats to internal validity include the following biases which could have been present in the populations I studied (namely, patients with PIDD who are listed in the IDF patient registry and completed the PROMIS-29 survey, and who did not complete the PROMIS-29 survey): (a) recall bias; (b) survey response bias (e.g. a tendency for a more positive or more negative response to survey questions or questions about health; (c) selection – history bias where patients using a given medical product might differ from one another; and (d) selection – maturation where patients who previously took the survey (which IDF solicits for completion twice annually) differ from those who have not previously taken the PROMIS-29 survey, or patients who have used multiple types of IGRT medical products versus those who have not (Blome & Augustine, 2015; Frankfort-Nachmias & Nachmias, 2008). In the analysis phase, upon receiving IRB approval, I looked to identify factors which compromise internal validity.

### **Threats to External Validity (Generalizability)**

The population of patients with PIDD could not be randomized. Thus, patients consenting to take the PROMIS-29 instrument might not represent patients in IDF's registry who did not take the PROMIS-29 survey. Likewise, patients with PIDD in IDF's registry, of whom my population was a subset of this broader population, might not represent the entire population of patients with PIDD globally. Ultimately, the goal was to generalize across all patients with PIDD. Upon data analysis, I looked to identify possible threats to external validity by comparing my dataset of individuals in IDF's patient registry who completed the PROMIS-29 survey with those in the same registry who did not.

### **Summary**

In this chapter, I presented the methods for understanding potential relationships between patient preferences for treatment (desire for fewer needle sticks, and a shorter infusion time) serving as the basis of manufacturers' innovations in medical products subsequently approved by the FDA and patients' well-being (ability to participate in social roles) and HRQOL (anxiety and depression) were presented. A query of all USIDNET patient registry participants who gave consent to complete a PROMIS-29 survey netted a non-randomized population of 162 participants in the three available study years 2015-2017. A query of the same patient registry from 2008 – 2017 netted a non-randomized population of 1,939 participants available for comparison. In the following chapter, statistical methods used to analyze data, and the results and meaning of the data are presented. Additionally, I describe changes made to how the number of

needle sticks was optimized upon examining the data, and how patients were categorized into medical product innovation category.

## Chapter 4: Results

### Introduction

The purpose of this dissertation was to compare the mean differences in HRQOL and well-being as measured by PROMIS-29 for patients with PIDD who used medical product manufacturers' innovative medical products designed to have (a) fewer needle sticks and (b) shorter infusion time to patients who did not use such products. I used a secondary dataset from IDF to address the research questions. The six formulated research questions had the following structure:

Needle Sticks: Is there a difference in X between patients with PIDD who report using medical products innovated to offer therapeutic dosing with fewer needle sticks every 3 or 4 weeks compared to those who report using medical products innovated to offer therapeutic dosing with more needle sticks every 3 or 4 weeks?

Where X is (a) the well-being proxy PROMIS-29 score for "Ability to Participate in Social Roles/ Activities," (b) the HRQOL proxy PROMIS-29 score for "Anxiety," or (c) the HRQOL proxy PROMIS-29 score for "Depression." Additionally, I defined fewer needle sticks per 3 or 4 weeks as 1-8. This marks a change from my definition, given in Chapters 1 and 3, of fewer needle sticks as 1 needle stick. This change in definition from 1 needle stick to fewer needle sticks accounts for patient choice to deliver less volume to a single infusion site (single needle stick) by using up to four needles to infuse simultaneously into four sites per infusion session, as allowed by the instructions on the medical product. Thus, a patient infusing once per 14 days, and infusing into the

maximum of four sites (hence four needles) would encounter eight needle sticks in 3 or 4 weeks. I defined more needle sticks per 3 or 4 weeks as greater than 8 needles.

Infusion Time: Is there a difference in  $X$  between patients with PIDD who report using medical products innovated for shorter infusion time compared to those who report using medical products not innovated for shorter infusion time?

Where  $X$  is (a) the well-being proxy PROMIS-29 score for “Ability to Participate in Social Roles/ Activities,” (b) the HRQOL proxy PROMIS-29 score for “Anxiety,” or (c) the HRQOL proxy PROMIS-29 score for “Depression.” Additionally, shorter infusion time was defined as 1-4 hours, and longer infusion time was defined as greater than 4 hours.

The null and alternate hypotheses for each question, as well as the independent and dependent variables were as follows:

$H_0$ : The mean differences were not statistically significant.

$H_a$ : The mean differences were statistically significant.

Independent variables: needle sticks, infusion time.

Dependent variable: PROMIS score (Likert scale mean).

Data analysis occurred October 12-November 18, 2017 after receipt of Walden IRB approval on September 28, 2017 (approval number 09-28-17-0389089) and upon receipt of datasets from IDF on October 12, 2017. IDF had already granted approval on October 20, 2016 (see Appendix A) and cosigned a revised Data Use Agreement with me on October 13, 2017.

In this chapter, I will address how I prepared the dataset for analysis. I will also present my results. At the end of the chapter, I will include a summary of key points.

### **Data Collection**

On September 28, 2017, I sent an e-mail to IDF requesting a refresh to the dataset corresponding to my original query to USIDNET (see Appendix B) in order to have PROMIS-29 data inclusive of the Spring 2017 issuance of the survey. Additionally, I submitted a second query to USIDNET to obtain a dataset of individuals over the age of 18 years who had not completed a PROMIS-29 survey. This second query was additional to the plan I outlined in Chapter 3. I submitted the second query for the purpose of noting similarities and differences (see Tables 5 and 6) between individuals in the patient registry who had completed a PROMIS-29 survey and those who had not.

### **Inclusion/Exclusion Criteria**

The dataset of individuals who had completed a PROMIS-29 survey through Spring 2017 included 162 subjects. Two of the 162 subjects received therapy via the intramuscular route instead of by either the subcutaneous or the intravenous route of administration. Although I included the two subjects in the data comparison with those individuals who did not complete a PROMIS-29 survey, I excluded these individuals from the data analysis supporting my research questions. Seven of the 162 subjects who completed a PROMIS-29 survey reported they were not using any immunoglobulin medical products. I considered that these seven individuals could be comparison controls for the PROMIS-29 dependent variables; however, there were too few individuals for inclusion to be a viable option. Although I excluded these seven individuals from the



research question data analysis, I included them in the comparison with individuals who did not complete a PROMIS-29 survey. The total number of subjects included in the analysis of my research questions was 153, representing 162 subjects minus nine excluded subjects.

The dataset of individuals who had not completed a PROMIS-29 survey included 1,939 subjects. The age range included 62 individuals who were 17 years old, and all others were aged 18 and older. The individuals who took the PROMIS-29 survey were aged 18 years and older. Therefore, the 62 individuals who were 17 years of age were excluded, leaving a total of 1,877 subjects aged 18 years and older in the analysis.

### **Adding Context to the Medical Product Innovation Categorical Values**

I originally planned to use medical product labeling to determine fewer versus more needle sticks. As such, I determined that one needle stick every 3 or 4 weeks could suffice as the operationalization of the concept term “fewer.” However, as I analyzed the dataset, I noted that some patients indicated the interval of days in which they infused a medical product. Therefore, a patient infusing a product at the allowed rate of once every 14 days, and using up to four injection sites allowed on the medical product labeling, would infuse using eight needles per month. A patient who infused the same medication daily as allowed by the medical product labeling would use 30 or more needles per month. The dataset revealed that patients who reported an infusion interval reported intervals of 1, 3, 4, 7, 14, 21, 25, 28, 30, or 42 days. Thus, when an individual provided interval of infusion, I categorized him or her according to this information along with medical product labeling information. In order to align the specific statement of one

needle stick in my research question with my dataset, I had to increase the number of needlesticks representing “fewer” to eight needle sticks. Thus, I defined more needle sticks as more than eight.

### **Demographics**

As mentioned in Chapter 3, for the purpose of my dissertation research, my dataset consisted of the entire population of individuals who had taken the PROMIS-29 survey. However, this population of PROMIS-29 survey takers is a subset of all patients in IDF’s patient registry. In order to support generalizability to the entire registry, I assessed available data which were common to all individuals in the patient registry in order to compare those who took the PROMIS-29 survey and those who did not. Table 5 shows demographics of individuals in the patient registry segmented into whether or not they had taken the PROMIS-29 survey.

Table 5

*Comparison Demographics of Individuals Who Took the PROMIS-29 Survey and Those Who Did Not Take the PROMIS-29 Survey*

	PROMIS-29 N (%)	Non PROMIS-29 N (%)
Gender	162 (100%)	1877 (100%)
Male	33 (20.4)	814 (43.4%)
Female	129 (79.6)	1063 (56.6%)
Race	162 (100%)	1397 (100%)
Asian	1 (0.6%)	22 (1.6%)
Black	0 (0)	67 (4.8%)
Native American	0 (0)	6 (0.4%)
White	161 (99.4%)	1195 (85.5%)
Hispanic Latin	0 (0)	53 (3.8%)
Other/ Mixed	0 (0)	54 (3.9%)
Administration	162 (100%)	1415 (100%)
IM	2 (1.2%)	3 (0.2%)
IV	76 (46.9%)	744 (52.6%)
SC	77 (47.5%)	308 (21.8%)
None	7 (4.3%)	360 (25.4%)
Disability	31 (100%)	697 (100%)
None	20 (64.5%)	400 (57.4%)
Partial	7 (22.6%)	250 (35.9%)
Full	4 (12.9%)	47 (6.7%)

**Gender and Race.** The majority of the individuals in both groups were White females. However, the population of individuals who took the PROMIS-29 survey was less balanced in terms of gender (79.6% female/ 20.4% male) compared with those in the registry who had not taken the PROMIS-29 survey (56.6% female/ 43.4% male). The same applied to race, where nearly all of the individuals who took the PROMIS-29 survey were White (99.4%), compared with those who did not take the PROMIS-29 survey (85.5%). I conducted a chi-square test of independence to determine whether

gender and race were equally distributed among the PROMIS-29 and non-PROMIS-29 individuals in the patient registry.

A chi-square test of independence was conducted between gender and PROMIS-29 survey status. All expected cell counts were greater than five. There was a statistically significant association, and the null hypothesis that there was no association between gender and whether or not individuals had taken the PROMIS-29 survey was rejected. Thus,  $\chi^2(1) = 32.476, p < .005$ . The association was small, *Cramer's V* = .126 (Cohen, 1988). Gender was not equally distributed between the two populations.

A chi-square test of independence was conducted between race and PROMIS-29 survey status. Two cells (16.7%), Asian and Native American for those who had taken the PROMIS-29 survey, had expected counts less than five. According to Yates, Moore, and McCabe (1999) if the number of cells with expected counts less than five is not more than 20% and if no single cell has an expected count less than one, the chi-square statistic might still be considered valid. There was a statistically significant association, and the null hypothesis that there was no association between race and whether or not individuals had taken the PROMIS-29 survey was rejected. Thus,  $\chi^2(5) = 24.973, p < .005$ . The association was small, *Cramer's V* = .127 (Cohen, 1988). I determined to perform the chi-square test again after collapsing the number of race categories by combining Asian, Black, and Native American into a single category. This time, all expected cell counts were greater than five. Both sets of chi-square results were similar. Again, there was a statistically significant association between race and PROMIS-29 survey status,  $\chi^2(3) =$

24.618,  $p < .005$ . The association was small, *Cramer's V* = .126. Race was not equally distributed between the two populations.

**Route.** Of the individuals reporting whether they received their IGRT regimen by IM, IV, SC, or None (i.e. they were not receiving IGRT medication), the population of PROMIS-29 survey takers were split roughly 50:50 between the IV and SC routes. Whereas, those who had not taken the PROMIS-29 survey were split between the majority using IV, followed by those who were not receiving IGRT, and lastly by the SC route. Notably, while all individuals who had taken the PROMIS-29 survey reported, the 524 missing values for those who had not taken the PROMIS-29 survey might have skewed the results.

A chi-square test of independence was conducted between PROMIS-29 survey status and route of administration. Two cells (25.0%), the IM route of therapy administration, had expected counts less than five. According to Yates, Moore, and McCabe (1999) if the number of cells with expected counts less than five is not more than 20% and if no single cell has an expected count less than one, the chi-square statistic might still be considered valid. Because my results did not meet this requirement, I used the two-tailed Fisher's Exact test to determine whether there was a statistically significant difference between those who had taken the PROMIS-29 survey and those who had not taken the PROMIS-29 survey as regards route of therapy administration. The results indicated that there was a statistically significant difference between the PROMIS-29 survey takers and the other individuals in the patient registry as regards route of therapy. The null hypothesis is that there was no difference. The results indicated there was a

significant association and the null hypothesis was rejected ( $p = <.001$ ,  $df = 3$ , Fisher's Exact Test = 76.464).

**Disability.** More than half of individuals in both groups reported having no disability (e.g. normal activity, and a range of none to some evidence of disease); followed by partial disability (e.g. ranging from ability to care for self but inability to carry out normal activities to requiring extensive care, and frequent medical care); and the fewest reported full disability (e.g. very ill, specialized care, and hospitalization). Though the percentages of the range of disability varied across those who took the PROMIS-29 survey versus those who did not, the results of a two-tailed Fisher's Exact Test failed to reject the null hypothesis that there is no difference between two sets of individuals in terms of disability ( $p = .166$ ,  $df = 2$ , Fisher's Exact Test = 3.562).

Individuals who completed a PROMIS-29 survey were also compared to those who did not in terms of chronological age and age at PIDD symptom onset, age at diagnosis, age at initiation of IGRT, and IGRT infusion interval. These comparisons are presented in Table 6.

Table 6

*Comparison Characteristics of Individuals Who Took the PROMIS-29 Survey and Those Who Did Not Take the PROMIS-29 Survey*

	PROMIS-29	Non PROMIS-29
Age (years)		
N	162	1877
Mean	53	39
Median	56	35
Mode	58	19
Min	18	18
Max	82	95
Age at PIDD symptom onset (years)		
N	43	1008
Mean	25	16
Median	24	10
Mode	0	0
Min	0	0
Max	58	77
Age at PIDD diagnosis		
N	100	1261
Mean	43	25
Median	46	19
Mode	51	2
Min	1	0
Max	78	82
IG Starting Age (years)		
N	71	678
Mean	45	29
Median	48	26
Mode	32	14
Min	15	0
Max	69	81
IG Infusion Interval (days)		
N	133	985
Mean	17	21
Median	14	28
Mode	7	28
Min	1	1
Max	42	90

Results shown in Table 6 reveal the mean age of individuals who completed the PROMIS-29 survey was 14 years older than those in the patient registry who did not. A Mann-Whitney U test was run to determine if there were differences in age between those who took the PROMIS-29 survey and those who did not. Distributions of age values were considered by visual inspection and were not similar. Age values for those who took the PROMIS-29 survey (mean rank = 196.03) were statistically significantly higher than for those who did not take the PROMIS-29 survey (mean rank = 132.66),  $U = 5,416.000$ ,  $z = 4.080$ ,  $p = <.001$ . Additionally, those who took the PROMIS-29 survey were on average nine years older when symptoms appeared. A Mann-Whitney U test was run to determine if there were differences in PIDD symptom onset between those who took the PROMIS-29 survey and those who did not. Distributions of PIDD symptom onset age values were considered by visual inspection and were not similar. PIDD symptom onset age values for those who took the PROMIS-29 survey (mean rank = 179.17) were statistically significantly higher than for those who did not take the PROMIS-29 survey (mean rank = 134.70),  $U = 4,910.000$ ,  $z = 2.862$ ,  $p = .004$ .

As a result of older age at symptom onset, on average, those who took the PROMIS-29 survey also were 18 years older when diagnosed and 16 years older when they started IGRT. A Mann-Whitney U test was run to determine if there were differences in age at PIDD diagnosis between those who took the PROMIS-29 survey and those who did not. Distributions of age at PIDD diagnosis were considered by visual inspection and were not similar. Age at PIDD diagnosis values for those who took the PROMIS-29 survey (mean rank = 206.20) were statistically significantly higher than for those who did not take the



PROMIS-29 survey (mean rank = 131.43),  $U = 5,721.000$ ,  $z = 4.811$ ,  $p < .001$ . Likewise, a Mann-Whitney U test was run to determine if there were differences in age at the start of IGRT between those who took the PROMIS-29 survey and those who did not.

Distributions of age at the start of IGRT were considered by visual inspection and were not similar. Age at the start of IGRT for those who took the PROMIS-29 survey (mean rank = 196.13) was statistically significantly higher than for those who did not take the PROMIS-29 survey (mean rank = 132.65),  $U = 5,419.000$ ,  $z = 4.085$ ,  $p < .001$ .

The mean delay in diagnosis (I defined this as the difference between the mean age at symptom onset and the mean age at diagnosis) was twice as long for those who took the PROMIS-29 survey (18 years) compared with those who did not take the PROMIS-29 survey (nine years). Lastly, the mode for infusion interval was 7 days for those who took the PROMIS-29 survey (suggesting a greater proportion of individuals who use the SCIG route of administration), versus 28 days for those who did not take PROMIS-29 (suggesting a greater proportion of individuals who use the IVIG route of administration). Aligned with Table 5, comparing across the two groups, these data support that a greater proportion of individuals who took the PROMIS-29 survey were using the SCIG route of administration (i.e. generally more frequent administration ranging from daily, to every few days, weekly, or every 14 days) and a greater proportion of individuals who did not take the PROMIS-29 survey were using the IVIG route of administration (i.e. generally monthly administration). A Mann-Whitney U test was run to determine if there were differences in interval of days of IGRT infusion between those who took the PROMIS-29 survey and those who did not. Distributions of IGRT infusion

days interval were considered by visual inspection and were not similar. The IGRT infusion days interval for those who took the PROMIS-29 survey (mean rank = 96.97) was statistically significantly shorter than for those who did not take the PROMIS-29 survey (mean rank = 144.65),  $U = 2,444.000$ ,  $z = -3.169$ ,  $p = .002$ .

### **Analysis of Research Questions**

In Chapter 3 I outlined a plan for using two-tailed independent t-tests to address my research questions. Additionally, I planned to use ANCOVA to analyze age, and median annual income as covariates. During the course of analysis, I found my data did not always meet some of the requirements regarding outliers, normality, and homogeneity of variances, even when I did a log10 or a square root transformation. Therefore, for each question I describe when assumptions were not met and the alternative methods applied.

Additionally, as I mentioned in Chapter 3, PROMIS-29 scores are written as a t-score where the average, based on the U.S. population, is 50.0. Each individual score was presented as an average t-score with a  $\pm$  standard error. In order to simplify the analyses, I used the PROMIS-29 scoring manual to convert the t-scores back to the Likert raw scores (PROMIS, 2015).

**Hypothesis 1 – Needle Sticks and Well-being (Ability).** The null hypothesis for research question 1 was that there would be no difference in mean PROMIS-29 “Ability to Participate in Social Roles/ Activities” scores for patients with PIDD who used medical products innovated for fewer needle sticks versus those who used medical products which were not innovated for fewer needle sticks.

A total of 92 individuals were categorized as having fewer needle sticks, and 51 individuals were categorized as having more needle sticks. I ran a two-tailed independent t-test to determine if there were mean differences in ability to participate in social roles/activities in those taking the innovative medical products compared to those who were not. There were outliers (see Figure 2) in the data, as assessed by inspection of a boxplot. Therefore, a Mann-Whitney U test was also conducted.

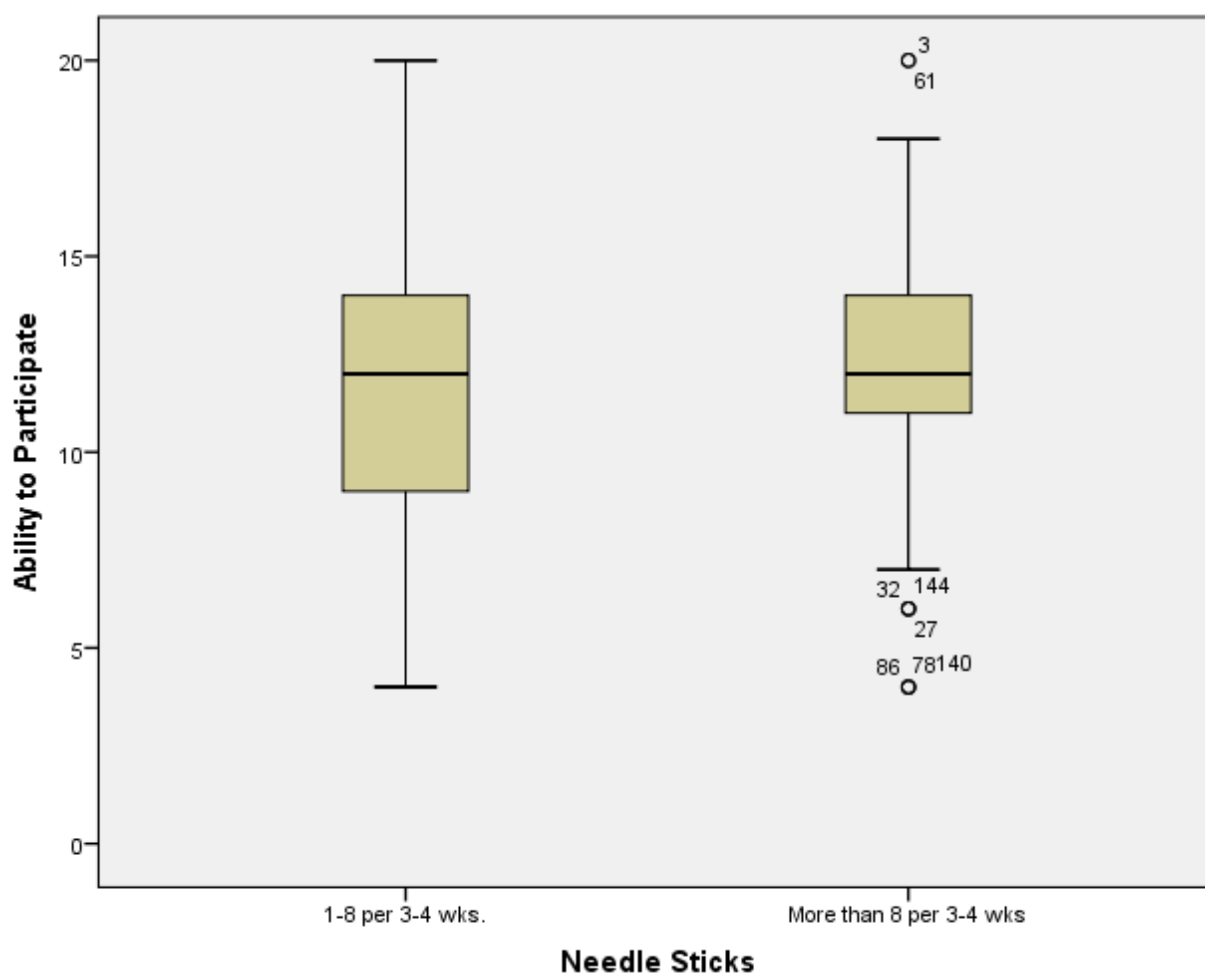


Figure 2. Boxplot of well-being (ability to participate in social roles/activities) and needle sticks.

PROMIS-29 scores were normally distributed as determined by skewness and kurtosis (.009 and -.498, respectively for fewer needle sticks; and -.320 and .285, respectively for more needle sticks) values between  $\pm 1$ , and by inspection of a histogram and Q-Q plot. There was homogeneity of variances as assessed by Levene's test for equality of variances ( $p = .197$ ).

A two-tailed independent t-test revealed individuals using medical products innovated for fewer needle sticks ( $M = 11.79$ ,  $SD = 3.946$ ) did not have statistically significant different levels of well-being/ ability to participate in social roles/ activities compared to individuals using medical products which were not innovated for fewer needle sticks ( $M = 12.08$ ,  $SD = 3.725$ ),  $M = -.285$ , 95% CI [-1.620, 1.050],  $t(141) = -.422$ ,  $p = .674$ .

Additionally, a Mann-Whitney U test revealed median PROMIS-29 scores for "Ability to Participate in Social Roles/ Activities" did not differ significantly for patients with PIDD who used medical products innovated for fewer needle sticks (Median = 12.00) compared to those who did not (Median = 12.00),  $U = 2782.000$ ,  $z = 0.252$ ,  $p = .801$ .

**Hypothesis 2 – Needle Sticks and HRQOL (Anxiety).** The null hypothesis for research question 2 was that there would be no difference in mean PROMIS-29 "Anxiety" scores for patients with PIDD who used medical products innovated for fewer needle sticks compared to those who used medical products which were not innovated for fewer needle sticks.

A total of 92 individuals were categorized as having fewer needle sticks, and 51 individuals were categorized as having more needle sticks. An independent t-test was run to determine if there were mean differences in anxiety in those taking the innovative medical products compared to those who were not. There were no outliers in the data, as assessed by inspection of a boxplot.

PROMIS-29 scores were fairly normally distributed as assessed by skewness and kurtosis values (-.070 and -1.160, respectively for fewer needle sticks, and .396 and -.412, respectively for more needle sticks) between  $\pm 1$ , and inspection of a histogram and a Q-Q plot. There was homogeneity of variance as assessed by Levene's test for equality of variances ( $p = .095$ ). Individuals using medical products innovated for fewer needle sticks ( $M = 9.50$ ,  $SD = 3.421$ ) did not have statistically significant different levels of anxiety, HRQOL/ anxiety than individuals using medical products not innovated for fewer needle sticks ( $M = 8.73$ ,  $SD = 3.020$ ),  $M = .775$ , 95% CI [-.359, 1.908],  $t(141) = 1.351$ ,  $p = .179$ .

Additionally, according to the Mann-Whitney U test, median PROMIS-29 scores for Anxiety did not differ significantly for patients with PIDD who used medical products innovated for fewer needle sticks (Median = 10.00) compared to those who did not (Median = 8.00),  $U = 2420.500$ ,  $z = -1.125$ ,  $p = .260$ .

**Hypothesis 3 – Needle Sticks and HRQOL (Depression).** The null hypothesis for research question 3 was that there would be no difference in mean PROMIS-29 “Depression” scores for patients with PIDD who used medical products innovated for fewer needle sticks versus those who used medical products which were not innovated

for fewer needle sticks.

A total of 92 individuals were categorized as having fewer needle sticks, and 51 individuals were categorized as having more needle sticks. I ran an independent t-test to determine if there were mean differences in depression in those taking innovative medical products compared to those who were not. There were no outliers in the data, as assessed by inspection of a boxplot. PROMIS-29 scores were fairly normally distributed as determined by skewness and kurtosis values (.456 and -.523, respectively for fewer needle sticks, and .365 and -1.019, respectively for more needle sticks) between  $\pm 1$ , and inspection of histograms and Q-Q plots. There was homogeneity of variances as assessed by Levene's test for equality of variances ( $p = .084$ ). Individuals using medical products innovated for fewer needle sticks ( $M = 8.86$ ,  $SD = 3.839$ ) did not have statistically significant different levels of HRQOL/ depression than individuals using medical products not innovated for fewer needle sticks ( $M = 8.00$ ,  $SD = 3.225$ ),  $M = .859$ , 95% CI [-.395, 2.113],  $t(141) = 1.354$ ,  $p = .178$ .

Additionally, a Mann-Whitney U test revealed median PROMIS-29 scores for Depression did not differ for patients with PIDD who used medical products innovated for fewer needle sticks (Median = 9.00) compared to those who did not (Median = 8.00),  $U = 2,471.000$ ,  $z = -.933$ ,  $p = .351$ .

**Hypothesis 4 – Infusion Time and Well-being (Ability).** The null hypothesis for research question 4 was that there would be no difference in mean PROMIS-29 “Ability to Participate in Social Roles/ Activities” scores for patients with PIDD who used medical products innovated for shorter infusion time versus those who used medical

products which were not innovated for shorter infusion time. A total of 71 individuals were categorized into having shorter infusion times, and 72 individuals were categorized into having longer infusion times. A Welch t-test was run to determine if there were differences in ability to participate in social roles between shorter infusion times and longer infusion times due to the assumption of homogeneity of variance being violated, as assessed by Levene's test for equality of variances ( $p = .027$ ). Additionally, visual inspection of a boxplot of the data revealed outliers. Data were normally distributed based on skewness and kurtosis values (-.541 and .514, respectively for shorter infusion time, and .251 and -.547, respectively for longer infusion time) between  $\pm 1$ , and inspection of histograms and Q-Q plots. There was no difference in the mean PROMIS-29 scores for individuals using medical products innovated for shorter infusion times ( $M = 12.34$ ,  $SD = 3.497$ ) and those innovated for longer infusion times ( $M = 11.46$ ,  $SD = 4.162$ ). Well-being for both groups was not statistically significantly different  $M = .880$ , 95%  $CI [-.391, 2.150]$ ,  $t(137.542) = 1.369$ ,  $p = .173$ .

The test for homogeneity of variance did not meet the assumption required for performing an independent t-test. Therefore, a Mann-Whitney U test was also conducted. Median PROMIS-29 scores for Ability to participate in social roles/ activities did not differ significantly for patients with PIDD who used medical products innovated for shorter infusion times (Median = 12.00) compared to those who did not (Median = 12.00),  $U = 2,486.000$ ,  $z = -1.619$ ,  $p = .105$ .

**Hypothesis 5 – Infusion Time and HRQOL (Anxiety).** The null hypothesis for research question 5 was that there would be no difference in mean PROMIS-29

“Anxiety” scores for patients with PIDD who used medical products innovated for shorter infusion time versus those who used medical products which were not innovated for shorter infusion time.

A total of 71 individuals were categorized into having shorter infusion times, and 72 individuals were categorized into having longer infusion times. A Welch t-test was run to determine if there were differences in anxiety between shorter infusion times and longer infusion times due to the assumption of homogeneity of variances being violated, as assessed by Levene’s test for quality of variances ( $p = .005$ ). There were no outliers. Data were fairly normally distributed based on skewness and kurtosis values (.227 and -.637, respectively for shorter infusion times, and -.062 and -1.272, respectively for longer infusion times). There was no difference in the mean PROMIS-29 scores for individuals using medical products innovated for shorter infusion times ( $M = 8.93$ ,  $SD = 2.885$ ) and those innovated for longer infusion times ( $M = 9.51$ ,  $SD = 3.650$ ), HRQOL/ Anxiety for both groups was not statistically significantly different  $M = -.584$ , 95% CI [-1.672, .503],  $t(134.644) = -1.063$ ,  $p = .290$ .

The non-parametric Mann-Whitney U test revealed similarly. Median PROMIS-29 scores for Anxiety did not differ significantly for patients with PIDD who used medical products innovated for shorter infusion time (Median = 9.00) compared to those who did not (Median = 10.00),  $U = 3,175.000$ ,  $z = -.914$ ,  $p = .361$ .

**Hypothesis 6 – Infusion Time and HRQOL (Depression).** The null hypothesis for research question 6 was that there would be no difference in mean PROMIS-29 “Depression” scores for patients with PIDD who used medical products innovated for



shorter infusion time versus those who used medical products which were not innovated for shorter infusion time.

A total of 71 individuals were categorized into having shorter infusion times, and 72 individuals were categorized into having longer infusion times. A Welch t-test was run to determine if there were differences in HRQOL /depression between shorter infusion times and longer infusion times due to the assumption of homogeneity of variances being violated, as assessed by Levene's test for quality of variances ( $p = .001$ ). There were no outliers, and the data were relatively normally distributed as determined by assessing skewness and kurtosis values (.236 and -1.009, respectively and .430 and -.775, respectively) between  $\pm 1$ , and histograms and Q-Q plots. There was no difference in the mean PROMIS-29 scores for individuals using medical products innovated for shorter infusion times ( $M = 8.14$ ,  $SD = 3.030$ ) and those innovated for longer infusion times ( $M = 8.96$ ,  $SD = 4.143$ ), HRQOL/ Depression for both groups was not statistically significantly different  $M = -.817$ , 95%  $CI [-2.017, .382]$ ,  $t(130.082) = -1.348$ ,  $p = .180$ .

According to the non-parametric Mann-Whitney U test, depression did not differ for patients with PIDD who used medical products innovated for shorter infusion time (Median = 8.00) than for those who did not (Median = 8.00),  $U = 3,119.000$ ,  $z = .708$ ,  $p = .479$ .

**Covariates Assessment.** I conducted an Analysis of Covariance (ANCOVA) to evaluate adjustments to the mean differences of the PROMIS-29 measures across each level of medical product innovation by treating age and median annual income as covariates. Inspection of a scatter plot revealed a linear relationship between the

PROMIS-29 measures and medical product innovation category for needle sticks and for infusion time. There was homogeneity of regression slopes as evidenced by non-statistically significant results. A Shapiro-Wilks test showed that some levels of the independent variable (e. g. fewer/ more needle sticks, and shorter/ longer infusion time) were non-significant while some were significant. There was homoscedasticity as evidenced through visual inspection of a scatterplot. The assumption of homogeneity of variance, as measured by Levene's test was not met. There were no instances of standardized residuals greater than  $\pm 3$  standard deviations. After adjusting for age and for median annual household income, there still was no statistical difference in the mean PROMIS-29 scores for individuals using medical products innovated for fewer needle sticks or shorter infusion time, and those who were not.

**PROMIS-29 Scores and Switching Therapy.** The dataset of individuals who had completed the PROMIS-29 survey included those who had reported, including dates, one or more changes of medical products. I ran a two-way independent t-test to determine whether there was a significant difference in mean PROMIS-29 scores for individuals who reported changing medical products ( $n = 24$ ) and those who had not ( $n = 129$ ). Inspection of boxplots showed the data had no outliers. Data were fairly normally distributed as evidenced by inspection of Q-Q plots and observation that skewness and kurtosis values were between  $\pm 1$  for each level of independent variable (with the exception of the anxiety PROMIS-29 measure for those who changed medical products: skewness =  $-0.074$ , kurtosis =  $-1.305$ ). Since those who changed medical products numbered less than 50 individuals, I also examined the Shapiro-Wilk test of normality

results. The Shapiro-Wilk results were not significant ( $p = .314$  for ability to participate;  $p = .100$  for anxiety; and  $p = .263$  for depression). Levene's tests for homogeneity of variance revealed the assumption of homogeneity was met for the PROMIS-29 HRQOL measures, anxiety ( $p = .875$ ) and depression ( $p = .327$ ).

The difference in mean PROMIS-29 HRQOL anxiety scores for individuals who changed medical product ( $M = 9.92$ ,  $SD = 3.269$ ) and those who did not change medical product ( $M = 9.19$ ,  $SD = 3.319$ ) was not statistically significant,  $M = -.723$ , 95% CI [-2.177, .732],  $t(151) = -.982$ ,  $p = .328$ .

The difference in mean PROMIS-29 HRQOL depression scores for individuals who changed medical product ( $M = 9.13$ ,  $SD = 3.379$ ) and those who did not change medical product ( $M = 8.53$ ,  $SD = 3.657$ ) was not statistically significant,  $M = .989$ , 95% CI [-2.178, .998],  $t(151) = -.734$ ,  $p = .464$ .

For the PROMIS-29 well-being variable, ability to participate in social roles/activities, the assumption of homogeneity of variances was violated as evidenced by Levene's test for equality of variances ( $p = .037$ ). Therefore, a Welch t-test was run. The difference in mean PROMIS-29 well-being scores for individuals who changed medical product ( $M = 11.04$ ,  $SD = 4.486$ ) and those who did not change medical product ( $M = 12.03$ ,  $SD = 3.618$ ) was not statistically significant,  $M = .989$ , 95% CI [-.994, 2.973],  $t(28.828) = 1.020$ ,  $p = .316$ .

#### ***Individuals who switched products and took multiple PROMIS-29 surveys***

The PROMIS-29 survey is offered approximately every six months, and three individuals who completed a survey at more than one-time point and also reported

changing medical products from one which had been on the market prior to 2010 to a medical product which has been approved between 2010 and present. Table 7 provides a summary of the data. The maximum raw score in each domain (i.e. ability, anxiety, and depression) is 20, and the minimum is four. For each domain, a higher score means the individual reported feeling more of that domain. Results show that each individual reported increased well-being, as measured by the PROMIS-29 ability to participate in social roles/ activities from their first to their second survey time point. Levels of HRQOL related to the PROMIS-29 domain for anxiety remained unchanged for Person ID 931 and Person ID 2685; and anxiety decreased for Person ID 8121 from their first to their second survey time point. Levels of HRQOL related to the domain for depression revealed Person ID 931 unchanged. However, Person ID 2685 and Person ID 8121 reported a decrease in depression from their first to their second time taking the PROMIS-29 survey. Overall gains in HRQOL and well-being totaled +1 point for Person ID 931, +6 points for Person ID 2685, and +15 points for Person ID 8121.

Table 7

*Scores for Individuals Who Changed Medical Products and Took the PROMIS-29 Survey at Two Different Time Points*

Person ID	PROMIS-29 measure	PROMIS-29 score - Time 1	PROMIS-29 score - Time 2
931	Ability	19	20
	Anxiety	5	5
	Depression	5	5
2685	Ability	9	11
	Anxiety	10	10
	Depression	11	7
8121	Ability	5	8
	Anxiety	16	13
	Depression	17	8

### Summary

In conclusion, individuals using medical products innovated for fewer needle sticks or for shorter infusion time had similar mean HRQOL and well-being as measured by the PROMIS-29 survey. The same held true when PROMIS-29 data were evaluated according to individuals who had reported switching medical products compared to those who had not. Thus, the null hypothesis of no mean difference between the two groups could not be rejected. Overall, individuals were equally able to participate in social activities/ roles. Overall, individuals were equally likely to be more or less anxious or depressed. Thus, individuals had the same HRQOL and well-being for the medical product they were using at the time they took the PROMIS-29 survey. However, when looking at the same individuals when they changed medical products to a newly

innovated product (e.g. approved 2010 to present) and also took the PROMIS-29 survey at approximately the time point of the change, the limited data suggest improvements in well-being and HRQOL.

An assessment of parameters common to all individuals in the patient registry demonstrated that those who took the PROMIS-29 survey and those who did not were similar in disability distribution. However, the groups differed in other key aspects such as gender, racial, and age distribution. Furthermore, the groups differed in disease state parameters such as age at: symptom onset, diagnosis, and initial use of IGRT. As a result of these differences, it is difficult to generalize the research question findings to the entire population of individuals in the patient registry.

In Chapter 5, I will consider the implications of the findings in context of the literature review from Chapter 2 and in terms of potential research areas of the future research.

## Chapter 5: Discussion, Conclusions, and Recommendations

### **Introduction**

In this quantitative dissertation, I evaluated the impact on well-being and HRQOL of medical products for PIDD innovated according to patient preferences for fewer needle sticks and shorter infusion times by analyzing PROMIS-29 survey scores. I used the PROMIS-29 domain “Ability to Participate in Social Roles/Activities” as a proxy for well-being, and the domains of “Anxiety” and “Depression” as proxies for HRQOL. As I noted in Chapter 1, well-being conceptualizes how people thrive in their daily life while HRQOL is associated with negative emotions (HealthyPeople.gov, 2017).

I used t-tests and Mann-Whitney tests to measure whether there were differences in the PROMIS-29 scores according to medical product innovation category. In each case, I failed to reject the null hypothesis that there is no mean difference. In order to determine generalizability between the 153 individuals who completed the survey and the 1,877 individuals in the patient registry who did not take the PROMIS-29 survey, I compared common characteristics such as age, gender, race, route of IGRT administration, level of disability, age at PIDD symptom onset, age at diagnosis, and age at first IRGT use. Statistical analyses revealed significant differences between the populations for all aspects compared, except for level of disability. Thus, I cannot generalize from individuals in the patient registry who took the PROMIS-29 survey to those individuals in the patient registry who did not.

Next, I compared the mean difference in PROMIS-29 scores between individuals who reported using a medical product approved in the time frame of 2010-2014 and those

who reported using a medical product approved prior to 2010. There was no statistically significant difference in PROMIS-29 scores, and I failed to reject the null hypothesis. Each group had similar levels of HRQOL and well-being.

Lastly, three individuals in my dataset reported having changed from a medical product innovated prior to 2010 to a medical product innovated in 2010 or later and also took the PROMIS-29 survey around the periods of time when they switched. My data suggest that there might be improvements in HRQOL and well-being as measured by PROMIS-29 due to the switch to innovative medical product for these individuals.

### **Interpretation of the Findings**

The underlying premise of the research questions is that patients have a treatment preference for shorter infusion time and fewer needle sticks (Jiang et al., 2015); thus, patients taking those medical products would have a higher mean HRQOL and a higher mean well-being than patients who did not take these products. However, the null hypothesis that there would be no mean difference could not be rejected. There might be several reasons for this finding, including: (a) perhaps patients were already optimized on a therapy regimen of their preference at the time they took the PROMIS-29 survey; (b) statistical power to detect a difference was not present; (c) other factors distributed among the groups were more influential; (d) preference for treatment, satisfaction with treatment, and HRQOL/well-being, while seemingly similar constructs, might be different enough that their measurement involves generating primary data asking specific linking questions between innovated medical products and the PROMIS-29 survey



questions; and (e) improvements in HRQOL and well-being are best measured using a longitudinal design rather than a cross-sectional design.

The study findings presented in Chapter 4 are similar to those of other studies. For instance, while some researchers have found statistically significant differences or changes in HRQOL and well-being, other researchers have found no significant differences or changes. Bienvenu et al (2016) and Espanol et al (2014) both found no statistical difference between the route of administration (IV and SC) and quality of life as measured by SF-36 and SF-12, respectively. Other researchers found no difference in QOL as measured by SF-12 between treatment bother (e.g., treatment convenience, interruptions to life, side effects and reactions, needle sticks, infusion time, number of infusions, infusion costs, and operation of infusion delivery medical devices) and route of administration (Rider et al., 2017).

In general, route of administration influences the number of needle sticks and the infusion time. Individuals receiving therapy via subcutaneous injections generally receive smaller doses daily to weekly, or biweekly. Therefore, there is potential for more needle sticks but shorter infusion times. Individuals receiving intravenous injections generally receive a large monthly dose and have the potential for fewer injections but longer infusion times. Medical product innovations include making available more concentrated formulations (e.g., 5%, 10%, 16%, and 20% formulations exist) so the same concentration of therapy can potentially be administered in reduced time and with fewer needle sticks. Other innovations include medical products which allow administration of more volume per infusion, thus potentially reducing the number of needle sticks and

infusion time (Kobrynski, 2012). However, the proportion of individuals who took the PROMIS-29 survey using newer innovative medical products might have been too few to detect a difference. For example, 63 patients were using medical products approved since 2010, and only 15 patients were using medical products approved since 2012.

The findings of this study are supported by literature. However, mean differences in HRQOL and well-being might also have been nonexistent due to patients having already been optimized according to the medical products available to them. For instance, data suggested potential improved HRQOL and well-being when the same individual took the PROMIS-29 survey around the same time point of changing medical products (see Table 7). Lastly, mean differences might also have been masked by lack of statistical power and the small numbers of individuals using the newer innovated medical products.

Some researchers have found that clinical condition (e.g., number and severity of infections and comorbidities such as impaired digestive, liver, lung, or neurological functioning) is a greater influence on HRQOL than therapy parameters (Rider et al., 2017; Tabolli et al, 2014). Rider et al. (2017) found that higher QOL was associated with patients having controlled PIDD and limited physical impairment. Additionally, patients who also were not bothered by requirements of treatment (including needle sticks and infusion times), and who received infusions at home (whether IGIV or SCIG), had higher QOL (Rider et al., 2017). Rider et al. (2017) found that patients who reported having no physical impairment scored higher than the U.S. population for QOL. The authors found this aspect surprising because patients with PIDD generally score lower than the U.S.

population on QOL measures (Rider et al., 2017). However, these findings align with the disability paradox theoretical framework (see Albrecht & Devlieger, 1999; Fellinghauer et al., 2012) discussed in Chapters 1 and 2.

My study findings might be indicative that the ultimate goal of aligning patients with medical products catering to their preferences, and thus optimizing their HRQOL and well-being has been achieved for this population of individuals with PIDD. For instance, researchers found that patients were satisfied with the therapy they were receiving (Bienvenu, 2016). According to Espanol et al., (2014), satisfaction with treatment was related to preferences. Individuals who preferred one needle stick once a month were satisfied if they were receiving IVIG. Additionally, individuals who were satisfied with SCIG preferred self-infusion at home (Espanol et al., 2014). The availability, since 2010, of medical products allowing more choice about when and where patients can potentially receive fewer needle sticks and which have a shorter infusion time (Ponsford, 2015; Wasserman, 2014) could shift preferences or reasons for patient satisfaction as more patients begin using these medications. In Chapter 1, I mentioned the medical product supply chain leading to medical product availability for physicians to prescribe. Espanol et al. (2014) and Seeborg et al. (2015) commented that therapy and route of administration are influenced to a large extent by the physician. These researchers urged the need to ensure patient preference considerations in order to facilitate better HRQOL and perceived health outcomes. The balancing act of maintaining stable blood serum levels of antibody at the clinical level to stave off chronic infections while measuring treatment preference and treatment satisfaction has been a

need demonstrated in the literature. In this study, I used the biopsychosocial model theoretical framework to study psychosocial factors assessed via the PROMIS-29 survey on IGRT standard and innovative medical products already proven and approved according to clinical outcomes (e.g. stable blood serum levels, fewer infections and hospitalizations, leading to fewer missed days of work/ school).

### **Limitations of Study**

I used a secondary dataset where the data collected was not specific to my research questions. Regarding needle sticks, some individuals provided information about the interval of days between infusions. This enabled patient-specific placement into a category based on their actual use. For patients who did not report IGRT interval, I inferred needle stick information from medical product labeling. Regarding infusion time, there was no available data about infusion time specific to each patient. Therefore, I also inferred this information from medical product labeling. However, there might have been a significant level of variability within my study population within the parameters of medical product labeling. Other limitations included potential confounding factors for which data were not available; for example, the length of time patients had been receiving their current medical product and/ or therapy, and how successful they feel therapy has been. Limitations associated with PROMIS-29 survey administration include those named in Chapter 1 and Chapter 3 regarding selection bias, recall bias, and survey response bias.

## **Recommendations**

Patient-reported outcomes such as preferences for treatment, satisfaction with treatment, and aspects of treatment which lead to increased HRQOL and well-being are not necessarily intuitive. For instance, Elliott & Richardson (2014) noted persons with epilepsy preferred not solely a reduction in the number and severity of seizures, they also preferred alleviation of the depressive and anxiety manifestations of epilepsy which prevented performing functions of life, such as work and school. Instead of a cure from the disease state for patients with rare and common chronic diseases, there is daily management and a series of tradeoffs (e.g. medication already in liquid form instead of as a lyophilized powder needing to be reconstituted with sterile water; medication which can remain at room temperature versus needing refrigeration; medication which can be taken less often, or on an empty stomach; or more than one option for route of administration). Thus, patient-reported outcomes are a powerful tool for understanding how to make outcomes better for patients. The biopsychosocial model demands a biomedical demonstration of medical product performance, and the model demands this clinical performance also considers the psychosocial world of the patient. Gathering primary data for further study of patient-reported outcomes using the biopsychosocial model framework would further the evidence base and scientific discourse for innovative medical product development and for regulatory decision-making.

## **Implications for Positive Social Change**

This is the first study which used the biopsychosocial model framework to test whether patient preferences realized into medical products and therapy regimens

translated to increased HRQOL and well-being when measured by the PROMIS-29 survey for patients with PIDD. Research aimed at studying patient psychosocial perspectives additional to biomedical perspectives has a potential impact at the individual level and at the societal/ policy level because it provides an evidence base for medical product development and approval. Implications for positive social change include helping medical product manufacturers and regulatory bodies to verify innovative medical products have impact on patient lives beyond solely biomedical parameters and clinical endpoints and then to make these products available to patients. This dissertation serves as a guide for how a theoretical framework such as the biopsychosocial model can be used along with the PROMIS-29 survey to gain patient feedback and to assess innovations made in response to patient feedback for PIDD and other chronic disease states.

I recommend this study be conducted using a longitudinal design where individuals about to experience an innovative medical product get a pretest and a posttest asking specific questions about their preferences and the medical product innovation, and they are provided the PROMIS survey instrument. Thus, the voice of the patient will have an opportunity to be heard with less confounding and with more statistical power to form a stronger evidence base.

### **Conclusions**

The findings of this study showed that patients with PIDD are generally equal in terms of HRQOL and well-being across the variety of IGRT medical products. Some of the prior studies reviewed support this finding. However, gaining the voice of the patient

is valuable to society. Thus, this study merits repeating using a longitudinal design and questions specifically aimed toward linking patient preferences for treatment with the PROMIS-29 survey, especially as additional data become available for the more recent FDA-approved innovated IGRT medical products.

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## Appendix A: E-Mail from Immune Deficiency Foundation

**Heckman, Niedre M**

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**From:** Christopher  
**Sent:** Thursday, October 20, 2016 11:54 AM  
**To:** [niedre.heckman@waldenu.edu](mailto:niedre.heckman@waldenu.edu)  
**Cc:** Marcia  
**Subject:** Immune Deficiency Foundation: Your dissertation

Dear Ms. Heckman;

My name is Christopher, I am Vice President of Research at the Immune Deficiency Foundation (IDF). I understand from Marcia that you have an interest in working with IDF in obtaining data on QoL issues in patients receiving IG therapy. She has asked me to respond to your inquiry.

We are happy to take a look and see how collaboration may be possible.

My first suggestion to you would be to query the United States Immunodeficiency Network (USIDNET). This is a NIH-funded research program of IDF's that was established to advance scientific research in primary immunodeficiency diseases (PI).

This is a patient consented registry that contains almost 5,000 registrants with a confirmed PI diagnosis.

Due to IDF's PI CONNECT program, funded in part by the Patient Centered Outcomes Research Institute (PCORI), we are now able to link patient data and reported outcomes from IDF's electronic personal health records with their clinical data as it exists in the USIDNET registry. As part of this project IDF has implemented use of the PROMIS-29 QoL instrument. It is built into the IDF ePHR and patients are prompted to take the survey every six months. Our next iteration of this will be this upcoming November. At the moment we have over 100 patients who have taken at least one PROMIS-29 and have clinical data in the USIDNET registry.

I would suggest as a first step that you submit a query to USIDNET. I would ask for records that contain PROMIS-29 QoL data (scores) as well as any clinical data in which you may be interested.

There is no cost to query or receive the data. The link to the data query form may be found here:

<https://usidnet.org/usidnet-registry/registry-data-query-form/>

On a related note, IDF incorporated the SF-12v2 QoL into our last IDF National Treatment Survey which was conducted at the end of 2013/beginning of 2014. The Treatment Survey is a survey where we take a deep dive into Ig therapy and its impact on reducing infections, hospitalizations, etc., This data is currently being leveraged and used in a manuscript that is a collaboration between Dr. Jordan and IDF. We have already submitted the manuscript for publication and are now addressing some reviewer comments.

Please check back with me after you have received and analyzed the data from your USIDNET query. That will help us shape the direction and conversation on any additional collaboration.

Please let me know if you have any questions, or need further assistance.

We look forward to seeing you complete a successful dissertation!

Regards,  
Chris

## Appendix B: USIDNET Query

**I have read the above data use policy and I agree to adhere by its standards.**

Agree

**Name**

Niedre Heckman

**Position**

Doctoral Student - Public Health

**Institution**

Walden University

**Email**

niedre.heckman@waldenu.edu

**I agree to allow the Registry Manager to contact me for follow-up data in the future.**

- Agree

**Purpose of Query**

- Research for publication
- Improved understanding of diseases (personal knowledge gain)

**What is your overall question (briefly)?**

What is the change in target audience (patients and caregivers) psychosocial perspectives as a result of treatment of PIDD with commercially available biologic therapies delivered through the subcutaneous route?

**What study population do you want to capture?**

All PIDD patients; caregivers

**How might the information obtained from the USIDNET registry benefit the primary immunodeficiency community?**

The information could help the primary immunodeficiency community understand changes (hopefully improvements) in quality of life (QOL) parameters resulting from using different therapies. For example, patient perspectives can inform drug development and even the regulatory process for drug approval. Once the drug is developed and on the market, which of the patient perspectives (specifically related to social parameters measured with instruments measuring QOL parameters) shifted as a result of using a given drug? Such knowledge could be useful for refining drug development protocol and regulatory policy in the future.

**Please list other individuals who will be accessing the requested USIDNET data.**

I am a doctoral student and I will need to conduct this study independently. I am, however, seeking to collaborate with IDF and was referred to USIDNET through IDF.

**Patient Diagnosis Information**

- Diagnosis
- Age of Symptom Onset
- Age of Diagnosis

#### Demographics

- Age
- Race
- Ethnicity
- Gender

#### Vitals

- Height
- Weight
- BMI

#### Patient Infections

Yes

#### Please Select Fields to Include

- ALL Infection Names

#### Non-Infectious Conditions

Yes

#### I would like to include fields for the following conditions:

- Constitutional
- Gastrointestinal
- Neurologic
- Psychosocial
- Skin

#### If you are interested in specific noninfectious conditions, please list in the space below.

records that contain PROMIS-29 QOL data (scores); educational attainment; household income; zip code; and SF-36; SGRQ; GHQ-12; EQ-5D; or other QOL measures such as those in the CVID\_QOL Questionnaire (Quinti, I., Pulvirenti, F., Giannantoni, P., Hajjar, J., Canter, D. L., Milito, C. et al. (2016). Development and initial validation of a questionnaire to measure health-related quality of life in adults with Common Variable Immune Deficiency: The CVID\_QoL Questionnaire. J. Allergy Clin Immunol. Pract)

#### Allergic Reactions

No

#### Live Agent Vaccines



No

### Ig Therapy

Yes

### I would like to include the following fields

- Starting Age
- Route
- Frequency
- Adverse Reactions
- Dose

### Dose Units

- g (total)
- mg / kg

If you would like to include additional fields related to Ig therapy, please note accordingly in the space below.

Name(s) of biologic and drug products used

### Anti-Infectives

No

### Immunomodulator Therapy

No

### Blood Transfusions

No

### Surgical Procedures

No

### Non-Surgical Treatments

No

### Complete Blood Count

No

### Lymphocyte Phenotype

No

### Memory B Cell Phenotype

No

### Immunoglobulin Evaluations

No

**Antibody Response**

No

**Pneumococcal Vaccine**

No

**TRECs**

No

**Lymphocyte Function**

No

**Delayed Hypersensitivity Skin Testing**

No

**Complement Function (CH50)**

No

**Phagocyte Function**

No

**Stem Cell Transplants**

No

**Solid Organ Transplants**

No

**Gene Therapy**

No

**Family History**

Yes

**I would like to include the following fields**

- Relation
- Diagnosis

**Genetic Information**

Yes

**I would like to include the following fields**

- Pattern of Inheritance

- Gene Mutation

#### Quality of Life Data

Yes

#### I would like to include the following fields

- Alive / Dead
- Disabilities
- Days in hospital related to PIDD
- Lansky/Karnofsky Index