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Establishing the minimum clinically important difference (MCID) of the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55)

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Abstract

The Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55) is a validated, parent-reported measure of health-related quality of life (HRQOL) in children with epilepsy (CWE). The QOLCE-55 currently has no minimum clinically important difference (MCID), which is the minimum amount of change required to be considered meaningful to patients. The primary objective of this study was to estimate the MCID for the QOLCE-55 using the Making Mindfulness Matter© in Children with Epilepsy trial data. Parent-child dyads (n=66) completed the QOLCE-55 at baseline (week 0) and follow-up (week 9). MCID values for the QOLCE-55 were calculated using two types of methods: anchor-based and distribution-based. Using an anchor-based approach, the MCID for the QOLCE-55 was 10 points and using a distribution-based method, the MCID was 6 points. This is the first study to report MCID values for the QOLCE-55. These MCID estimates should be used with caution pending replication in subsequent studies.

Keywords

Health-related quality of life, minimum clinically important difference, children, epilepsy, Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55) (QOLCE-16)

Summary for Lay Audience

The Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55) is used to measure the health-related quality of life (HRQOL) of children with epilepsy (CWE). HRQOL represents a person's perception of how their health affects their physical, psychological, and social well-being. Measuring the HRQOL in CWE is important because this population is at risk for psychological, behavioural, and cognitive impairments, which can negatively affect their HRQOL. The primary objective of this thesis is to estimate the minimum clinically important difference (MCID) of the QOLCE-55. MCID is the minimum amount of change required to be considered meaningful to a patient. The MCID value for the QOLCE-55 is estimated using data from the Making Mindfulness Matter© in Epilepsy (M3-E) randomized controlled trial. Establishing a MCID for the QOLCE-55 will be helpful in determining whether differences in HRQOL observed are meaningful to the CWE themselves. The literature typically recommends the use of both anchor-based and distribution-based methods to estimate the MCID. This thesis reports the findings from both methods. The MCID for the mean change in HRQOL score from baseline to follow-up using an anchor-based method was 10 points. The MCID for the mean change in HRQOL score using a distribution-based approach is 6 points. As there is a difference in magnitude between these two MCID values, this thesis provides a discussion of the factors that should be considered to help future investigators decide which MCID value to use in their analysis. Ultimately, these MCID estimates should be used with caution pending replication in subsequent studies. Further research is also required to provide clear guidelines on how to address the differences in the MCID values obtained.

Co-Authorship Statement

All chapters of this thesis were written by me, Mariela Leda, to partially fulfill the requirements of the degree of Master of Science in Epidemiology. I developed the research objectives, study methodology, data analysis, and interpreted the results to make conclusions. My supervisory committee, Dr. Kathy Nixon Speechley, Dr. Klajdi Puka, and Dr. Joel Gagnier, provided guidance and feedback on all aspects of the thesis. As a part-time research assistant on the Making Mindfulness Matter© in Epilepsy research team, I assisted with patient recruitment, data collection, and data entry.

Dedication

To those living with epilepsy

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CHAPTER 1

INTRODUCTION

1.0 Introduction

The Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55) is a validated and widely-used parent-reported measure of health-related quality of life (HRQOL) in children with epilepsy (CWE) (Goodwin et al., 2015). This measure allows researchers to evaluate interventions aiming to improve the HRQOL of CWE and compare HRQOL scores across study populations. The minimum clinically important difference (MCID), which is the minimum amount of change required to be considered meaningful to a patient (Hays & Woolley, 2000), has not yet been established for the QOLCE-55. This makes interpretation of outcome scores challenging for clinicians and researchers who aim to understand the clinical significance of interventions (Wiebe et al., 2002). One common approach to evaluating interventions is testing for a statistically significant difference in the mean change scores for HRQOL across intervention groups. However, this method alone does not demonstrate whether differences observed are clinically meaningful to the participants receiving the intervention. Establishing a MCID for the QOLCE-55 would provide clinicians and researchers a more useful interpretation of HRQOL scores.

1.1 Why is health-related quality of life important?

HRQOL is recognized as one of the most important patient-reported outcome measures in clinical research (Lin et al., 2013). Although the terms quality of life (QOL) and HRQOL are often used interchangeably in the literature, they are two distinct concepts (Hand, 2016). QOL comprises several domains including physical health, mental style, mindfulness, relationships, money, and self-esteem (Jones & Drummond, 2021). HRQOL is a more focused concept defined as those aspects of QOL that directly or indirectly relate to health (Karimi & Brazier, 2016). Specifically, HRQOL is defined as "those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment" (Ebrahim, 1995). Measures of HRQOL seek to obtain information regarding an individual's health perception, functional status, and their preferences and values (Clancy & Eisenberg, 1998). A key aspect of the evaluation of HRQOL is that it is subjective as it involves an individual's self-assessment of their own physical, social, and psychological well-being (Testa & Simonson, 1996).

Advancements in medical technology have led clinicians to place a greater emphasis on the prevention and management of chronic illnesses (de Wit & Hajos, 2013). Consequently, the use of HRQOL measures has grown increasingly important as it helps clinicians understand the daily experiences of patients living with a chronic illness (de Wit & Hajos, 2013). Measurement of HRQOL has important applications in research and medicine. The use of HRQOL measures allows for the inclusion of a patient's perspective in the clinical decision making process, shifting the clinical focus from a disease-based approach to a patient-centered approach (Chen et al., 2005; Lin et al., 2013; Osoba, 1999). Inclusion of the patient perspective ensures that clinical

decisions are guided by a patient's needs, values, and preferences (Kuipers et al., 2019). Results from HRQOL measures can also aid in the comparison of various medical interventions (Guyatt et al., 2007; Lin et al., 2013). For instance, if the aim is to find an intervention that improves how a patient is feeling, measurement of HRQOL is essential in obtaining that information (Guyatt et al., 2007). Clinical decision-makers can also use tools that assess HRQOL accurately at the individual and population level (Chen et al., 2005). Therefore, the use of HRQOL measures can make significant contributions toward patient screening and population health monitoring (Chen et al., 2005). Assessing HRQOL is important to pharmaceutical evaluations since using patient-reported HRQOL measures aid in the identification of treatment benefits for patients that cannot be discovered using only traditional clinical instruments (Chen et al., 2005). HRQOL measures also have important applications in risk prediction (Chen et al., 2005; Lin et al., 2013). Data obtained from patient-reported measures can help refine risk prediction models which can, in turn, aid in planning care (Chen et al., 2005). Researchers can also integrate HRQOL and survival time into quality-adjusted life years for use in the comparison of specific treatments and evaluation of health care interventions (Hwang & Wang, 2004).

1.2 Thesis Objective

The primary objective of this thesis is to determine the MCID of the QOLCE-55. The secondary objective of this thesis is to determine the MCID for the shortened version of the QOLCE-55, the QOLCE-16.

CHAPTER 2

LITERATURE REVIEW

2.0 Introduction

The goal of this chapter is to provide readers with an understanding of why measuring HRQOL in CWE is important and why determining MCIDs for the QOLCE-55 and QOLCE-16 will help facilitate the investigation of HRQOL in CWE. Prior to discussing the importance of establishing a MCID for the QOLCE-55 and the QOLCE-16, it is crucial to first introduce the topics of epilepsy, HRQOL, the impact of epilepsy on HRQOL, measures of HRQOL in CWE, and the concept of MCID itself. This chapter provides an overview of epilepsy and its formal definition, incidence rates, classification system, and how epilepsy presents itself in children. An overview is also given of the impact epilepsy can have on children's psychological, behavioral, and cognitive functioning, which may negatively impact their HRQOL and thus why consideration of HRQOL is essential in the management of CWE. The QOLCE-55 and QOLCE-16 were developed specifically for the measurement of HRQOL in CWE. The psychometric properties of these outcome measures will be discussed further. This chapter also defines MCID, outlines the value of MCIDs to researchers and clinicians using the QOLCE-55 and/or QOLCE-16, and the various methods used for MCID calculation.

2.1 Overview on Epilepsy

Epilepsy is one of the most prevalent neurological conditions, affecting over 70 million people globally (Thijs et al., 2019). The International League Against Epilepsy (ILAE) is a professional organization recognized globally as an advocate for the improved education, awareness, diagnosis, and treatment of epilepsy (Guekht et al., 2021). One of the responsibilities of the ILAE is to formulate the official definition of epilepsy for the purpose of clinical diagnosis (Fisher et al., 2014). The current official definition for epilepsy entails meeting any of the following criteria: 1) at least two unprovoked seizures take place over 24 hours apart; 2) one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and 3) diagnosis of an epilepsy syndrome (Fisher et al., 2014). Back in 2005, the International League against Epilepsy (ILAE) defined epilepsy as an "enduring predisposition of the brain to generate epileptic seizures, with neurobiologic, cognitive, psychological, and social consequences" (Fisher et al., 2005). This definition required at least one epileptic seizure to occur; an epileptic seizure defined by the ILAE is "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (Fisher et al., 2005). Several concerns were raised by epileptologists regarding this formal definition of epilepsy as it failed to: 1) include the risk for future seizures after the first unprovoked epileptic seizure (Fisher et al., 2014); 2) consider the possibility of someone outgrowing epilepsy, which often happens for individuals who have seizures in childhood (Fisher et al., 2014); and 3) include individuals diagnosed with an epilepsy syndrome (Fisher & Bonner, 2018). As a result of these limitations,

the definition for epilepsy was altered in 2014 by the ILAE Task Force to make it more suitable for clinical application (Fisher et al., 2014). In the updated 2015 definition, epilepsy became characterized as a curable disease instead of a disorder (Fisher & Bonner, 2018). This change in terminology was done deliberately by the ILAE to increase public attention surrounding epilepsy since diseases are generally considered to be more pressing than disorders (Fisher & Bonner, 2018).

Epilepsy is a prevalent condition worldwide, with an overall incidence rate of 61 per 100,000 person-years and lifetime prevalence of 7 per 1,000 people (Fiest et al., 2017). Incidence varies by a country's income, with an incidence rate of 49 per 100,000 person-years in high-income countries and 139 per 100,000 person-years in low and middle-income countries (Fiest et al., 2017).

Incidence of epilepsy also varies by age. The incidence rate of epilepsy in individuals 18 years old and younger is 47 per 100,000 person-years and 35 per 100,000 person-years in individuals 19 years old and older (Fiest et al., 2017). In terms of age-specific prevalence, the point prevalence of active epilepsy appears to increase with age until 30 years of age (Fiest et al., 2017). In the 0 to 9-year old group, the point prevalence of active epilepsy is 5.19 per 1,000 people (Fiest et al., 2017). This increases to 8.86 per 1,000 people in the 10 to 19 year old group and 9.14 per 1,000 people in the 20 to 29 year old group (Fiest et al., 2017). The point prevalence of active epilepsy then reduces to 7.94 per 1,000 in the 30 to 59 year old group and 7.17 per 1,000 in the 60+ years old group (Fiest et al., 2017). Although epilepsy affects all ages (Holmes, 2012), children and adolescents represent a significant proportion of people with epilepsy

(Wallace & Farrell, 2004). It is estimated that 3.5 million people are diagnosed with epilepsy annually, 40% of whom are under 15 years old (Wallace & Farrell, 2004). In Canada, the prevalence of epilepsy in children aged 0 to 15 years old has been estimated to be 5.26 per 1,000 children (Prasad et al., 2011).

2.1.1 Classification of epilepsy

The most recent classification of epilepsies and seizures for clinical use was published by the ILAE in 2017 for clinical use (Fisher et al., 2017). This revision classifies seizures based on three features: 1) origin of the seizure in the brain; 2) level of awareness during seizure; 3) degree of body movement (Fisher et al., 2017). The ILAE 2017 seizure classification provides basic and expanded frameworks (Fisher et al., 2017). This section provides an overview on the basic classification of seizures and epilepsies. Seizures are first defined according to their origin in the brain (Fisher et al., 2017). Focal onset seizures are characterized by abnormal electrical activities that begin in one cerebral hemisphere and can potentially spread to the other side (Sarmast et al., 2020). Generalized onset seizures occur when abnormal electrical activities originate from both cerebral hemispheres and progress to additional neuronal networks (Sarmast et al., 2020). Seizures are described as having an unknown onset if a seizure occurs while an individual is asleep, alone, or when it cannot be described adequately by a witness (Sarmast et al., 2020). However, reclassification of unknown onset seizures is possible with sufficient information (Fisher et al., 2017). Classification beyond the first criterion is optional in the basic framework of classifying seizure. Based on the second criterion, a patient can have intact or

impaired awareness during a seizure. ILAE defines awareness as “knowledge of self and the environment.” Furthermore, a seizure can have motor or non-motor onset. Seizures of unknown onset can be classified as motor seizures, non-motor seizures, or unclassified. A seizure is considered unclassified if its presentation does not fit into the other categories or the seizure presents with inadequate information for classification. When using basic classification, the seizure’s type of motor or non-motor activity does not need to be specified. The expanded ILAE 2017 classification system describes the different types of motor and non-motor seizures in detail (Fisher et al., 2017).

In the basic classification framework, classification of epilepsy is based on three levels: seizure type, epilepsy, and epilepsy syndrome (Scheffer et al., 2017b). Classification of epilepsy is first done according to the seizure type, then by the type of epilepsy. Following this, diagnosis of an epilepsy syndrome can be provided. This multilevel classification system was created to allow for the diagnosis of epilepsy in various clinical settings. As such, the level of classification is dependent on the diagnostic resources available to a clinician. When feasible, diagnosis of epilepsy should be done at all three levels. The first step for classifying epilepsy is identifying the seizure type. This step assumes the clinician had already concluded the diagnosis is epilepsy and is not meant to be a diagnostic guide for differentiating epileptic and nonepileptic events. Classifying seizure type can be facilitated by the 2017 ILAE classification of seizure types (Fisher et al., 2017). In certain clinical settings, classification of epilepsy may end at the seizure type if clinicians have no access to electroencephalography, video, and imaging tests (Scheffer et al., 2017b). Further classification may also not be possible if inadequate information is available,

such as when a patient has experienced only one seizure. The second phase of epilepsy classification involves determining the patient's epilepsy type. This level assumes the patient has been diagnosed with epilepsy according to the definition outlined by the ILAE in 2014 (Fisher et al., 2014; Scheffer et al., 2017b). In the basic framework, epilepsy is categorized into four main types: 1) focal; 2) generalized; 3) combined generalized and focal; 4) unknown (Scheffer et al., 2017b). The third level of epilepsy classification is determining a patient's epilepsy syndrome. Identification of an epilepsy syndrome is dependent on a cluster of a patient's clinical features that can include seizure types, EEG and imaging findings, age of onset and remission, and seizure triggers. An epilepsy syndrome may also be associated with a certain etiology, prognosis, and treatment plan (Scheffer et al., 2017b).

2.1.2 Epilepsy in children

Childhood absence epilepsy (CAE) and juvenile absence epilepsy (JAE) are two examples of pediatric epilepsy syndromes that have significant clinical overlap (Scheffer et al., 2017a; Yadala & Nalleballe, 2022). CAE is a common type of pediatric idiopathic generalized epilepsy, representing 12% of all diagnosed epilepsy cases in children under 16 years old (Berg et al., 1999). The age of onset of CAE is typically between 4 and 10 years old (Waaler et al., 2000). This epilepsy is characterized by impaired awareness, unresponsiveness, and frequent typical absence seizures (Blumenfeld, 2012; Matricardi et al., 2014). Absence seizures result in "transient impairment of consciousness and staring unresponsive for a few seconds usually accompanied by 3 Hz spike and slow wave activity on EEG" (Uysal-Soyer et al., 2012). Most

children with CAE also experience complete arrest of activity (Sadleir et al., 2006). With proper CAE diagnosis, the likelihood of successful remission of seizures is high (Roger, 2005). Previous literature report remission rates ranging from 54% to 95% (Berg, Levy, et al., 2014; Berg, Rychlik, et al., 2014; Callenbach et al., 2009; Loiseau et al., 1995; E. C. Wirrell et al., 1996). In one study, mean ages at remission were 3.9 and 9.5 years old, respectively, with older remission ages in children who continued to have seizures more than 6 months after recruitment (Callenbach et al., 2009). Although CAE is typically self-limited and age-dependent, prophylactic antiepileptic treatment is still recommended (Matricardi et al., 2014). JAE is another epilepsy syndrome characterized by absence seizures, impaired awareness, and generalized tonic-clonic seizures (Koutroumanidis et al., 2017). Although JAE and CAE share similarities in clinical presentation, there are some notable distinctions between these epilepsy syndromes (Vidaurre et al., 2009). Specifically, the age of onset in JAE is between 8 years old to early adulthood (Koutroumanidis et al., 2017). Furthermore, the frequency of absence seizures in JAE is less than that of CAE and JAE is not self-limiting (Koutroumanidis et al., 2017; Trinka et al., 2004). JAE is also less common than CAE, accounting for 1-2% of childhood epilepsy (Wirrell, 2016). Previous literature has reported varied remission rates ranging from 29 to 88% (Healy et al., 2018; Kleveland & Engelsen, 1998; Panayiotopoulos et al., 1994; Siren et al., 2002; Sokic et al., 2007). However, the likelihood of seizure relapse is high for patients who discontinue their antiepileptic medication. For instance, one study reports a relapse rate of 100% following withdrawal of antiepileptic medication among 123 patients who were previously in remission for at least three years (Chakravarty et al., 2007). Additional literature has reported relapse rates

higher than 80% following medication withdrawal (Healy et al., 2018; Höfler et al., 2014; Panayiotopoulos et al., 1994). This suggests that adolescents with JAE may require long-term antiepileptic use (Aiguabella Macau et al., 2011; Pearl, 2018).

Diagnosis of epilepsy in children can be difficult (Hindley, 2006; Uldall et al., 2006). Instances of epilepsy misdiagnosis have been recorded in the literature (Hindley, 2006; Uldall et al., 2006; White, 2003). In one study where 380 children were referred with "fits, faints, and funny turns" to a secondary care clinic, 53 (14%) children were categorized as "unclassified" and no active treatment was provided (Hindley, 2006). As these children were not subsequently seen for further clinical investigations, it is possible some cases of epilepsy were missed. One potential explanation for misdiagnosis is the large differential diagnosis of epilepsy in children (Ferrie, 2006). Furthermore, descriptions of seizure episodes are dependent on parents and other witnesses, such as school teachers (Uldall et al., 2006). Ideally, direct observations by trained clinicians would add value to a patient's seizure history, but this is difficult to acquire in a usual pediatric ward setting (Uldall et al., 2006). Thus, diagnosis by clinicians is normally done in an outpatient setting using interictal EEG results and descriptions of seizure history (Uldall et al., 2006). Misdiagnosis is a concern because it delays a child from receiving the correct diagnosis and treatment in a timely manner. One study reported that a diagnostic delay of over a month occurred in 70 (41%) of children (Berg, Loddenkemper, et al., 2014). At 8 to 9 years following enrollment, participants were asked to complete the Wechsler Intelligence Scales for Children (Berg, Loddenkemper, et al., 2014). Following analysis, authors reported that diagnostic delay of epilepsy was associated with a significant decrease in full scale IQ, verbal comprehension,

perceptual organization, processing speed, and freedom from distractibility (Berg, Loddenkemper, et al., 2014). This suggests that delays in the management of epilepsy can result in long-term cognitive and social consequences, which has important implications in the health-related quality of life (HRQOL) of a child (Berg, Loddenkemper, et al., 2014).

2.2 Health-related quality of life

2.2.1 Health-related quality of life in epilepsy

Childhood epilepsy is associated with numerous psychological, behavioral, and cognitive impairments (Baca et al., 2011; Baker, 2006; Ott et al., 2003; Reilly et al., 2011, 2014; Schraegle & Titus, 2016). In one community-based study of children with active epilepsy, 80% of participants had a behavioral disorder and/or cognitive impairment (defined as an IQ of less than 85) as classified by the Diagnostic and Statistical Manual, Fourth Edition-Text Revision (DSM-IV-TR) (Reilly et al., 2014). Within this sample, the most common behavioral diagnoses were attention-deficit/hyperactive disorder (33%), autism spectrum disorder (21%), and developmental coordination disorder (18%) (Reilly et al., 2014). Another community-based study involving CWE reported that 39% of the sample had a neurodevelopmental spectrum disorder which includes developmental delay, language delay, language problem, dyslexia, and/or autism (Baca et al., 2011). Furthermore, 26% had a psychiatric disorder which includes depression, anxiety, oppositional defiant disorder, ADHD, and/or conduct disorder (Baca et al., 2011). These comorbidities are often unrecognized as epilepsy management traditionally focuses

on seizure control and minimizing undesirable side effects from medication (Malhi & Singhi, 2005; William J. Marks & Garcia, 1998). This can negatively impact the HRQOL of CWE (Malhi & Singhi, 2005). In a HRQOL study involving 103 CWE, the average HRQOL score was 46.4 out of 100 on the Pediatric Quality of Life Inventory 4.0 measure (Rozensztrauch & Kołtuniuk, 2022). The presence of any comorbidity was found to be a significant predictor of poor HRQOL and had substantial impacts on the work/school functioning, emotional functioning, and psychosocial health domains of HRQOL (Rozensztrauch & Kołtuniuk, 2022). Therefore, consideration of HRQOL is very important in the management of childhood epilepsy.

2.2.2 How is health-related quality of life quantified and interpreted?

HRQOL can be quantified using generic or disease-specific outcome measures (Lin et al., 2013). Generic HRQOL measures are broad outcome measures that collect information on an individual's physical, emotional, and social state and their perception of health and well-being (Anderson et al., 1993). Generic HRQOL measures can be used to compare HRQOL across different types of illnesses, treatments, and patient groups (Guyatt et al., 1993). In contrast, disease-specific measures are typically used to measure and compare responsiveness or clinically significant changes in HRQOL within a specific patient population (Guyatt et al., 1986; Patrick & Deyo, 1989). In studies involving CWE, a childhood epilepsy-specific HRQOL measure is often used to reflect the particular experiences CWE have associated with their condition that may not be captured by a generic measure.

HRQOL measures can also be unidimensional or multidimensional (Lin et al., 2013). Unidimensional HRQOL measures use one global question to reflect an individual's overall HRQOL status (Ferrans, 2007). For instance, the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C36) has one item that asks "How would you rate your overall quality of life during the past week?" (Aaronson et al., 1993). This item presents a scale that ranges from 1 to 7 (Aaronson et al., 1993). A higher score indicates better HRQOL with 1 representing very poor HRQOL, and 7 representing excellent HRQOL (Aaronson et al., 1993). However, most HRQOL outcome measures have multiple domains that include their own set of relevant questions and are scored individually (Testa & Simonson, 1996). These HRQOL measures are multidimensional and can report the scores separately to create a profile score (Gill & Feinstein, 1994; Lin et al., 2013). For instance, the Nottingham Health Profile measures an individual's perceived health and reports a profile comprising separate scores for each of its six subscales (Hunt & McEwen, 1980). A higher score indicates a greater severity of problems (Hunt & McEwen, 1980). It is important to note that each HRQOL measure has its own methods for scoring and interpreting the results. Therefore, identifying an outcome score as "poor" or "excellent" HRQOL is dependent on the specific outcome measure used.

2.2.3 Measurement properties of the Quality of Life in Childhood Epilepsy Questionnaire

The QOLCE is a parent-reported measure of HRQOL designed for use in CWE (Sabaz et al., 2000). It was first developed within the context of a sample of Australian children with refractory epilepsy aged 4 to 18 years old as a 77-item measure with 13 multi-item subscales and three single-item subscales. This same sample was also used to evaluate the validity and internal consistency reliability of the QOLCE. The 13 multi-item subscales were reported to have good internal consistency with Cronbach's α coefficients ranging from 0.72 of 0.93. Correlation coefficients between scores on the QOLCE and similar sub-scales of the Child Health Questionnaire (CHQ) were calculated to assess the measure's convergent validity. Nine subscales in the QOLCE were shown to measure similar constructs to seven of the 14 subscales in the CHQ with statistically significant convergent validity coefficients greater than 0.5, demonstrating strong correlation between similar subscales. The subscales in the QOLCE assessing cognitive aspects were compared with the subscales assessing competence and attention problems in the Child Behavior Checklist (CBCL). The QOLCE subscales of attention ($r=0.47$; $p<0.01$), memory ($r=0.47$; $p<0.01$), language ($r=0.55$; $p<0.01$), and other cognitive features ($r=0.37$; $p<0.01$) were significantly correlated with the school competence scale in the CBCL. The QOLCE subscale assessing attention was also negatively correlated with the attention problems in the CBCL ($r = -0.67$; $p<0.01$). These assessments of the psychometric properties of the QOLCE suggested that it is a reliable and valid parent-reported measure of HRQOL in CWE (Sabaz et al., 2000).

With regards to the parent-reported nature of the QOLCE, evaluation of HRQOL in young children is often difficult due to factors such as their developmental stage, language comprehension, or cognitive functioning (Chang & Yeh, 2005; Matza et al., 2004, 2013; Rebok et al., 2001). Previous literature indicates that children under 8 years old are unlikely to self-report their HRQOL reliably (Cremeens et al., 2006; Ronen et al., 2003). For instance, one review of 53 self-reported health measures for children in this age group found only 51% of the measures to have adequate internal consistency reliability (Cronbach's $\alpha = 0.70\text{-}0.9$) and only 23% had adequate test-retest reliability (ICC=0.70-0.90) (Cremeens et al., 2006). Similarly, a patient-reported HRQOL measure for CWE demonstrates an increase in test-retest reliability from children aged 6 to 7 years old (ICC = 0.18-0.52) to children aged 8 to 15 years old (ICC= 0.59-0.69) (Ronen et al., 2003). Language comprehension is also an important factor to consider when assessing HRQOL. One study assessing the ability of children to understand terms often used in health outcome measures such as "nervous", "pain", and "comfortable" is limited at 5 years old (Rebok et al., 2001). However, comprehension of these terms increased between 6 to 8 years old (Rebok et al., 2001). Parents of CWE have been identified as valid proxies for their children on QOL outcome measures (Fayed et al., 2019). As such, these findings suggest that parent-reported measures are an appropriate method of HRQOL measurement in children.

The QOLCE was later adapted and validated a North American sample of CWE aged 4 to 18 years old (Sabaz et al., 2003). This version of the QOLCE is a 79-item measure with 16 subscales comprising five main domains: physical activity, cognition, well-being, social activity, and behaviour. Similar to the original QOLCE, the 79-item version demonstrated robust

psychometric properties. The multi-item scales had internal consistency reliability coefficients between 0.76 and 0.97. Furthermore, subscales of the QOLCE had moderate to high correlation coefficients with theoretically similar constructs of the CHQ, demonstrating convergent validity of the QOLCE subscales (Sabaz et al., 2003).

In 2015, a shortened version of the QOLCE was initially developed and validated in a sample of Canadian children with new-onset epilepsy aged 4 to 12 years old although it has subsequently been validated in CWE aged 4 to 18 years old as well as young adults with epilepsy aged 18 to 29 years old (Conway et al., 2017; Goodwin et al., 2015; Puka, Goodwin, et al., 2020). The QOLCE-55 is a 55-item measure comprising four primary subscales: cognitive, social, emotional, and physical (Goodwin et al., 2015). The QOLCE-55 was found to have better internal consistency reliability than the original QOLCE (Goodwin et al., 2015). Each of the subscales had Cronbach's α coefficients ranging from 0.82 to 0.97 and the overall measure had a reliability coefficient of 0.96 (Goodwin et al., 2015). Convergent validity was assessed by calculating Spearman correlation coefficients between subscales on the QOLCE-55 with similar subscales of the Child Health Questionnaire (Goodwin et al., 2015). Support for the measure's convergent validity was observed, with moderate or high correlation coefficients between the QOLCE physical subscale to the CHQ physical functioning subscale ($\rho = 0.42$) and between the QOLCE emotional subscale and the CHQ psychosocial subscale ($\rho = 0.70$) (Goodwin et al., 2015). With 22 fewer items than the original version, the QOLCE-55 lessens respondent burden while retaining the validity and reliability of the original QOLCE (Goodwin et al., 2015). The QOLCE-55 has been recommended as one of two epilepsy-specific measures for assessing

HRQOL in children based on its strong measurement properties reported in a systematic review (Crudgington et al., 2020). The QOLCE-55 was found to have good structural validity, construct validity, and internal consistency across several studies (Crudgington et al., 2020).

A shortened-version of the QOLCE-55, the 16-item QOLCE (QOLCE-16), was also developed and validated in the same Canadian sample of CWE to further reduce respondent burden (Goodwin et al., 2018). The mean scores for each subscale and total score obtained from the QOLCE-16 were close in magnitude to those obtained from previous studies using the QOLCE-55, except that the scores for the emotional and physical functioning subscales varied slightly. For instance, the emotional functioning score obtained from the QOLCE-55 at baseline was 72.5 points while the same score obtained from the QOLCE-16 was 70.6 points. Furthermore, the physical functioning score obtained from the QOLCE-55 at baseline was 62.3 points while the physical functioning score obtained from the QOLCE-16 at the same time point was 68.7 points. The maximum difference in mean scores between the emotional and physical functioning subscales on the QOLCE-16 and QOLCE-55 was 6.4 points. Despite these differences, the mean overall HRQOL score of both scales remained very close in magnitude. Due to the slight differences in scores for the emotional and physical functioning subscales, the developers of the QOLCE-16 concluded that it is well-suited for the measurement of overall HRQOL scores, while the QOLCE-55 may be more suitable for researchers who are interested in measuring domain-specific scores in addition to the overall HRQOL (Goodwin et al., 2018).

2.3 Minimum Clinically Important Difference

2.3.1 Definition of the Minimum Clinically Important Difference

There is widespread agreement on the importance of evaluating changes in patient outcomes based on the MCID for an outcome measure (Copay et al., 2007; Guyatt & Cook, 1994; Wright et al., 2012). MCID was first defined in 1989 as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management" (Jaeschke et al., 1989). A modified and simpler definition of MCID is "the smallest change that is important to patients" (Stratford et al., 1998). Measurement of MCID is essential as it helps researchers and clinicians produce meaningful interpretation of research findings.

2.3.2 Common methods for calculating the Minimum Clinically Important Difference

There are two main approaches to establishing the MCID in scores for an outcome measure: the distribution-based approach and the anchor-based approach (Rai et al., 2015). The distribution-based method creates a distribution of the outcome scores and uses its statistical properties to determine the MCID (Lassere et al., 2001). Statistical properties such as the standard deviation, effect size, standard error of measurement, or the reliable change index can be used to represent the MCID (Rai et al., 2015). According to a recent systematic review, the most commonly used distribution-based approach is the Multiples of Standard Deviation

(Mouelhi et al., 2020). Specifically, 0.5 standard deviation of the mean change score has been most frequently used by authors who employed the multiples of standard deviation approach to represent the MCID of their outcome measure (Mouelhi et al., 2020). The other main method, the anchor-based approach, compares the change in outcome scores on a HRQOL measure to another clinical measure of change, which acts as the "anchor" (Lydick & Epstein, 1993). The "anchor" is typically a scale patients use to rate the change they experienced in the outcome and is administered at one point at follow-up, such as after an intervention has been completed (Jaeschke et al., 1989; Sedaghat, 2019). For instance, an anchor question asking about changes in HRQOL might be, "Since [intervention], how has your HRQOL changed?" An anchor question normally has an odd number of discrete response options (centered on no change) and the number of response options is dependent on the outcome and condition being assessed (Sedaghat, 2019). Some anchor-based methods include the Change Difference, Receiver Operating Curve, and the Average Change (Mouelhi et al., 2020). Using the Change Difference approach, the anchor helps researchers identify those who responded to the intervention and those who did not respond (Mouelhi et al., 2020). The MCID is then established by calculating the difference in the mean HRQOL change scores between responder and non-responder patients (Mouelhi et al., 2020). The Receiver Operating Curve method involves selecting different cutoff points to categorize participants into those who improved meaningfully and those who did not (Wright et al., 2012). Once cutoff values are chosen, investigators create a ROC by plotting the outcome measure's sensitivity and specificity associated with each cutoff value (Wright et al., 2012). The resulting MCID is the most upper left point of the ROC as this indicates the change

of score associated with the highest true positive rate and lowest false positive rate (Wright et al., 2012). The Average Change approach involves using the anchor to identify patients who responded to the intervention and then determining the average change in HRQOL score experienced by responder patients (Mouelhi et al., 2020). This average is used to define the MCID of the HRQOL measure (Mouelhi et al., 2020).

2.3.3 How do we interpret the Minimum Clinically Important Difference?

The aim of many clinical trials is to determine the efficacy of a new intervention (Sedaghat, 2019). This can be accomplished by determining whether positive, meaningful changes occurred among participants who received the intervention. In the context of this thesis, the primary objective is to define the MCID of the QOLCE-55 (Sedaghat, 2019). Once this number has been established, it can be used as a marker to indicate which patients have experienced a meaningful change. For instance, if the MCID was established to be 5 points, then patients who experienced an increase of at least 5 points between their pre and post-intervention HRQOL scores can be described as having experienced a positive, meaningful change in HRQOL. Patients who experienced no change or less than a 5-point increase from their pre- to post-intervention HRQOL scores can be described as not having experienced a meaningful change in their HRQOL.

2.3.4 Methods to be used to establish the minimum clinically important difference

There is currently no gold standard approach to determining the MCID of an outcome measure, however, it is typically recommended to use and report the findings from both anchor-

based and distribution-based methods (Guyatt et al., 2002; Mouelhi et al., 2020; Sedaghat, 2019; Wyrwich et al., 2005). Since distribution-based methods do not incorporate the perspective of patients receiving an intervention, they should only be used alone if using anchor-based methods is not feasible (Revicki et al., 2008). In fact, a recent systematic review of studies calculating MCIDs demonstrated that almost half of the 47 studies included used both types of methods (Mouelhi et al., 2020). In another systematic review, 37 of 46 (80%) studies used both anchor-based and distribution-based approaches to establish a MCID in cancer-specific outcome measures (Ousmen et al., 2018). Revicki et al. (2008) advocated for the use of an anchor-based method to provide the primary MCID estimate and a distribution-based approach to provide support for the estimate obtained from the anchor-based method. Despite this suggestion, there is currently no universal approach for how to derive a single MCID value if anchor-based and distribution-based calculation methods lead to different values (Sedaghat, 2019). Since MCID values likely differ across patient populations or anchors, it is suggested to report a range of MCIDs rather than one value (Guyatt et al., 2002; Hays & Woolley, 2000). Previous literature has reported more than one MCID value obtained from both anchor-based and distribution-based approaches (Alma et al., 2019; Gagnier et al., 2018; Terwee et al., 2010; Yost et al., 2005). Establishing a MCID range from multiple methods can be facilitated by plotting the estimates obtained from both distribution- and anchor-based methods on the same graph (Yost & Eton, 2005). However, presenting a MCID range may make interpretation difficult in certain scenarios (Yost et al., 2005). For instance, when a participant experiences a change in outcome score that falls within the MCID range, choosing whether to interpret the change using the higher or lower

end of the MCID range depends on two factors (Yost et al., 2005). First, it is important to consider that the false negative rate may increase (i.e., classifying a change in an outcome score as not meaningful when it is) when interpreting an outcome score based on the high end of the MCID range (Yost et al., 2005). Similarly, if one chooses to interpret a study finding on the lower end of the MCID range, the false positive rate may increase (i.e., classifying a change in an outcome score as meaningful when it is not) (Yost et al., 2005). Furthermore, deciding which end of the range to use depends on whether change is assessed in each individual participant or as an average change experienced by a group of participants (Yost et al., 2005). Previous literature suggests that the approach to interpreting meaningful change varies at the group level, where smaller changes can be defined as significant, and the individual level, where a greater change is needed to define a change as meaningful (Beaton et al., 2001; Crosby et al., 2003; Rai et al., 2015). Due to the phenomena of intra-individual variability and measurement error, it may be more appropriate to interpret changes in individual participants according to the higher end of the MCID range (Yost et al., 2005). If the outcome of interest is the mean change score in a group, which better controls for measurement error, then it may be more appropriate to interpret the findings based on the lower end of the MCID range (Yost et al., 2005). Based on these findings, both anchor and distribution-based methods will be used here to report plausible estimates for the MCID of the QOLCE-55.

In terms of relevant anchor-based methods, simple linear regression analysis has been used to calculate the MCID values of several HRQOL measures administered to a sample of adult patients with epilepsy (Wiebe et al., 2002). In this study, a fifteen-point global ratings scale

ranging from -7 (a very great deal worse) through 0 (no change) to +7 (a very great deal better) was used as the anchor (Jaeschke et al., 1989; Wiebe et al., 2002). This study identified a global rating score of 3 (somewhat better) as the MCID and calculated the associated change in HRQOL from a fitted regression line (Wiebe et al., 2002). This value was obtained from an earlier study in which adult patients with medically refractory epilepsy were asked to identify what they perceived was the minimum amount of meaningful change in HRQOL on a seven-point scale ranging from 1 (no change at all) to 7 (a very great deal of change) (Wiebe & Matijevic, 2000). Following the precedent that has been set by Wiebe et al. (2002), the same cutoff score and approach will be used here to establish the MCID for a HRQOL measure administered to parents of CWE. Furthermore, given that regression analysis would be useful in providing estimates of the mean change in HRQOL score for all levels of perceived change on the global ratings scale (Coeytaux et al., 2006), simple linear regression analysis will be used as the anchor-based approach here to establishing the MCID for the QOLCE-55 and QOLCE-16.

In the context of distribution-based methods, a systematic review of 38 MCID studies reported that most meaningful changes in HRQOL fell within 0.5 standard deviation units of the score distribution (Norman et al., 2003). Furthermore, the method employing multiples of standard deviation method was highlighted as the most commonly used distribution-based approach in two recent systematic reviews of studies determining a MCID (Mouelhi et al., 2020; Ousmen et al., 2018). Accordingly, 0.5 standard deviation units of the mean change in QOLCE-55 and QOLCE-16 score will be used as the distribution-based approach to calculate MCID. The

findings obtained from both the regression and standard deviation methods will be used to provide a range of plausible MCID values for the QOLCE-55 and QOLCE-16.

CHAPTER 3

METHODS

3.0 Introduction

The purpose of this chapter is to discuss the specific methodology used in this thesis. The first section discusses the source of the data, the Making Mindfulness Matter© in Children with Epilepsy trial (M3-E), being used to estimate the MCID values of the QOLCE-55 and QOLCE-16. The study population, intervention and timeline are also discussed in this chapter. How HRQOL, sociodemographic features, and clinical characteristics of the sample are measured is outlined. This chapter also includes a section discussing the scoring process for the QOLCE-55, QOLCE-16, and PCGRC. The next section discusses the methodology used to estimate the MCID values in detail. Finally, the last section in this chapter will go over the additional steps taken to ascertain the validity of the estimates obtained from the anchor-based method for MCID estimation.

3.1 Methods

3.1.1 Data source and study population

The data for this thesis were obtained from the Making Mindfulness Matter© in Children with Epilepsy trial (M3-E) (Puka, Bax, et al., 2020). This trial was approved by the Western

University Health Sciences Ethics Board Western Research Ethics Board (ethics # 113896). M3-E is a pilot, parallel, partially nested randomized controlled trial designed to evaluate the feasibility of implementing a program, Making Mindfulness Matter (M3)©, as an intervention for CWE (Puka, Bax, et al., 2020). The evidence related to the mental health, cognitive functioning, behaviour, and overall HRQOL of CWE demonstrated a need for an intervention that addresses these concerns (Baca et al., 2011; Baker, 2006; Malhi & Singhi, 2005; Ott et al., 2003; Reilly et al., 2011, 2014; Schraegle & Titus, 2016). Although cognitive behavioural therapy is a commonly used intervention in adults, the associated costs and wait times limit its accessibility as an intervention for CWE (Puka, Bax, et al., 2020). Mindfulness-based programs are more accessible as they can be delivered in group settings at low-cost by non-clinician staff (Puka, Bax, et al., 2020). Previous research also found that mindfulness-based interventions improved HRQOL among adult patients with epilepsy (Tang et al., 2015). As such, M3 was evaluated as an intervention in CWE and their families, and delivered online by non-clinician staff from a local epilepsy agency, Epilepsy Southwestern Ontario (ESWO) (Puka, Bax, et al., 2020).

M3-E participants were recruited from the population of pediatric patients being managed for epilepsy by one pediatric neurology clinic in Windsor, Ontario and the Division of Pediatric Neurology, Children's Hospital at London Health Sciences Center between December 2nd, 2019 and December 12th, 2022 (Puka, Bax, et al., 2020). Passive recruitment strategies were also implemented in collaboration with community agencies through the form of social media posts and e-posters. Child-parent dyads were randomized 1:1 into the intervention or control group

(Puka, Bax, et al., 2020). Inclusion criteria for participants are as follows: 1) child ages 4 to 10 years old; 2) child diagnosed with epilepsy for at least 6 months, according to the 2014 ILAE operational definition (Fisher et al., 2014); 3) child and parent have an adequate understanding of verbal messages and the ability to follow straightforward verbal instructions; 4) child and parent are willing to attend all M3 sessions; 5) child and parent have an adequate understanding of English language (Puka, Bax, et al., 2020). Since M3 was delivered online, CWE and their families were required to have reliable access to a computer and/or mobile device and the Internet (Puka, Bax, et al., 2020). Participants were also required to be Ontario residents so they can be mailed the program materials in a timely manner. Exclusion criteria are as follows: 1) diagnosed with other progressive or degenerative neurological disorders; 2) have other non-neurological comorbidities; 3) scheduled for epilepsy surgery during the study period; 4) child or parent routinely participates in complementary health interventions such as meditation; 5) currently enrolled in other intervention trials.

3.1.2 Study Intervention

Making Mindfulness Matter (M3)© is a mindfulness-based program that teaches skills in mindful awareness, social-emotional learning, neuroscience, and positive psychology (Puka, Bax, et al., 2020). The lessons in mindful awareness encourage participants to take a moment to consider their breathing, thoughts, feelings, and environment. Social-emotional learning teaches participants how to regulate their emotions and behaviour, especially in times of stress, and also teaches perspective taking. Neuroscience is discussed to teach children and parents how parts of

the brain function in times of stress. Lessons in positive psychology encourage participants to practice gratitude and frame negative thoughts into more positive ones. The program was delivered over the course of 8 weeks with a weekly 1-hour session for CWE and 1.5-hour session for parents. M3 was delivered online by non-clinician staff from a local epilepsy agency. To ensure standardization across groups, facilitators were provided the same protocol, script, and presentation slides for each session. There was also a research assistant present throughout all sessions for both the child and parent groups. The role of the research assistant was to assist with the research tasks associated with the program such as taking session notes and facilitating the completion of participant questionnaires. The intended goal of M3 is to teach skills that can ultimately improve the HRQOL of CWE, reduce parental stress, and promote a healthy child-parent relationship (Puka, Bax, et al., 2020).

3.1.3 Study Design

The HRQOL of CWE was measured at three time points for participants randomized to the intervention group: 0-2 weeks prior to the first M3 session (week 0; baseline), one week after the last M3 session (week 9; immediate follow-up) and 10 weeks after the last M3 session (week 18; extended follow-up). For participants randomized to the waitlist control group, measurement was conducted at two time points: baseline and immediate follow-up. Participants in the waitlist control group completed the baseline and immediate follow-up questionnaires at similar times relative to the intervention group. After completing the immediate follow-up questionnaire, participants in the waitlist control group were enrolled in the next scheduled M3 session rather

than having to wait to complete the extended follow-up questionnaire before being offered the intervention. The intent of this decision was to retain participants and avoid a potentially higher attrition rate in the waitlist control group (Puka, Bax, et al., 2020). Since data were collected at extended follow-up (week 18) only from participants in the intervention group, all analyses for this thesis were conducted using data obtained at immediate follow-up (week 9), henceforth referred to here as the "follow-up". In terms of MCID calculation, the HRQOL scores of participants from different arms (intervention or waitlist control) were merged to generate one variable for analyses in this thesis. As for participants who were lost to follow-up, we compared the baseline characteristics of those without follow-up data (QOLCE-16 or QOLCE-55) with the baseline characteristics of participants who remained in the study to determine if there are any differences between these subsamples. This can provide information regarding the generalizability of the study findings.

3.2 Measurement

3.2.1 Measurement of sociodemographic characteristics

All participant data were collected through the Research Electronic Data Capture (REDCap) data management platform (Harris et al., 2019). Parents self-reported the sociodemographic characteristics of their family such as the child's gender, age, and comorbidities (Puka, Bax, et al., 2020). Parents were also asked to report on their own gender,

age, educational level, occupation, and marital status (Puka, Bax, et al., 2020). The demographics questions completed by parents can be found in the appendix (See Appendix A).

3.2.2 Measurement of clinical characteristics

Parents were asked to rate the severity of their child's epilepsy using the Global Assessment of the Severity of Epilepsy (GASE), which is a single-item, 7-point global rating scale (Speechley et al., 2008). Additional items were added to collect information from the parent regarding their child's epilepsy, such as the frequency of their child's seizures (i.e., daily, weekly, monthly, every 3 months, every 6 months, or no seizures in the last year).

Information regarding children's comorbidities was also collected using parent self-report. Parents were specifically asked: "Has your child ever been formally diagnosed by a health or mental health professional with:" for a list of seven specific conditions (developmental delay, learning disability, autism, oppositional defiant disorder, depression, and anxiety). The section completed by parents regarding their child's clinical characteristics can be located in the appendix (See Appendix A).

3.2.3 Measurement of health-related quality of life

The QOLCE-55 was used to evaluate the HRQOL of CWE as reported by their parents and results in a total score ranging from 0 to 100, with a higher score indicating better HRQOL (Goodwin et al., 2015; Puka, Goodwin, et al., 2020). The QOLCE-55 can be found in the appendix (See Appendix B). The QOLCE-55 comprises four subscales assessing children's physical, emotional, social, and cognitive functioning (Goodwin et al., 2015).

In the event that a participant withdrew, they were provided the opportunity to complete the parent-reported QOLCE-16 at the immediate and/or extended follow-up. The QOLCE-16 is a validated and shortened version of the QOLCE-55 comprising 16 items and taking approximately 5 minutes to complete (Goodwin et al., 2018; Puka, Goodwin, et al., 2020). The questions found in the QOLCE-16 can also be located in the appendix (See Appendix C).

It is important to note that parents completed either the QOLCE-55 or the QOLCE-16 at follow-up. Since the QOLCE-16 consists of a subset of sixteen questions contained within the QOLCE-55, it is possible to calculate QOLCE-16 scores from completed QOLCE-55 questionnaires. Furthermore, the literature demonstrates that the QOLCE-16 generates mean overall HRQOL scores comparable to those obtained from the QOLCE-55 (Goodwin et al., 2018). As such, for participants who completed the QOLCE-55 at a time point, it was possible to generate scores for both the QOLCE-55 and the QOLCE-16. For participants who withdrew but completed the QOLCE-16 at follow-up, only their QOLCE-16 scores were included in the analyses.

The Patient-Centered Global Ratings of Change (PCGRC) was used to ask parents to report any changes their child had experienced since baseline in five areas assessed by the QOLCE-55: overall HRQOL, physical function, emotional function, cognitive function, and social function (Jaeschke et al., 1989). The PCGRC can be viewed in the appendix (See Appendix D). The PCGRC acted as the anchor for MCID calculation, which means the scores from the PCGRC were compared to the scores from the QOLCE-55 and QOLCE-16 to calculate their MCIDs. Participants first rated the five areas as worse, about the same, or better compared

to 9 and/or 18 weeks earlier (i.e., compared to the time when they completed the initial QOLCE-55/QOLCE-16 questionnaire). The scale offered no further follow-up questions if a participant responded “About the same” in an area on the PCGRC. If a participant reported improvement in an area, the scale offered 7 response options: (+1) a tiny bit better (almost the same); (+2) a little bit better; (+3) somewhat better; (+4) moderately better; (+5) quite a bit better; (+6) a great deal better; (+7) a very great deal better. If a participant reported deterioration in an area, the scale offered 7 response options: (-1) a tiny bit worse (almost the same); (-2) a little bit worse; (-3) somewhat worse; (-4) moderately worse; (-5) quite a bit worse; (-6) a great deal worse; (-7) a very great deal worse. For ease of interpretation of the results, the global ratings have been categorized into 4 categories of change: no change, small change, moderate change, and large change. Global rating scores between 0 and ±1 represent a benchmark for no change, -2 to -3 or 2 to 3 for a small change, -4 to -5 or 4 to 5 for a moderate change, and -6 to -7 or 6 to 7 for a large change (Juniper et al., 1994). These categories have been validated and used in studies with various patient populations (Bächinger et al., 2020; Basra et al., 2015; Juniper et al., 1994; Myles et al., 2016; Wiebe et al., 2002).

Prior to performing data analyses, a quality control process of the data was conducted. For instance, the credibility of responses to items in the QOLCE-55 and QOLCE-16 was evaluated. Some items were positively worded (e.g., question 1.2 part (j) asks “During the past 4 weeks, how much of the time do you think your child felt valued?”) while others were more negatively worded (e.g., question 1.2 part (k) asks “During the past 4 weeks, how much of the time do you think your child felt no one cared?”) (See Appendix B). Including positively and

negatively worded items in the questionnaire encourages engaged participants to respond differently for subsequent items (Sauro & Lewis, 2011). When responses do not vary in a way that matches the pattern of positivity vs. negativity, there is reason to question validity, especially if the completion time for a particular measure stands out as being much shorter than typical for other respondents.

3.2.4 Scoring Process

To generate a total HRQOL score from the QOLCE-55 data following the scoring guidelines, the numeric value of each response option on the QOLCE-55 was converted to a 0-100 point scale (Goodwin et al., 2015). Scores for items with the response options of "Very Often/All of the time", "Fairly Often/Most of the time", "Sometimes/Some of the time", "Almost Never/A little of the time", and "Never/None of the time" were coded as 0, 25, 50, 75, and 100, respectively, with higher scores indicating better HRQOL. The response options for fourteen items in the QOLCE-55 were then recoded in reverse order so that higher scores consistently indicate higher well-being. For example, the item 1.2 part (a) asks "During the past 4 weeks, how much of the time do you think your child felt down or depressed?" (See Appendix B). The response option "All of the time" should be coded as 0 for this item as it indicates lower well-being. On the contrary, the item 1.2 part (b) asks "During the past 4 weeks, how much of the time do you think your child felt happy?" (See Appendix B). The response option "All of the time" should be reverse coded as 100 as it indicates higher well-being. Scores for the response options "All of the time", "Most of the time", "Some of the time", "A little of the time", and

"None of the time" were recoded as 100, 75,50, 25, and 0 for items 1.2 parts (b),(f),(g), (h), and (j). Items with the response options "Very Often", "Fairly Often", "Sometimes", "Almost Never", and "Never" were coded as 100, 75,50, 25, and 0 for item 1.3 part (e) and question 1.5 parts (b) through (i). The response option "Not applicable" was coded as a missing value. The mean value of each QOLCE-55 subscale (cognitive, social, emotional, and physical) was calculated with the number of items answered as the denominator. The total HRQOL score was determined by calculating the unweighted mean of the four subscales (Goodwin et al., 2015). In the context of missing data, a subscale was considered missing and excluded from total score calculation if more than 20% of the items were left unanswered (Goodwin et al., 2015; E. Wirrell et al., 2005). Furthermore, if one or no subscale was missing, the total HRQOL score was determined by calculating the mean of the remaining subscales and assigning the resulting value to the missing subscale. In the event that more than one subscale was missing, the total HRQOL score for a participant was considered missing and excluded from analyses (Goodwin et al., 2015; Wirrell et al., 2005).

A similar process was used to create a total HRQOL score from the QOLCE-16 data (Goodwin et al., 2018). The response options "Very Often/All of the time", "Fairly Often/Most of the time", "Sometimes/Some of the time", "Almost Never/A little of the time", and "Never/None of the time" were coded as 0, 25, 50, 75, and 100, respectively, with higher scores indicating better HRQOL. Four items in the QOLCE-16 were then recoded in reverse order. The response options "All of the time", "Most of the time", "Some of the time", "A little of the time", and "None of the time" were recoded as 100, 75,50, 25, and 0 for section 2 part (d) (See

Appendix C). The response options “Very Often”, “Fairly Often”, “Sometimes”, “Almost Never”, and “Never” were recoded as 100, 75,50, 25, and 0 for section 4 parts (a), (b), and (c). The response option “Not applicable” was coded as a missing value. A mean value was calculated for each of the four QOLCE-16 subscales. The denominator (maximum of 4 items) was adjusted to include non-missing items. If more than two items were missing in a subscale, the subscale was considered missing. The total HRQOL score was calculated by taking the unweighted mean of the four subscales. If more than one subscale was missing, the total score was considered missing (Goodwin et al., 2018).

At follow-up, parents reported any changes their child experienced since baseline in five areas on the PCGRC. As mentioned in section 3.2.3, the PCGRC scale offers no further follow-up questions if a participant responded “about the same” for an area on the PCGRC. If a participant reported improvement or deterioration in an area, the PCGRC offered 7 response options. To generate a total score for the PCGRC, the responses for the first question in each subscale was recoded as: Worse (missing), about the same (0), and better (missing). The responses for the second question in each subscale, which provides the specific amount of change, were recoded as: A very great deal worse (-7); a great deal worse (-6); a good deal worse (-5); moderately worse (-4); somewhat worse (-3); a little worse (-2); almost the same, hardly worse at all (-1); almost the same, hardly better at all (+1); a little better (+2); somewhat better (+3); moderately better (+4); a good deal better (+5); a great deal better (+6); a very great deal better (+7). The response option “Not applicable” was also coded as a missing value. A mean

value was calculated for each subscale and the mean of the five PCGRC subscales was used as the total PCGRC score in analysis.

3.3 Data Analysis

All statistical analyses were conducted using SAS software Version 16.1. Both anchor-based and distribution-based methods were used to provide a range of plausible values for the MCID of the QOLCE-55. In terms of the distribution-based methods, 0.5 standard deviation units of the QOLCE-55 change score distribution was used to calculate the MCID. In the context of anchor-based approaches, linear regression analysis was used to evaluate the relationship between the parent-reported PCGRC score and QOLCE-55 change score (immediate follow-up score minus baseline score) as well as between the PCGRC ratings and QOLCE-16 change score (follow-up score minus baseline score). Using Cohen's conventions, Revicki et al. (2008) suggested that the correlation between the outcome measure and the anchor should be at least 0.30 for an anchor to be considered appropriate for MCID calculation. Cohen's conventions state that a correlation of 0.1 is considered a small correlation, a correlation of 0.3 is considered a moderate correlation, and a correlation of 0.5 is considered a large correlation (Cohen, 1977). The guideline suggested by Revicki et al. (2008) has been commonly used in MCID literature (Bedard et al., 2014; Chan et al., 2018; Mathias et al., 2011; Raman et al., 2018; Sagberg et al., 2014; Yost et al., 2011). In this thesis, the guideline suggested by Revicki et al. (2008) was used to help ascertain the appropriateness of the PCGRC as an anchor. The correlation between the QOLCE-55 and QOLCE-16 change scores and the corresponding PCGRC ratings was assessed

using the Spearman rank correlation coefficient. Using methods similar to Wiebe et al. (2002), estimates of change in HRQOL, and the associated 95% confidence intervals, were obtained from a fitted regression line based on the midpoint of the four categories of change established by Juniper et al. (1994): 0.5 as no change; 2.5 as small change; 4.5 as moderate change; and 6.5 as large change. The fitted regression line was forced through the origin, since a zero on both the PCGRC and QOLCE-55 change score indicate no change in HRQOL has occurred. The estimated HRQOL score difference associated with a global rating of 3 on the PCGRC was also obtained from the fitted regression line to represent the MCID of the QOLCE-55. In other words, the MCID was calculated using the formula: QOLCE-55 score change = $\beta 1$ x PCGRC rating, where the estimated HRQOL score change associated with a global rating of 3 on the PCGRC was used to represent the MCID.

Additional steps were taken to ascertain the validity of the estimates obtained from the regression analyses. The following assumptions of linear regression were checked: a) there is a linear relationship between the dependent and independent variable; b) the residuals are normally distributed; c) the residuals are uncorrelated; and d) presence of homoscedasticity, or the variance of the residuals is constant (Barker & Shaw, 2015). To ascertain linearity, a scatterplot of the QOLCE-55 (or QOLCE-16) change scores and the PCGRC ratings was created. Normality of the residuals was assessed using the Kolmogorov-Smirnov test (Berger & Zhou, 2014). For this test, the null hypothesis states that the data are normally distributed, therefore, a p value greater than 0.05 indicates the residuals are normally distributed (Barker & Shaw, 2015). Normality of the residuals was also assessed graphically by plotting the empirical quantiles of

the residuals against the theoretical quantiles of a normal distribution, commonly known as a quantile-quantile (QQ) plot. In a QQ plot, a straight line suggests normality of the residuals while a non-linear relationship suggests non-normality. The correlation of the residuals was assessed using the Durbin-Watson (DW) test. The null hypothesis states that there is a lack of correlation in the residuals, therefore, a p value < 0.05 indicates that there is evidence of correlation in the residuals. Presence of homoscedasticity was assessed graphically, where residuals were plotted against the predicted values of the dependent variable. If the homoscedasticity assumption is met (residuals have constant variance), there should be no pattern or linear relationship visualized in the data (Barker & Shaw, 2015). If all assumptions are met, we can have confidence in the regression coefficients obtained from analyses.

CHAPTER 4

RESULTS

4.0 Introduction

This chapter includes the results obtained from the analyses. The first section reports the findings obtained from the descriptive analyses. The next section includes the mean scores and mean change scores for the QOLCE-55 and QOLCE-16 at baseline and follow up. The following section provides the mean PCGRC ratings. Before the MCID values are reported, we included a section on the results from the assumption check for linear regression. The subsequent section reports the MCID values obtained from the anchor-based and distribution-based approaches. The last section in this chapter includes the estimates of change in HRQOL, and the associated 95% confidence intervals, based on the four categories of HRQOL change on the PCGRC: 0.5 as no change; 2.5 as small change; 4.5 as moderate change; and 6.5 as large change.

4.1 Sample Characteristics

4.1.1 Sociodemographic and Clinical Characteristics (for sample with follow-up data)

The M3-E randomized controlled trial randomized a total of 85 parent-child dyads to the intervention or waitlist group. We have QOLCE-55 or QOLCE-16 data from 75 parent-child dyads at baseline and follow-up. During the data quality checking process, the decision was made to exclude one parent-child dyad from the analyses as their HRQOL data at follow-up were considered invalid based on the fact that the parent responded “Never” or “None of the time” for all items on the QOLCE-55, regardless of whether the item was positively or negatively worded and the length of time taken to complete the QOLCE-55 (42 seconds) was considerably shorter than other participants. For context, the mean QOLCE-55 completion time was 7.5 minutes (standard deviation = 4.0) at baseline and 6.5 minutes (standard deviation = 4.4) at follow-up. Thus, the final sample available for analysis using QOLCE-55 or QOLCE-16 data was 74 parent-child dyads.

In the study sample of 74 CWE, more than half were male (58%) and the average age was 8 years old. The frequency of seizures varied greatly across the sample. In the sample of 74 parent-child dyads, a fifth (19%) of parents reported that their child had seizures daily while almost half (39%) of parents reported their child have had no seizures in the past year. The remainder of parents reported that their children had seizures weekly (14%), monthly (8%), every 3 months (9%), or every 6 months (11%). The presence of comorbidities such as

developmental delay, learning disability, depression, ADHD or ADD, autism, oppositional defiant disorder or conduct disorder, and anxiety was also documented by parent-report. In the sample of 74 parent-child dyads, 36 parents (49%) reported that their child had been formally diagnosed with at least one of the listed comorbidities. The most common comorbidities present in this sample were developmental delay (28%), learning disability (30%), ADD or ADHD (19%), and anxiety (18%).

In terms of parents' characteristics, most parents who participated in M3-E were female (95%), had attended college or university (66%), were currently working (65%), and living with a spouse or partner (89%). The baseline characteristics of all child and parent participants (n=74) in M3-E are reported in Table 1 and Table 2, respectively.

4.1.2 Sociodemographic Characteristics, Clinical Characteristics, and Mean QOLCE Scores (for sample with no follow-up data)

The M3-E randomized controlled trial randomized a total of 85 parent-child dyads to the intervention or waitlist group. During the data quality checking process, the decision was made to exclude one parent-child dyad from the analyses as their HRQOL data at follow-up were considered invalid for reasons stated in section 4.1.1. In the remaining sample of 84 parent-child dyads, follow-up data is missing for 10 dyads.

In the sample of 10 CWE, more than half were female (56%) and the average age was 7 years old. The frequency of seizures also varied across this sample. In the sample of 10 parent-child dyads, two parents (20%) reported that their child had seizures daily while six parents

(60%) reported their child have had no seizures in the past year. Of the remaining two parents, one reported their child had seizures weekly (10%) while the other parent reported their child had seizures monthly (10%). The presence of comorbidities such as developmental delay, learning disability, depression, ADHD or ADD, autism, oppositional defiant disorder or conduct disorder, and anxiety was also documented by parent-report. In the sample of 10 parent-child dyads, five parents (50%) reported that their child had been formally diagnosed with at least one of the listed comorbidities. The most common comorbidities present in this sample were developmental delay (20%), learning disability (20%), and ADD or ADHD (40%). In terms of the mean QOLCE scores, the mean (standard deviation) QOLCE-55 score at baseline (n=8) was 64.3 (13.3) and the mean (standard deviation) QOLCE-16 score at baseline (n=10) was 58.9 (19.4).

4.2 Mean QOLCE Scores

The mean (standard deviation) QOLCE-55 scores at baseline and follow-up were 58.9 (16.6) and 62.7 (16.7), respectively. The mean QOLCE-55 score change from baseline to immediate follow-up was 2.9 (11.7).

For the QOLCE-16, the scores at baseline and immediate follow-up were 60.6 (18.8) and 64.8 (18.1), respectively. The mean QOLCE-16 score change from baseline to follow-up was 4.2 (13.2). The mean QOLCE-55 and QOLCE-16 scores and change scores at baseline and follow-up were provided in Table 2.

4.3 Mean PCGRC Scores

A total of 73 participants completed the PCGRC at follow-up. The mean (standard deviation) of the summary global ratings score was 0.7 (1.5). Using the categories of change established by Juniper at. al (1994) (0.5 as no change; 2.5 as small change; 4.5 as moderate change; and 6.5 as large change), 50 parents reported no change (-1, 0, or 1 on the PCGRC) in their children's HRQOL, 20 parents reported a small change (-2, -3, 2, or 3 on the PCGRC), 2 parents reported a moderate change (-4, -5, 4, or 5 on the PCGRC), and 1 parent reported a large change (-6, -7, 6, or 7 on the PCGRC). The PCGRC shows that 23 parents reported improvement in their child's overall HRQOL (>1 on the PCGRC), 44 as unchanged (-1, 0,1 on the PCGRC), and 6 reported their child's overall HRQOL worsened (<-1 on the PCGRC).

4.4 MCID Values

4.4.1 Assumptions: QOLCE-55 change score and PCGRC ratings

In figure 1, the relationship between QOLCE-55 change scores and the PCGRC ratings can be visualized. There seems to be a positive linear relationship between these two variables, thus, the linearity assumption has been met. Next, normality of the residuals was assessed using the Kolmogorov-Smirnov test (Berger & Zhou, 2014). The statistic obtained was 0.10 with a p-value of 0.07, meaning that we failed to reject the null hypothesis. The null states that the residuals are normally distributed, indicating that a p value greater than 0.05 is evidence for normality. Since the Kolmogorov-Smirnov can only detect strong evidence of non-normality (Barker & Shaw, 2015), we also assessed normality graphically. A QQ plot was used to assess

the normality of the residuals (See Appendix E). Most of the data follows a straight line, demonstrating that the data is approximately normal. The correlation of the residuals was assessed using the Durbin-Watson test. The Durbin-Watson statistic obtained was 1.92 (Pr < DW of 0.37 and Pr > DW of 0.63). When conducting a Durbin-Watson test on SAS, it is noted that Pr < DW is the p-value testing for positive correlation in the residuals while Pr > DW is the p-value testing for negative correlation. Both p-values obtained are greater than 0.05, thus, we have evidence to suggest that the residuals are not correlated. Finally, homoscedasticity was checked by plotting the residuals against the predicted values of the QOLCE-55 change score (See Appendix E) (Barker & Shaw, 2015). There does not seem to be any clear linear or non-linear patterns between the residuals and the predicted values of the QOLCE-55 change scores. This indicates that the data meets the homoscedasticity assumption of linear regression. Therefore, linear regression analysis is appropriate to conduct between the QOLCE-55 change scores and PCGRC ratings.

4.4.2 Assumptions: QOLCE-16 change score and PCGRC ratings

The relationship between QOLCE-16 change scores and the PCGRC ratings can be visualized in Figure 2. There seems to be a positive linear relationship between these two variables, thus, the linearity assumption has been met. The normality of the residuals using the Kolmogorov-Smirnov test, which gave a statistic of 0.09 (p-value=0.10). Failing to reject the null implies that there is evidence suggesting normality in the residuals. We also assessed normality using a QQ plot (See Appendix E). Most of the data follows a straight line, suggesting

that the residuals of the QOLCE-16 change scores is approximately normal. The Durbin-Watson statistic obtained was 1.93 (Pr < DW of 0.39 and Pr > DW of 0.61). Both p-values obtained are greater than 0.05, thus, correlation was not detected between the residuals. Finally, homoscedasticity was evaluated by plotting the residuals against the predicted values of the QOLCE-16 change score (See Appendix E). The data do not appear to have a pattern and seem randomly dispersed throughout. This finding suggests that the QOLCE-16 data meets the homoscedasticity assumption of linear regression. Therefore, linear regression analysis is appropriate to conduct between the QOLCE-16 change scores and PCGRC ratings.

4.4.3 MCID Values for the QOLCE-55

Prior to calculating the MCID using anchor-based methods, correlation between the QOLCE-55 change scores and PCGRC ratings was assessed using Spearman's rank correlation coefficient. The Spearman correlation coefficient between the PCGRC and QOLCE-55 change score (baseline and follow-up) was 0.33 (p=0.007), which aligns with the guideline recommended by Revicki et al. (2008), described in section 3.3. This supports the suitability of the PCGRC as an anchor for the QOLCE-55.

Using the anchor-based approach, the MCID obtained for the QOLCE-55 was 10 points for changes in HRQOL score between baseline to follow-up, more specifically it was 9.8 [95% CI: 5.1, 14.5]. The regression coefficient that describes the association between the QOLCE-55 change score and the PCGRC ratings at follow-up was 3.3 (p<0.0001). This indicates that for each 1-unit increase in the parent-reported PCGRC rating, the QOLCE-55 score change from

baseline to follow-up increased by approximately 3.3 points. Figure 1 displays the scatterplot and fitted linear regression line showing the observed and predicted relationship between the change in QOLCE-55 scores (baseline to follow-up) and PCGRC ratings, respectively.

Using the distribution-based method, the MCID obtained for changes in HRQOL score between baseline to follow-up was 6 points for the QOLCE-55, more specifically 5.9. The standard deviation obtained for the QOLCE-55 score change between baseline to follow-up was 11.7 [95% CI: 10.0, 14.1]. The 0.5 standard deviation approach was used to determine the MCID, yielding 6 points.

4.4.4 MCID Values for the QOLCE-16

Prior to calculating the MCID using anchor-based methods, correlation between the QOLCE-16 change scores and PCGRC ratings was assessed using Spearman's rank correlation coefficient. For changes in QOLCE-16 score between baseline and follow-up, the Spearman correlation coefficient between the QOLCE-16 and PCGRC was 0.36 ($p=0.002$). The correlation coefficient between the QOLCE-16 change score and the PCGRC at follow-up was greater than 0.30, supporting its appropriateness as an anchor for MCID calculation.

Using the linear regression anchor-based approach, the MCID obtained for the mean change in QOLCE-16 score between baseline to follow-up was 13 points, more specifically 13.3 [95% CI: 8.3, 18.3]. The regression coefficient obtained for the immediate follow-up QOLCE-16 and PCGRC scores was 4.4 ($p<0.0001$), indicating that for each 1-unit increase in the parent-reported PCGRC score, the QOLCE-16 score change from baseline to follow-up increases by

approximately 4.4 points. The MCID was calculated using the formula: QOLCE-16 score change = β_1 x PCGRC rating, where the estimated HRQOL score change associated with a global rating of 3 on the PCGRC was used to represent the MCID. Figure 2 shows the scatterplot and fitted linear regression line demonstrating the observed and predicted relationship between the change in QOLCE-16 scores (baseline to follow-up) and PCGRC ratings, respectively.

Using the distribution-based approach for the QOLCE-16, the MCID obtained for changes between baseline to follow-up was 7 points for the QOLCE-16, more specifically 6.6. The standard deviation obtained for the score change was 13.2 [95% CI: 11.4, 15.8] between baseline to follow-up. The 0.5 standard deviation method was used to obtain the MCID using a distribution-based approach, yielding 7 points.

4.5 HRQOL scores and PCGRC ratings

Using the regression coefficient obtained from the regression analyses, the predicted mean change in QOLCE-55 score (baseline to follow-up) that corresponds to no change, small change, moderate change or large change on the PCGRC and their corresponding 95% confidence intervals were obtained. A change score of 1.6 on the QOLCE-55 [95% CI: 0.8, 2.4] was associated with no change (-1, 0, or 1 rating) on the PCGRC, a change score of 8.2 on the QOLCE-55 [95% CI: 4.2, 12.1] was associated with small change (-2, -3, 2, or 3 rating) on the PCGRC, a change score of 14.7 on the QOLCE-55 [95% CI: 7.6, 21.8] was associated with moderate change (-4, -5, 4, or 5 rating) on the PCGRC, and a change score of 21.2 on the QOLCE-55 [95% CI: 11.0, 31.4] was associated with large change (-6, -7, 6, or 7 on the

PCGRC) on the PCGRC. The predicted mean change score on the QOLCE-55 associated with the MCID (3 on the PCGRC) is 9.8 (95% CI: 5.1, 14.5).

Using the results from regression analysis, the predicted mean change on the QOLCE-16 (baseline to follow-up) that corresponds to no change, small change, moderate change or large change on the PCGRC and their corresponding 95% confidence intervals were also obtained. A change score of 2.2 on the QOLCE-16 [95% CI: 1.4, 3.0] was associated with no change (-1, 0, or 1 rating) on the PCGRC, a change score of 11.1 on the QOLCE-16 [95% CI: 6.9, 15.2] was associated with small change (-2, -3, 2, or 3 rating) on the PCGRC, a change score of 20 on the QOLCE-16 [95% CI: 12.5, 27.4] was associated with moderate change (-4, -5, 4, or 5 rating) on the PCGRC, and a change score of 28.8 on the QOLCE- [95% CI: 18.0, 39.6] was associated with large change (-6, -7, 6, or 7 on the PCGRC) on the PCGRC. The predicted mean change score on the QOLCE-16 associated with the MCID (3 on the PCGRC) is 13.3 (95% CI: 8.3, 18.3).

4.6 Summary of the MCID Values

4.6.1 Summary of the MCID Values for the QOLCE-55

The MCID obtained for the mean change in QOLCE-55 score between baseline to follow-up using an anchor-based method was 10 points. The MCID for the mean change in QOLCE-55 score between baseline to follow-up obtained using a distribution-based method was 6 points.

4.6.2 Summary of the MCID Values for the QOLCE-16

The MCID obtained for the mean change in QOLCE-16 score between baseline to follow-up using an anchor-based method was 13 points. The MCID for the mean change in QOLCE-16 score between baseline to follow-up obtained using a distribution-based method was 7 points.

Table 1: Baseline Characteristics of Child Participants

Variable	Mean (SD)
Age (years) (n=74)	8.2 (1.8)
	n (%)
Female (n=74)	31 (41.9)
Presence of at least one comorbidity (n=74)	36 (48.7)
Developmental delay (n=74)	21 (28.4)
Learning disability (n=74)	22 (29.7)
ADD or ADHD (n=74)	14 (18.9)
Autism, pervasive developmental disorder, or Asperger's syndrome (n=74)	1 (1.4)
Oppositional defiant disorder / conduct disorder (n=74)	2 (2.7)
Depression (n=74)	3 (4.1)
Anxiety (n=74)	13 (17.6)
Group assignment based on age/developmental level (n=74)	
Younger (4-6.99 years old)	14 (18.9)
Older (6-10.99 years old)	60 (81.1)
Severity of child's epilepsy (n=74)	
Extremely severe	3 (4.1)
Very severe	1 (1.3)
Quite severe	3 (4.1)
Moderately severe	10 (13.5)
Somewhat severe	12 (16.2)
A little severe	16 (21.6)
Not at all severe	29 (39.2)
Frequency of seizures (n=74)	
Daily	14 (18.9)
Weekly	10 (13.5)
Monthly	6 (8.1)
Every 3 months	7 (9.5)
Every 6 months	8 (10.8)
No seizures in the last year	29 (39.2)

Table 2: Baseline Characteristics of Parent Participants

Characteristic	n (%)
Female (n=74)	70 (94.6)
Work status (n=74)	
Not working due to child's health	7 (9.4)
Not working for other reasons	13 (17.6)
Working full-time	33 (44.6)
Working part-time	15 (20.3)
Not working outside the home	4 (5.4)
Student	2 (2.7)
Education (n=74)	
8-12 years	1 (1.4)
Completed high school	10 (13.5)
Completed vocational/technical training	2 (2.7)
Completed college/university	49 (66.2)
Completed a Masters, PhD, or professional degree	12 (16.2)
Living with a spouse or partner (n=74)	66 (89.2)

Table 3: Mean scores and mean change for QOLCE-55 and QOLCE-16

Instrument	Baseline	Follow-up	Change Score (Baseline to Follow-up)
QOLCE-55	58.9 (16.6)	62.7 (16.7)	2.9 (11.7)
n	70	70	66
QOLCE-16	60.4 (18.8)	64.8 (18.1)	4.2 (13.2)
n	74	74	74

Values are mean (SD)

Table 4: Predicted change in QOLCE-55 and QOLCE-16 scores from baseline to follow-up associated with no change, small change, moderate change, and large change categories and MCID on the PCGRC

Instrument	Regression Coefficient†	p-value	Magnitude of change in PCGRC	Predicted Change‡	95% CI
QOLCE-55 (Follow-up)	3.27	<0.0001	**MCID**	**9.80**	**(5.10, 14.51)**
			No change	1.63	(0.85, 2.42)
			Small	8.17	(4.25, 12.09)
			Moderate	14.70	(7.65, 21.76)
			Large	21.24	(11.04, 31.44)
QOLCE-16 (Follow-up)	4.43	<0.0001	**MCID**	**13.30**	**(8.33, 18.28)**
			No change	2.22	(1.39, 3.05)
			Small	11.08	(6.94, 15.23)
			Moderate	19.95	(12.49, 27.41)
			Large	28.82	(18.04, 39.60)

†The regression coefficients indicate the amount of change in HRQOL scores per 1-unit increase on the PCGRC

‡Predicted change = regression coefficient × amount of change in PCGRC

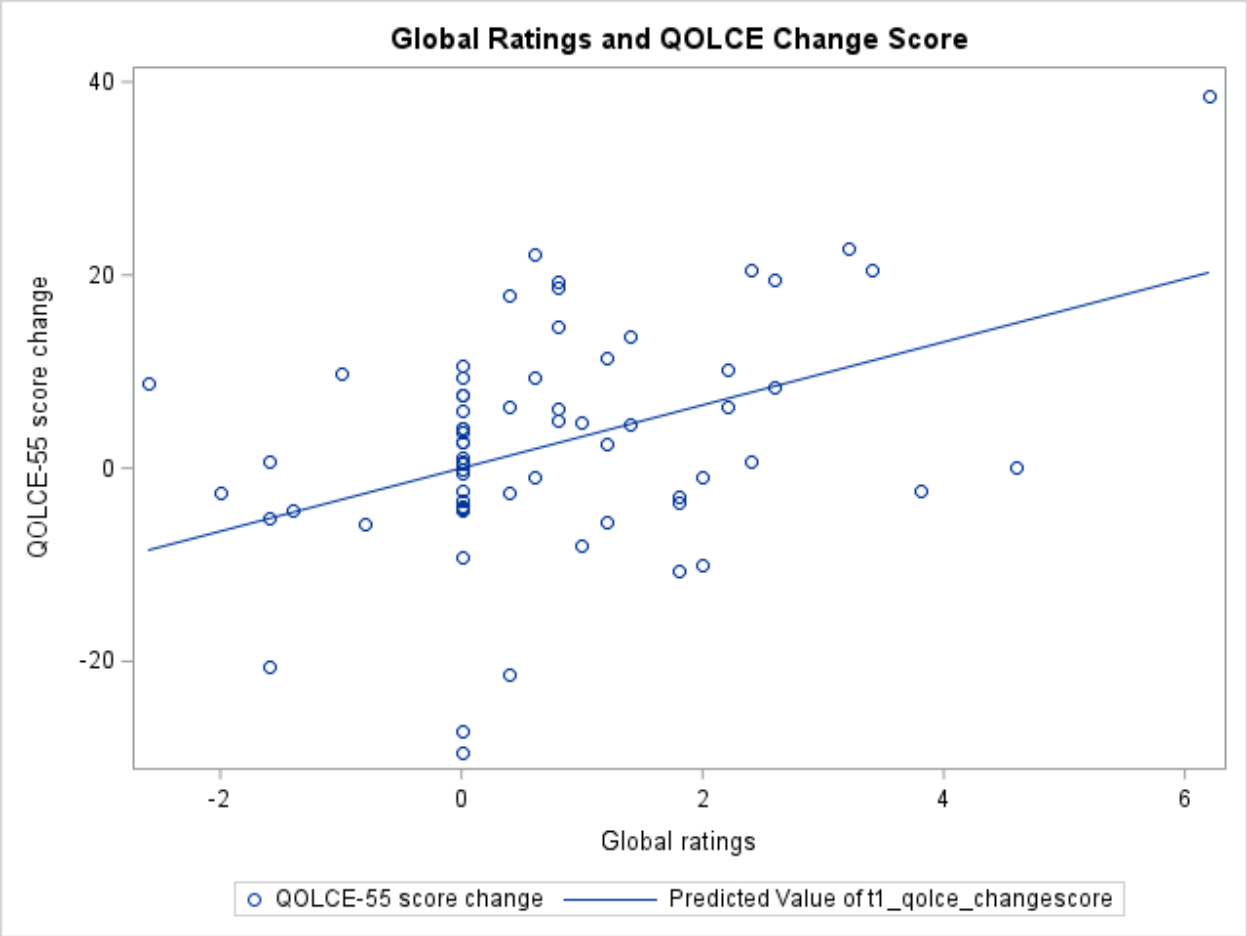

Figure 1: Scatterplot and fitted regression line demonstrating the observed and predicted relationship between the QOLCE-55 change scores (baseline to follow-up) and PCGRC ratings, respectively. The regression line has no intercept because zero indicates no change on the PCGRC and QOLCE-55 score change scale. The slope coefficient (β_1) is 3.27 and R^2 is 0.21. The regression equation is QOLCE-55 score change = β_1 x PCGRC rating. For a global rating of 3 on the PCGRC, the associated QOLCE-55 score change from baseline to follow-up is 9.8.

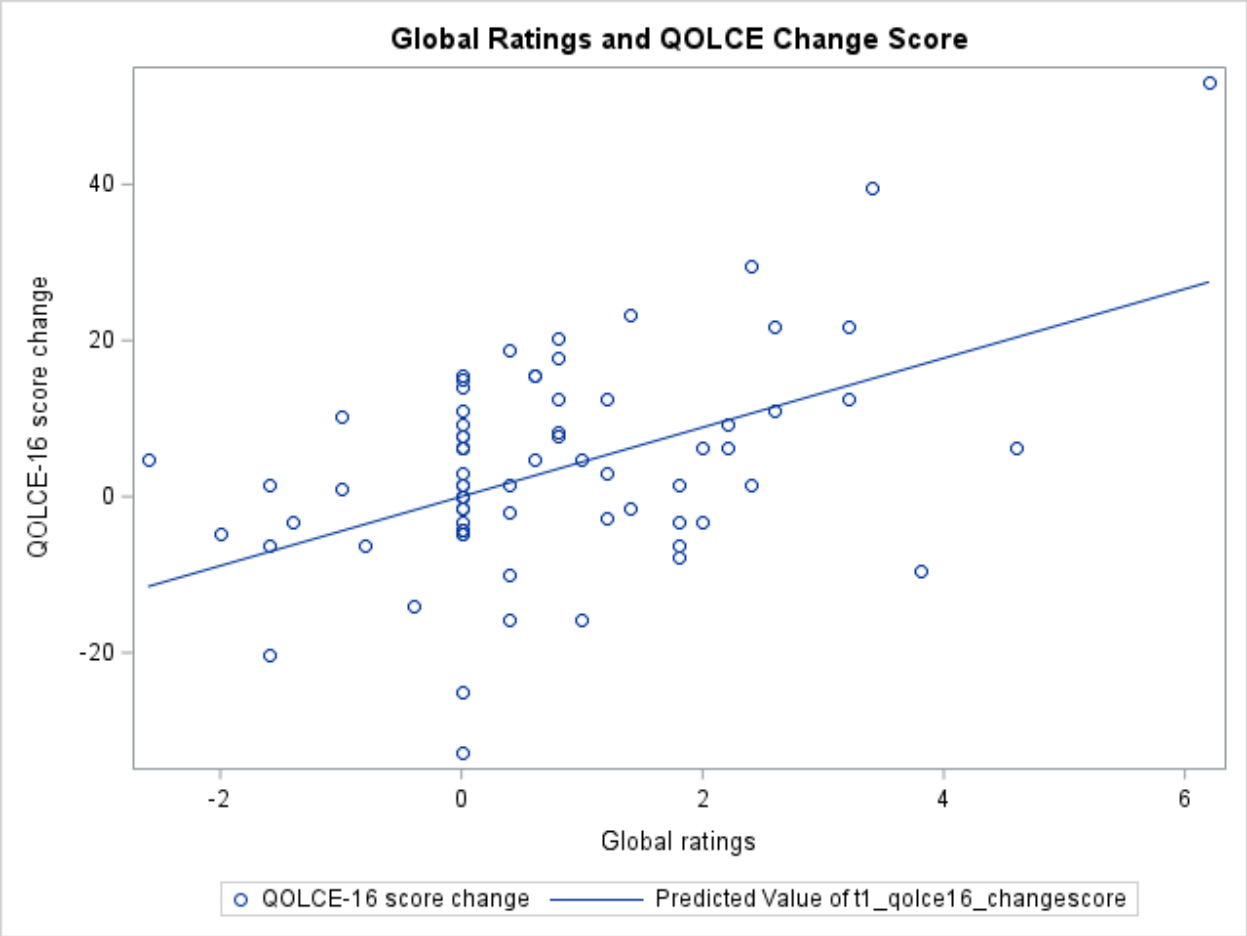

Figure 2: Scatterplot and fitted regression line demonstrating the observed and predicted relationship between the QOLCE-16 change scores (baseline to follow-up) and PCGRC ratings, respectively. The regression line has no intercept because zero indicates no change on the PCGRC and QOLCE-16 score change scale. The slope coefficient (β_1) is 4.43 and R^2 is 0.28. The regression equation is QOLCE-16 score change = β_1 x PCGRC rating. For a global rating of 3 on the PCGRC, the associated QOLCE-16 score change from baseline to follow-up is 13.3.

CHAPTER 5

DISCUSSION

5.0 Introduction

The goal of this chapter is to discuss the findings reported in the results section. First, a summary and interpretation of the MCID values in HRQOL scores reported for the QOLCE-55 and QOLCE-16 is provided. Since the MCID estimates obtained from the anchor-based and distribution-based methods differ in magnitude, the subsequent section discusses the factors that should be considered to help future investigators determine which MCID value to use in their research. The following section discusses anchor-based methods and distribution-based methods and provides an overview on which approach is preferred in the literature. Following this, an interpretation of the HRQOL estimates corresponding with the categories of HRQOL change on the PCGRC is provided. The subsequent sections provide an overview of the strengths and limitations of this thesis. Finally, this chapter ends with future directions that can be taken in subsequent studies and offers summary conclusions.

5.1 MCID Values

We estimated the MCID values in HRQOL score for the QOLCE-55 and QOLCE-16. To the best of our knowledge, this is the first study to provide MCID estimates for both of these HRQOL measures. For the QOLCE-55, the MCID for the mean change in HRQOL score from

baseline to follow-up using an anchor-based method was 10 points. The MCID for the mean change in HRQOL score using a distribution-based approach was 6 points.

In the context of the QOLCE-16, the MCID for the mean change in HRQOL score from baseline to follow-up using an anchor-based method was 13 points. The MCID for the mean change in HRQOL score from baseline to follow-up using the distribution-based approach was 7 points.

The MCID values obtained using anchor-based and distribution-based methods for both the QOLCE-55 and QOLCE-16 differ in magnitude. Therefore, section 5.2 will discuss which MCID values should be used in subsequent studies assessing changes in HRQOL score.

5.2 Interpretation of the MCID Values

Reporting a range of MCIDs rather than one MCID value may make interpretation difficult in scenarios where a participant experiences a change in HRQOL score that falls within the MCID range (Yost et al., 2005). Investigators should consider some factors when deciding which end of the MCID range to use in interpretation.

First, investigators should consider the implication of false negatives and false positives when using varying MCID estimates. If the higher end of the MCID range is chosen, investigators must recognize that the false negative rate may increase (i.e., classifying participants as not having experienced a meaningful change when, in fact, they have). On the contrary, the false positive rate may increase if the lower end of the MCID range is used for interpretation (i.e., classifying participants as having experienced a meaningful change when, in fact, they have not) (Yost et al., 2005). The consequences of increasing the false positive or false

negative rate should be thoroughly considered before deciding which value of the MCID range to use. Here are two examples to help illustrate this. In one hypothetical scenario, investigators conducting a pilot randomized controlled trial of an educational program to evaluate its impact on the HRQOL of CWE. They might decide to analyze the results of such a pilot trial using the lower end of the MCID range. This decision would likely increase the false positive rate, however, the consequences of this would not be serious. Even if investigators obtain preliminary results showing that the intervention has an effect on HRQOL, they would have to conduct larger subsequent trials to validate this finding. Furthermore, administering an educational program would have minimal to no negative consequences on a participant's health. Therefore, choosing the lower end of the MCID range is acceptable in this scenario. In another scenario, investigators conducting a large-scale randomized controlled trial to compare the impact two medications has on the HRQOL of CWE may choose to analyze their results using the lower end of the MCID range. As medications are involved in this study, the decision to choose the lower end of the MCID range might raise the false positive rate and lead to the recommendation of a drug that may not have a "true" positive impact on HRQOL. In this hypothetical trial involving medications, it may be more appropriate to analyze the results using the higher end of the MCID range to conduct a more conservative evaluation of the medication's effectiveness. Therefore, investigators should consider the context of their research along with the potential consequences of having higher false positive or false negative rates when deciding which end of the MCID range to use for their analysis.

The second factor to consider is the level at which change in HRQOL is being assessed. The method for interpreting meaningful change in HRQOL varies between the group and the

individual level (Beaton et al., 2001; Crosby et al., 2003; Rai et al., 2015). A greater change in HRQOL score (i.e., higher end of the MCID range) is required to be considered meaningful at the individual level due to the possibility of intra-individual variability and measurement error occurring (Yost et al., 2005). On the other hand, a smaller change in HRQOL (i.e., the lower end of the MCID range) can be identified as meaningful in group analysis because measurement error is better controlled for at the group level (Yost et al., 2005). Given these findings, it is important for investigators to consider the context in which HRQOL change will be assessed when deciding which value of the MCID range to use.

5.3 Anchor-based methods or distribution-based methods: Which are preferred?

Although there is no universal approach to estimating the MCID of an outcome measure, some authors recommend the use of anchor-based methods over distribution-based methods for estimating the MCID (Bonini et al., 2020; Hays et al., 2005; Make et al., 2005; McGlothlin & Lewis, 2014). Since the definition of MCID is “the smallest change that is important to patients” (Stratford et al., 1998), distribution-based methods are said to overlook the concept behind MCID due to their lack of patient-reported nature and should not be used as the primary method for MCID estimation (Bonini et al., 2020; McGlothlin & Lewis, 2014; Turner et al., 2010). In fact, some authors believe that results obtained from distribution-based methods should be used as an indicator for statistical significance rather than a MCID (Bonini et al., 2020; McGlothlin & Lewis, 2014; Turner et al., 2010).

Distribution-based methods can be used to estimate the minimum detectable change (MDC), which is a statistical parameter that represents "the smallest change in score that can be detected beyond measurement error" (Mokkink et al., 2010; Turner et al., 2010). As a measure of reliability, the MDC should be measured in participants who did not experience a change in the outcome using a test-retest design and the formula: $1.96 * SD_{change,}$ which equals $1.96 * \sqrt{2} *$ SEM (de Vet et al., 2011). The MDC reflects the random variation (e.g., measurement error) that occurs in score within participants (van der Willik et al., 2021). Therefore, any changes in an outcome that surpass the MDC can be considered statistically significant (van der Willik et al., 2021). Some studies suggest that distribution-based methods, such as the MDC, should be used to assist in the interpretation of MCID values obtained rather than to estimate the MCID (Bonini et al., 2020; McGlothlin & Lewis, 2014; Turner et al., 2010). Here are two examples to illustrate this. In a hypothetical scenario, investigators want to ascertain how many participants in their sample experienced a change in an outcome that is equal to or greater than the MCID, however, they have to choose between two different MCID values they obtained after applying two anchor-based methods to their sample. In another scenario, investigators with the same goal (of ascertaining how many participants experienced meaningful change) are having difficulty choosing between different MCID values reported by different studies for the same outcome measure. In both scenarios, comparing these MCID values to the minimum detectable change can facilitate the selection of one single MCID if the other value(s) falls below the minimum detectable change. Given these findings, subsequent researchers may consider interpreting changes in outcome score primarily based on the MCID values obtained from anchor-based

methods while using the minimum detectable change to help discriminate “true” changes from random variation (van der Willik et al., 2021).

5.4 Study Strengths

This thesis has several strengths. First, the data for this thesis came from randomized controlled-trial study with strong engagement among participants. Of the 85 participants who were randomized to a group for the M3-E trial, we have data for 74 participants on the QOLCE-16 at baseline and immediate follow-up and 66 participants on the QOLCE-55 at baseline and follow-up. Children who participated in M3-E were representative of various types of seizure frequencies, comorbidities, and socioeconomic backgrounds, which supports the generalizability of the findings.

This is the first study to estimate MCID values for the QOLCE-55, a commonly used measure of HRQOL in CWE, along with its shortened, validated measure, the QOLCE-16. As there is no universally accepted approach to estimating a MCID, this thesis used and reported the findings from both anchor-based and distribution-based methods, which is typically recommended (Guyatt et al., 2002; Mouelhi et al., 2020; Sedaghat, 2019; Wyrwich et al., 2005). This thesis also utilized recommended methods previously used in MCID estimation. We employed the standard deviation approach, which is cited as the most common distribution-based method (Mouelhi et al., 2020; Ousmen et al., 2018). In terms of anchor-based approaches, we performed linear regression analysis with the PCGRC acting as an anchor. In the study led by Wiebe et al. (2002), linear regression was employed to estimate MCID values for the Quality of Life in Epilepsy Inventory-89 (QOLIE-89) and its shortened version, the Quality of Life in

Epilepsy Inventory-31 (QOLIE-31) (Cramer et al., 1998; Devinsky et al., 1995). In this study, the PCGRC was also used as an anchor with a global rating of 3 as the cut-off for the MCID (Wiebe et al., 2002). The systematic review led by Mouelhi et al. (2020) found that there was no consistency in how cut-off values for anchors were assigned by authors. Therefore, using methods and cut-off values similar to Wiebe et al. (2002) is a strength because it maintains consistency with previous literature estimating MCID values for epilepsy-specific HRQOL measures. In addition, linear regression analysis was appropriate to perform using the M3-E data as the assumptions for linear regression were met (assumptions of linearity, normality, no correlation, and homoscedasticity) and it can provide estimates of the mean change in HRQOL score for all levels of change on the PCGRC rather than just the MCID alone (Coeytaux et al., 2006). The use of the PCGRC was also a strength because it incorporates the patient's perspective, it is intuitively easy to understand and administer, simple to score, and has been used in multiple studies (Basra et al., 2015; Fulk et al., 2010; Jaeschke et al., 1989; Kamper et al., 2009; Kvam et al., 2010, 2011; Kwakkenbos et al., 2013; Wiebe et al., 2002).

5.5 Study Limitations

This thesis also has some limitations. As the MCID values for this thesis were estimated using data from the M3-E trial, the original sample size calculation performed was not done for the purpose of detecting the MCID with 80% power ((Puka, Bax, et al., 2020). This was the first study to estimate MCID values for the QOLCE-55 and the sample size used was small (n=74). Therefore, it is important to consider these initial MCID estimates for the QOLCE-55 to be preliminary pending replication in large sample size.

Although the PCGRC is a good anchor to use, its cross-sectional nature comes with some limitations. Recall bias may be a concern since parents are asked if their child's HRQOL has improved over a period of 9 weeks (McGlothlin & Lewis, 2014). This limitation is based on Ross' theory of implicit change (Ross, 1989), which hypothesizes that people are less likely to remember their previous condition with accuracy. Instead, they examine their current state and then retrospectively construct an idea of how much change they experienced over time (Kamper et al., 2009; Ross, 1989). Therefore, when parents complete the global ratings of change scale, their responses may be more heavily influenced by the perception of their child's current health status rather than the actual change in HRQOL over time. Recall bias may result in an inaccurate reporting of the PCGRC ratings, which can lead to a biased estimate of the regression coefficients obtained in analyses.

Furthermore, the M3-E trial only included children between 4 to 10 years old. The QOLCE-55 is a validated measure of HRQOL in children between 4 to 18 years old as well as young adults between 18 to 29 years old (Conway et al., 2017; Puka, Goodwin, et al., 2020). Therefore, obtaining MCID values from a sample of CWE up to 10 years old reduces the generalizability of the results to CWE and young adults with epilepsy older than 10 years old. Repeating these MCID calculations in a sample of older CWE and young adults with epilepsy may help address this limitation.

There is also the possibility of attrition bias affecting the results, given there was a difference in mean HRQOL scores and prevalence of anxiety between participants who stayed in the study and those who were lost to follow-up. Participants lost to follow-up had a higher mean (standard deviation) QOLCE-55 score at baseline 64.3 (13.3) compared to participants retained

in the study 58.9 (16.6). Regarding anxiety, none of the parents lost to follow-up (n=10) reported their child had been formally diagnosed with anxiety while 13 parents in the retained subsample (n=74) reported their child had been formally diagnosed with anxiety. This indicates that retained participants on average had a lower HRQOL score at baseline and were more likely to have been diagnosed with anxiety than those lost to follow-up. This may limit the generalizability of the findings presented here.

5.6 Future directions

As this is the first study to report MCID values for the QOLCE-55 and QOLCE-16, further research is required to validate these findings and address the differences in the MCID values obtained. Several components of this thesis can be improved upon in subsequent research. Subsequent investigations with the primary goal of calculating a MCID for the QOLCE will provide the opportunity to ensure a sample size with adequate statistical power. Obtaining similar MCID values for the QOLCE-55 in a larger sample can help validate the findings reported in this thesis. Repeating MCID estimation in a larger sample size may also lead to more precise HRQOL estimates across all categories of change on the PCGRC. With the findings presented here, there is considerable overlap between the confidence intervals for the QOLCE-55 estimates corresponding with the small (95% CI: 4.25, 12.09), moderate (95% CI: 7.65, 21.76), and large change (95% CI: 11.04, 31.44) on the PCGRC. Confidence interval overlaps were also observed for the QOLCE-16 estimates corresponding with small (95% CI: 6.94, 15.23), moderate (95% CI: 12.49, 27.41), and large change (95% CI: 18.04, 39.60) on the PCGRC. Studies with a larger sample size, with a greater spread of participants reporting varied levels of

change in HRQOL on the PCGRC, may be able to more precisely estimate what a 'small', ‘moderate’, and 'large' change means in terms of QOLCE-55 and QOLCE-16 scores. Precise HRQOL estimates across these categories of change in HRQOL would be useful in distinguishing between participants who experienced a small clinically important change in HRQOL from participants who experienced moderate and large clinically important change in HRQOL.

The QOLCE-55 is designed to be administered to CWE and young adults with epilepsy up to 29 years old. Thus, it is important that subsequent investigations are conducted to provide MCID estimates applicable to the full age range for which the QOLCE-55 is intended.

Given the gap found between the MCID values calculated through anchor-based methods and distribution-based methods for both the QOLCE-55 and the QOLCE-16, it is important that the discussion continues among experts regarding guidelines on preferred methodologies. Although two factors were discussed to help in deciding which MCID would be more appropriate to use, using the minimum detectable change can also help with this decision. The minimum detectable change is said to be a parameter that should be estimated in “persons who have not changed over time (i.e., clinically stable patients) using a test-retest design” (van der Willik et al., 2021). Since the M3-E trial administered an intervention intended to improve the HRQOL of participants and did not have a test-retest design, we were unable to calculate the minimum detectable change using our sample. Obtaining an estimate of the minimum detectable change for the QOLCE-55 and QOLCE-16 can help address the gap between the MCID estimates obtained in this thesis as well as provide other benefits, such as using it as an indicator for statistically significant change.

5.7 Conclusion

Overall, we estimated the MCID values in HRQOL score for the QOLCE-55 and QOLCE-16 using both anchor-based and distribution-based approaches. This is the first study to report MCID values for the QOLCE-55 and the QOLCE-16 in a population of CWE. Although reporting the findings from both methods is typically recommended, some studies suggest that distribution-based methods should be used to assist in the interpretation of MCID values obtained rather than for MCID estimation. Therefore, it may be appropriate for future investigators to interpret changes in HRQOL score based on the MCID values obtained from the anchor-based methods. Ultimately, these MCID estimates should be used with caution pending replication in subsequent studies with larger samples. Further research with study design adjustments is required to validate our findings and provide guidelines on how to address the differences in the MCID values obtained.

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Appendices

APPENDIX A: Demographics/clinical characteristics

Section 9: Demographics / clinical Characteristics - BASELINE ONLY

9.1. What is your child's sex?

☐ Male

☐ Female

9.2 What is your child's date of birth?

☐☐ / ☐☐ / ☐☐☐☐

DAY MONTH YEAR

9.3 How many people live in the same household as your son/daughter?

☐☐ (including your son/daughter)

9.4 How many people aged 18 years or older live in the same household as your son/daughter?

☐☐

9.5 How often does your child have seizures? (Please provide your best guess)

☐ Daily

☐ Weekly

☐ Monthly

☐ Every 3 months

☐ Every 6 months

☐ No seizures in the last year

Notes: _____

9.6 In the past 30 days, how many seizures did your child have? _____ (# of seizures)
(Please provide your best guess)

9.7 In the past 30 days, how many seizure-free days did your child have? _____ (# seizure-free days)
(Please provide your best guess)

9.8 Taking into account all aspects of your child's epilepsy, how would you rate its severity currently?

Please check one answer.

- ☐ Extremely severe
- ☐ Very severe
- ☐ Quite severe
- ☐ Moderately severe
- ☐ Somewhat severe
- ☐ A little severe
- ☐ Not at all severe

9.9 Rate the following aspects of your child's epilepsy currently.
Check one box using the following 7-point scale:
1 = none or never 7 = extremely frequent, severe or high

	1	2	3	4	5	6	7
Frequency of seizures	☐	☐	☐	☐	☐	☐	☐
Intensity of seizures	☐	☐	☐	☐	☐	☐	☐
Falls or injuries during seizures	☐	☐	☐	☐	☐	☐	☐
Severity of period immediately following a seizure	☐	☐	☐	☐	☐	☐	☐
Amount of antiepileptic drugs	☐	☐	☐	☐	☐	☐	☐
Side effects of antiepileptic drugs	☐	☐	☐	☐	☐	☐	☐
Interference of epilepsy or drugs with daily activities	☐	☐	☐	☐	☐	☐	☐

9.10 Has your child ever been formally diagnosed by a health or mental health professional with:

Developmental delay / intellectual disability	☐ No	☐ Yes
A learning disability	☐ No	☐ Yes
Attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD)	☐ No	☐ Yes
Autism, pervasive developmental disorder (PDD) or Asperger's syndrome	☐ No	☐ Yes
Oppositional defiant disorder / conduct disorder	☐ No	☐ Yes
Depression	☐ No	☐ Yes
Anxiety	☐ No	☐ Yes

9.11 Does your child take any medications for any of the conditions listed above?

☐ No

☐ Yes → Please list the name(s) of the medications _____

9.12 Has your child been identified as exceptional through the Ministry of Education guidelines through an Identification, Placement, and Review Committee (IPRC) at your child's school?

☐ No

☐ Yes → For what reason? _____

9.13 Does your child have an Individualized Education Plan (IEP) at school?

☐ No → Continue to question 9.14

☐ Yes

9.13a (If yes) Is this because of your child's epilepsy diagnosis? ☐ No ☐ Yes

9.13b Are there any other reasons why your child received an IEP at school?

☐ No

☐ Yes → For what reason? _____

Now we would like to ask some questions about you.

9.14 What is your sex:

☐ Male

☐ Female

☐ Self-identified ⟶ _____

9.15 What is your date of birth?

☐☐ / ☐☐ / ☐☐☐☐

DAY MONTH YEAR

9.16 Which of the following best describes your current work status? (check one box only)

☐	☐	☐	☐	☐	☐
Not working due to my child's health	Not working for other reasons	Working full time	Working part time	Not working outside the home	Student

9.17 What is your relationship to the person with epilepsy? (check one box only)

☐	☐	☐	☐	☐	☐
Biological parent	Step parent	Foster parent	Adoptive parent	Guardian	Other (please explain on the line below)

_____

The next questions will help us compare your child's health to that of other people in the study who are similar to you.

9.18 In which category is your total yearly household income before taxes? (check one box only)

☐ Less than $25,000
☐ $25,000 - $49,999
☐ $50,000 - $74,999
☐ $75,000 - $99,999
☐ $100,000 - $124,999
☐ $125,000 - $149,000
☐ $150,000 or more
☐ Don't know

9.19 What is the highest grade of school you have completed?

☐ less than 8 years
☐ 8-12 years
☐ completed high school
☐ completed vocational/technical training

☐ completed college/university
☐ completed a Masters, PhD, or professional degree

9.20 Are you currently living with a spouse or partner?

☐ No → Continue to question 9.21 (next page)
☐ Yes

9.20a (If yes) What is your spouse's/partner's relationship to the person with epilepsy? (check one box only)

☐	☐	☐	☐	☐	☐
Biological parent	Step parent	Foster parent	Adoptive parent	Guardian	Other (please explain on the line below)

_____

9.20b Which of the following best describes your spouse's/partner's current work status? (check one box only)

☐	☐	☐	☐	☐	☐
Not working due to my child's health	Not working for other reasons	Working full time	Working part-time	Not working outside the home	Student

9.20c What is the spouse's/partner's highest grade of school completed?

☐ less than 8 years
☐ 8-12 years
☐ completed high school
☐ completed vocational/technical training
☐ completed college/university
☐ completed a Masters, PhD, or professional degree

9.21 Is there any additional important information about this child's epilepsy not captured by our questions?

_____

_____

_____

9.22 If there are any other issues concerning your child's physical and mental health and quality of life that we did not ask but that you would like us to know about, please feel free to mention here.

_____

_____

_____

9.23 Date this questionnaire was completed:

☐☐ / ☐☐ / ☐☐☐☐

DAY MONTH YEAR

Appendix B: QOLCE-55

YOUR CHILD'S COGNITIVE FUNCTIONING.

The following questions ask about some problems children have with concentrating, remembering, and speaking.

1.1 Compared to other children of his/her own age, how often during the past 4 weeks has your child:

	Very Often	Fairly Often	Some-Times	Almost Never	Never	Not Applicable
a. had difficulty attending to an activity?	☐	☐	☐	☐	☐	☐
b. had difficulty reasoning or solving problems?	☐	☐	☐	☐	☐	☐
c. had difficulty making plans or decisions?	☐	☐	☐	☐	☐	☐
d. had difficulty keeping track of conversations?	☐	☐	☐	☐	☐	☐
e. had trouble concentrating on a task?	☐	☐	☐	☐	☐	☐
f. had difficulty concentrating on reading?	☐	☐	☐	☐	☐	☐
g. had difficulty doing one thing at a time?	☐	☐	☐	☐	☐	☐
h. reacted slowly to things being said and done?	☐	☐	☐	☐	☐	☐
i. found it hard remembering things?	☐	☐	☐	☐	☐	☐
j. had trouble remembering names of people?	☐	☐	☐	☐	☐	☐
k. had trouble remembering where s/he put things?	☐	☐	☐	☐	☐	☐
l. had trouble remembering things people told him/her?	☐	☐	☐	☐	☐	☐
m. had trouble remembering things s/he read hours or days before?	☐	☐	☐	☐	☐	☐
n. planned to do something then forgot?	☐	☐	☐	☐	☐	☐
o. had trouble finding the correct words?	☐	☐	☐	☐	☐	☐
p. had trouble understanding or following what others were saying?	☐	☐	☐	☐	☐	☐

q. had trouble understanding directions?	☐	☐	☐	☐	☐	☐
r. had difficulty following simple instructions?	☐	☐	☐	☐	☐	☐
s. had difficulty following complex instructions?	☐	☐	☐	☐	☐	☐
t. had trouble understanding what s/he read?	☐	☐	☐	☐	☐	☐
u. had trouble writing?	☐	☐	☐	☐	☐	☐
v. had trouble talking?	☐	☐	☐	☐	☐	☐

YOUR CHILD'S EMOTIONAL FUNCTIONING.

Below is a list that describes how your child might feel in general.

1.2 During the past 4 weeks, how much of the time do you think your child:

	All of the time	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**	**Not Applicable**
a. felt down or depressed?	☐	☐	☐	☐	☐	☐
b. felt happy?	☐	☐	☐	☐	☐	☐
c. wished s/he was dead?	☐	☐	☐	☐	☐	☐
d. felt frustrated?	☐	☐	☐	☐	☐	☐
e. worried a lot?	☐	☐	☐	☐	☐	☐
f. felt confident?	☐	☐	☐	☐	☐	☐
g. felt excited or interested in something?	☐	☐	☐	☐	☐	☐
h. felt pleased about achieving something?	☐	☐	☐	☐	☐	☐
i. felt nobody understood him/her?	☐	☐	☐	☐	☐	☐
j. felt valued?	☐	☐	☐	☐	☐	☐
k. felt no one cared?	☐	☐	☐	☐	☐	☐

Below are statements that describe some children's behaviour.
Please try to answer all questions as well as you can, even if some do not seem to apply to your child.

1.3 Compared to other children his/her own age, how often during the past 4 weeks do each of the following statements describe your child?

	Very Often	Fairly Often	Some-Times	Almost Never	Never	Not Applicable
a. was socially inappropriate (said or did something out of place in a social situation)	☐	☐	☐	☐	☐	☐
b. angered easily	☐	☐	☐	☐	☐	☐
c. hit or attacked people	☐	☐	☐	☐	☐	☐
d. swore in public	☐	☐	☐	☐	☐	☐
e. was obedient	☐	☐	☐	☐	☐	☐
f. demanded a lot of attention	☐	☐	☐	☐	☐	☐

YOUR CHILD'S SOCIAL FUNCTIONING

Below are statements that describe some children's social interactions and activities.
Please try to answer all questions as well as you can, even if some do not seem to apply to your child.

1.4 During the past 4 weeks, how often has your child's epilepsy:

	Very Often	Fairly Often	Some-Times	Almost Never	Never	Not Applicable
a. limited his/her social activities (visiting friends, close relatives, or neighbours)?	☐	☐	☐	☐	☐	☐
b. affected his/her social interactions at school or work?	☐	☐	☐	☐	☐	☐
c. limited his/her leisure activities (hobbies or interests)?	☐	☐	☐	☐	☐	☐
d. isolated him/her from others?	☐	☐	☐	☐	☐	☐
e. made it difficult for him/her to keep friends?	☐	☐	☐	☐	☐	☐

f. frightened other people?	☐	☐	☐	☐	☐	☐
g. <u>During the past 4 weeks</u>, how limited are your child's social activities compared with others his/her age because of his/her epilepsy or epilepsy-related problems?	☐ Yes, limited a lot	☐ Yes, limited some	☐ Yes, limited a little	☐ Yes, but rarely	☐ No, not limited	

<u>YOUR CHILD'S PHYSICAL FUNCTIONING</u>

The following questions ask about physical activities your child might do.

1.5 In his/her daily activities during the <u>past 4 weeks,</u> how often has your child:

	Very Often	**Fairly Often**	**Some-Times**	**Almost Never**	**Never**	**Not Applicable**
a. needed more supervision than other children his/her age?	☐	☐	☐	☐	☐	☐
b. played freely in the house like other children his/her age?	☐	☐	☐	☐	☐	☐
c. played freely outside the house like other children his/her age?	☐	☐	☐	☐	☐	☐
d. gone swimming (i.e., swam independently)?	☐	☐	☐	☐	☐	☐
e. participated in sports activities (other than swimming)?	☐	☐	☐	☐	☐	☐
f. stayed out overnight (with friends or family)?	☐	☐	☐	☐	☐	☐
g. played with friends away from you or your home?	☐	☐	☐	☐	☐	☐
h. gone to parties without you or without supervision?	☐	☐	☐	☐	☐	☐
i. been able to do the physical activities other children his/her age do?	☐	☐	☐	☐	☐	☐

Appendix C: QOLCE-16

SECTION 1: YOUR CHILD'S COGNITIVE FUNCTIONING

The following questions ask about some problems children have with concentrating, remembering, and speaking.

Compared to other children of his/her own age, how often during the past 4 weeks has your child:

		Very	Fairly Often	Some-- times	Almost Never	Never	Not Often Applicable
a.	had trouble understanding directions?	☐	☐	☐	☐	☐	☐
b.	had difficulty following complex instructions?	☐	☐	☐	☐	☐	☐
c.	had difficulty following simple instructions?	☐	☐	☐	☐	☐	☐
d.	had trouble remembering things people told him/her?	☐	☐	☐	☐	☐	☐

SECTION 2: YOUR CHILD'S EMOTIONAL FUNCTIONING

Below is a list that describes how your child might feel in general.

During the past 4 weeks, how much of the time do you think your child:

		All of the time	Most of the time	Some of the time	A little of the time	None of the time	Not Applicable
a.	felt nobody understood him/her?	☐	☐	☐	☐	☐	☐
b.	felt down or depressed?	☐	☐	☐	☐	☐	☐
c.	felt frustrated?	☐	☐	☐	☐	☐	☐
d.	felt confident?	☐	☐	☐	☐	☐	☐

SECTION 3: YOUR CHILD'S SOCIAL FUNCTIONING

Below are statements that describe some children's social interactions and activities.

a. During the past 4 weeks, how limited are your child's social activities compared with others his/her age because of his/her epilepsy or epilepsy--related problems?

☐	☐	☐	☐	☐	☐
Yes, limited a lot	Yes, limited some	Yes, limited a little	Yes, but rarely	No, not limited	Not Applicable

During the past 4 weeks, how often has your child's epilepsy:

		Very Often	Fairly Often	Some-- times	Almost Never	Never	Not Applicable
b.	affected his/her social interactions at school or work?	☐	☐	☐	☐	☐	☐
c.	isolated him/her from others?	☐	☐	☐	☐	☐	☐
d.	made it difficult for him/her to keep friends	☐	☐	☐	☐	☐	☐

SECTION 4: YOUR CHILD'S PHYSICAL FUNCTIONING

The following questions ask about physical activities your child might do.

In his/her daily activities during the past 4 weeks, how often has your child:

		Very Often	Fairly time	Some--	Almost Never	Never	Not Applicable
a.	played freely outside the house like other children his/her age?	☐	☐	☐	☐	☐	☐
b.	been able to do the physical activities other children his/her age do?	☐	☐	☐	☐	☐	☐
c.	played freely in the house like other children his/her age?	☐	☐	☐	☐	☐	☐
d.	needed more supervision than other children his/her age?	☐	☐	☐	☐	☐	☐

Appendix D: PCGRC

SECTION 0: Patient Centred Global Ratings of Change (FOLLOW-UP)

We would like you to think about your child's everyday life now as compared to 9 weeks ago when you entered the study. (NOTE: At Follow-up 2, all of these questions ask about "**18** week ago when you entered the study")

1. Overall, compared to 9 weeks ago, would you say that your child's quality of life now is:

☐ Worse ☐ About the same ☐ Better

If you selected 'worse', please specify

☐ Almost the same, hardly worse at all
☐ A little worse
☐ Somewhat worse
☐ Moderately worse
☐ A good deal worse
☐ A great deal worse
☐ A very great deal worse

If you selected 'better, please specify

☐ Almost the same, hardly better at all
☐ A little better
☐ Somewhat better
☐ Moderately better
☐ A good deal better
☐ A great deal better
☐ A very great deal better

2. Overall, compared to 9 weeks ago, would you say that your child's cognitive functioning (e.g. memory and thinking) now is:

☐ Worse ☐ About the same ☐ Better

If you selected 'worse', please specify

☐ Almost the same, hardly worse at all
☐ A little worse
☐ Somewhat worse
☐ Moderately worse
☐ A good deal worse
☐ A great deal worse
☐ A very great deal worse

If you selected 'better, please specify

☐ Almost the same, hardly better at all
☐ A little better
☐ Somewhat better
☐ Moderately better
☐ A good deal better
☐ A great deal better
☐ A very great deal better

3. Overall, compared to 9 weeks ago, would you say that your child's emotional well-being now is:

☐ Worse ☐ About the same ☐ Better

If you selected 'worse', please specify

☐ Almost the same, hardly worse at all
☐ A little worse
☐ Somewhat worse
☐ Moderately worse
☐ A good deal worse
☐ A great deal worse
☐ A very great deal worse

If you selected 'better, please specify

☐ Almost the same, hardly better at all
☐ A little better
☐ Somewhat better
☐ Moderately better
☐ A good deal better
☐ A great deal better
☐ A very great deal better

4. Overall, compared to 9 weeks ago, would you say that your child's social activities/well-being now are:

☐ Worse ☐ About the same ☐ Better

If you selected 'worse', please specify

☐ Almost the same, hardly worse at all
☐ A little worse
☐ Somewhat worse
☐ Moderately worse
☐ A good deal worse
☐ A great deal worse
☐ A very great deal worse

If you selected 'better, please specify

☐ Almost the same, hardly better at all
☐ A little better
☐ Somewhat better
☐ Moderately better
☐ A good deal better
☐ A great deal better
☐ A very great deal better

5. Overall, compared to 9 weeks ago, would you say that your child's physical activities/well-being now are:

☐ Worse ☐ About the same ☐ Better

If you selected 'worse', please specify

☐ Almost the same, hardly worse at all
☐ A little worse
☐ Somewhat worse

If you selected 'better, please specify

☐ Almost the same, hardly better at all
☐ A little better
☐ Somewhat better

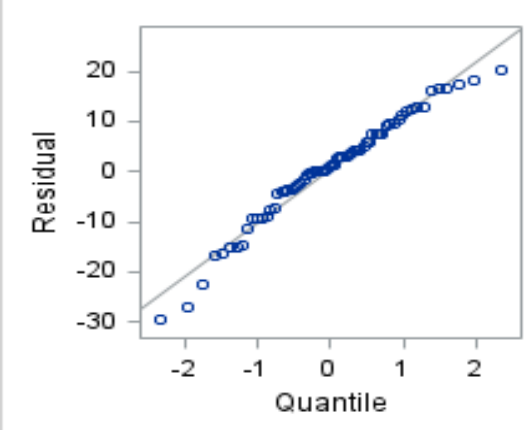
- ☐ Moderately worse
- ☐ A good deal worse
- ☐ A great deal worse
- ☐ A very great deal worse

- ☐ Moderately better
- ☐ A good deal better
- ☐ A great deal better
- ☐ A very great deal better

Appendix E: Results of the Validation of Linear Regression Models

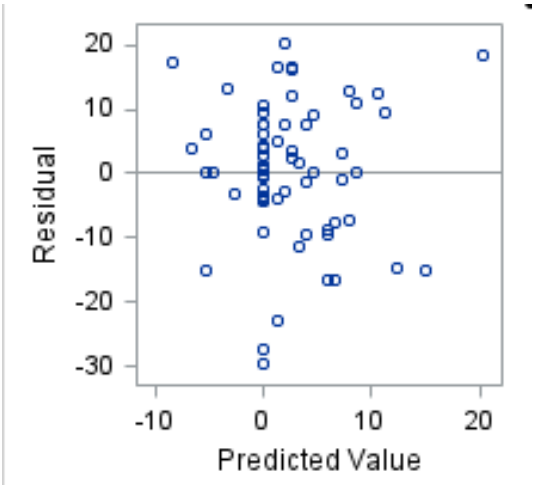
1. QOLCE-55

Normality of residuals:



A QQ plot of the empirical quantiles of the residuals (QOLCE-55 change scores) against the theoretical quantiles of a normal distribution, commonly known as a quantile-quantile (QQ) plot. In this plot, most of the data follow the straight line aside from a few points that deviate slightly from the line. Overall, the data is approximately normal.

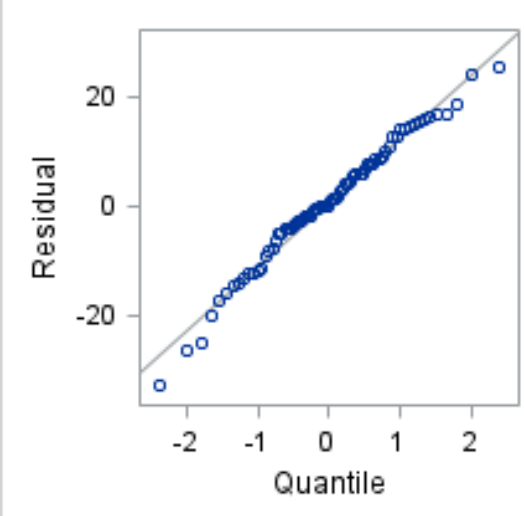
Homoscedasticity:



A scatter plot of the residuals plotted against the predicted values of the QOLCE-55 change score. No pattern or linear relationship can be seen, demonstrating that the homoscedasticity assumption is met.

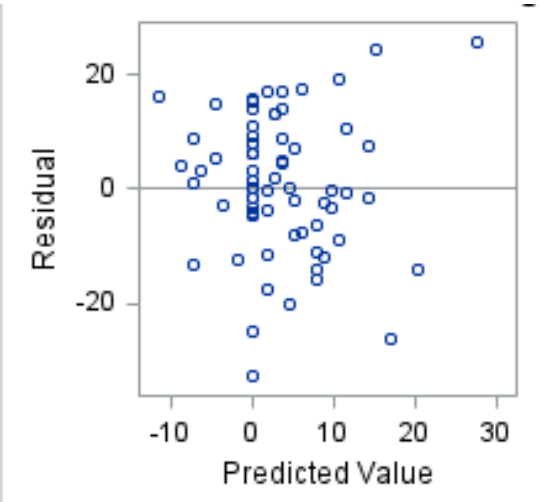
2. QOLCE-16

Normality of residuals:



A QQ plot of the empirical quantiles of the residuals (QOLCE-16 change scores) against the theoretical quantiles of a normal distribution, commonly known as a quantile-quantile (QQ) plot. In this plot, most of the data follow the straight line aside from a few points that deviate slightly from the line. Overall, the data is approximately normal.

Homoscedasticity:



A scatter plot of the residuals plotted against the predicted values of the QOLCE-16 change score. No pattern or linear relationship can be viewed, demonstrating that the homoscedasticity assumption is met

Curriculum Vitae

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