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Global Assessment of Severity of Epilepsy (GASE) Scale in Children with Epilepsy: Construct Validity, Stability, and Responsiveness

Cindy J. Chan
The University of Western Ontario

Supervisor
Dr. Kathy N. Speechley
The University of Western Ontario

Graduate Program in Epidemiology and Biostatistics
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science
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GLOBAL ASSESSMENT OF SEVERITY OF EPILEPSY (GASE) SCALE
IN CHILDREN WITH EPILEPSY: CONSTRUCT VALIDITY, STABILITY, AND
RESPONSIVENESS

(Thesis format: Monograph)

by

Cindy Jauhrur Chan

Graduate Program in Epidemiology and Biostatistics

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

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Abstract

The Global Assessment of Severity of Epilepsy (GASE) Scale is a single-item, 7-point global rating scale designed for neurologist-report of overall severity of epilepsy in children. Preliminary evidence suggested it may be valid and reliable for research and clinical use. Data from the Health-Related Quality of Life in Children with Epilepsy Study (HERQULES) was analyzed to evaluate validity, stability, and responsiveness of GASE scores. Spearman's Rho indicated that GASE was moderately correlated with key aspects of epilepsy but weakly correlated with parents' perceptions of child health. Frequency and intensity of seizures and interference of epilepsy or drugs with daily activities were most strongly correlated with GASE. Intra-class correlation coefficients (ICC) provided modest evidence that GASE could detect stability. Distribution- and anchor-based indices suggested that GASE was responsive to changes in clinical criteria. Results support the construct validity, stability, and responsiveness to change of the GASE Scale in children with epilepsy.

Keywords

Global Assessment of Severity of Epilepsy (GASE) Scale, children, epilepsy, severity, measurement properties, validity, stability, reliability, responsiveness, sensitivity to change

Dedication

To the children and families affected by epilepsy

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List of Abbreviations

| | |
|----------|---|
| AEDs | anti-epileptic drugs |
| AUROC | Area under the Receiver Operating Characteristic Curve |
| CCTILAE | Commission on Classification and Terminology of the International League Against Epilepsy |
| CHQ | Child Health Questionnaire |
| CI | confidence interval |
| CSE | convulsive status epilepticus |
| EEGs | electroencephalograms |
| ES | effect size |
| ESSS-C | Epilepsy Syndrome Severity Scale-Child |
| GASE | Global Assessment of Severity of Epilepsy Scale |
| GRS | Guyatt's Responsiveness Statistic |
| HASS | Hague Seizure Severity Scale |
| HERQULES | Health-Related Quality of Life in Children with Epilepsy Study |
| HRQL | health-related quality of life |
| IBE | International Bureau for Epilepsy |
| ICC | intraclass correlation coefficient |
| ICE | International Classification of Epilepsies and Epileptic Syndromes |
| ICES | International Classification of Epileptic Seizures |
| ILAE | International League Against Epilepsy |
| LSSS | Liverpool Seizure Severity Scale |
| NHS3 | National Hospital (Chalfont) Seizure Severity Scale |
| QOLCE | Quality of Life in Childhood Epilepsy Questionnaire |
| ROC | receiver operating characteristic curve |
| SD | standard deviation |
| SRM | standardized response mean |
| SSQ | Seizure Severity Questionnaire |
| VA | Veterans Administration Seizure Frequency and Severity Rating Scale |
| WHO | World Health Organization |

CHAPTER 1

INTRODUCTION

1.1 Introduction

Assessment of the severity of epilepsy is important for both treatment and research aiming to improve health-related quality of life (HRQL). Characterizing the severity of epilepsy in individuals assists clinicians in decision-making and monitoring treatment, while facilitating communication and counselling for patients and families. It enables researchers to test and compare the effectiveness of interventions within and across studies. While advances in neuroscience have prompted the revision of past definitions and classifications of epilepsy, the development of health measurement tools that provide valid and reliable data continues to be a challenge for both researchers and clinicians. Multiple tools for measuring the severity of seizures, syndromes, and epilepsy have been developed but there is no universally accepted standard scale of severity (Thurman et al., 2011). The severity of epilepsy is predominantly assessed with measures of the severity of seizures. These measures fail to address other dimensions of epilepsy such as disability due to disease and side effects of antiepileptic drugs (AEDs). Although there is some evidence to support limited use of these scales, most existing scales are limited by the difficulty of use and inadequate evidence supporting validity, reliability, and responsiveness to change.

1.2 Purpose and Rationale

The International League Against Epilepsy (ILAE) reviewed epilepsy-related severity assessment instruments and emphasized the importance of broader assessment tools to better capture the severity of epilepsy. In its review, the ILAE describes the Global Assessment of Severity of Epilepsy (GASE) Scale as demonstrating reliability and validity (Thurman et al., 2011). The GASE Scale is a single-item, 7-point global rating scale. It was developed as a clinician-report measure to assess the overall severity of epilepsy in children and to provide a simple and efficient tool to capture the

multidimensional nature of epilepsy. This thesis aims to extend the assessment of the measurement properties of the GASE Scale.

Severity of illness is a complex concept that involves biology, physical function, and the psychosocial impact of disease (Stein et al., 1987). Numerous factors such as the purpose of an instrument, the viewpoint (physician, patient, and caregiver), time frame, and population of interest all influence the interpretation of the assessment of severity (Speechley et al., 2008). Validation of measures involves an ongoing process of obtaining repeated evidence to verify its accuracy and reliability in measuring its intended construct (Streiner and Norman, 2008, pp.250-2).

To improve confidence in the GASE Scale, it is important that multiple analyses, different criteria, and methods can support the central theory that the scale measures the overall severity of epilepsy in children. Within the realm of validating theories for measurement tools, construct validity has become a well-established concept and encompasses the specific tests of validation (Smith, 2005). To further assess the quality of information collected by the GASE Scale beyond preliminary evidence that supported its validity and reliability (Speechley et al., 2008), this thesis project aims to assess the construct validity, stability, and responsiveness to change in severity of the GASE in a sample of Canadian children. Previous preliminary research provided evidence to support the GASE Scale's face and content validity, convergent validity, inter-rater and test-retest reliability using hypothetical case scenarios, and discriminative properties for three types of epilepsy syndromes (Speechley et al., 2008). Continuing this process of validation should involve the following analyses, among others: evaluation of construct validity, both convergent and discriminant using primary clinical data in the course of studies in which the GASE was used; assessment of the inter-rater and test-retest reliability in a clinical sample; comparison of this physician-rated scale with other commonly used clinical measures in childhood epilepsy; and assessment of the responsiveness of the GASE Scale to clinically meaningful changes in severity of epilepsy.

This thesis builds on the previous work that evaluated the convergent validity of the GASE Scale in a cross-sectional analysis of 134 children (Speechley et al., 2008), by

examining a larger sample of children treated at multiple centres across Canada ($n = 373$) with newly-diagnosed epilepsy in a two-year longitudinal research study assessing the course and determinants of HRQL. Expanding the scope of construct validation for the GASE Scale, new comparisons are introduced with several physician-rated clinical aspects of epilepsy not previously evaluated, as well as the parents' perception of their children's health. In addition to construct validity, this thesis will provide critical new information on the stability of the scale, and how it responds to clinically meaningful changes in severity over time, which has not been assessed previously.

Although construct validation has been reconceptualized to include all forms of validity testing (Streiner and Norman, 2008, pp.251-2), in the interest of clarity, this thesis will continue to refer to the specific types of validity.

1.3 Thesis Objectives

This thesis has three main objectives:

1. To assess the construct validity of the GASE Scale;
2. To assess the stability of the GASE Scale;
3. To assess the responsiveness of the GASE Scale to changes in severity of epilepsy.

For each of these objectives, several hypotheses will be tested.

Hypotheses associated with Objective 1: To assess the construct validity of the GASE Scale:

- a) GASE scores will be correlated with several clinical aspects of epilepsy rated by neurologists. These correlations are predicted to be at least moderate ($r \geq 0.3$), given that the GASE Scale was developed to take into account all aspects of a patient's epilepsy (Speechley et al., 2008).
 - "Frequency of seizures" will be the clinical aspect with the strongest correlation with GASE scores, given its importance in the assessment of the severity of epilepsy in past research (Cramer and French, 2001, O'Donoghue et al., 1996, Speechley et al., 2008).

- b) GASE scores will be correlated at least moderately ($r \geq 0.3$) with the “total number of AEDs” reported by neurologists, given that patients with worse seizure control and adverse side effects of AEDs are reported to have been treated with a greater number of medications (Moran et al., 2004).
- c) GASE scores will indicate more severe epilepsy for children who have experienced convulsive status epilepticus (CSE) than for those who have not, since the condition is recognized as being associated with significant morbidity and mortality (Raspall-Chaure et al., 2006, Martinos et al., 2013).
- d) GASE scores will indicate less severe epilepsy for children whose seizures are exclusively nocturnal, since seizures that occur exclusively during sleep generally have better prognosis and tend to be less disruptive than seizures during the day (Bazil, 2003, Ekizoglu et al., 2011).
- e) GASE scores will be correlated with parents’ perception of child health. The correlation will be at least moderate ($r \geq 0.3$) with GASE scores indicating more severe epilepsy associated with parents reporting children’s health as poorer, given that parents’ perceptions of their children’s health are likely to reflect recent status of epilepsy.

Hypothesis associated with Objective 2: To assess the stability of the GASE Scale:

- a) In patients for whom neurologists’ reports of key clinical aspects of epilepsy and a composite score indicate stability in the patient’s epilepsy over a period of 6 months, GASE scores will remain stable over the same time period.
- b) In patients whose parents’ reports of child health status indicate stability in the patient’s epilepsy over a period of 6 months, GASE scores will remain stable over the same time period.

Hypotheses associated with Objective 3: To assess the responsiveness of the GASE Scale:

Distribution-based methods (internal responsiveness):

- a) The GASE Scale will be able to detect statistically significant changes in the severity of epilepsy over time (from baseline to 6, 12, and 24 months post-diagnosis).

Anchor-based methods (external responsiveness):

- b) Change in severity of epilepsy reported using the GASE Scale over a period of 12 months will be correlated with neurologists' reports of changes in key clinical aspects of epilepsy and a composite score of the aspects over the same time period.
- c) Change in severity reported using the GASE Scale over a period of 12 months will be correlated with changes in parents' perceptions of child health status over the same time period.
- d) In patients for whom neurologists' reports of key clinical aspects of epilepsy and the composite score indicate change in the patient's epilepsy over a period of 12 months, common responsiveness statistics will show that GASE scores also change over the same time period.
- e) In patients whose parents' reports of child health indicate change in the patient's epilepsy over a period of 12 months, common responsiveness statistics will show that GASE scores also change over the same time period.

1.4 Overview on Epilepsy

Epilepsy is one of the most common neurological disorders in the world. The World Health Organization (WHO) estimates that 2.4 million people are newly diagnosed each year and that a total of 50 million cases were estimated in 2005. Epilepsy can affect any person regardless of age, sex and race. However, children and adolescents suffer the greatest impact as 50% of diagnoses occur prior to adulthood (World Health Organization et al., 2005).

Known to Hippocrates of the ancient Greeks and documented as early as the Babylonians over 3000 years ago, defining and classifying epilepsy have been important challenges in the history of understanding the condition (World Health Organization et al., 2005).

The term epilepsy was conceptually defined in 2005 by the ILAE and the International Bureau for Epilepsy (IBE) as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition". This definition of epilepsy

required the occurrence of at least one epileptic seizure (Fisher et al., 2005). An epileptic seizure was defined as “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” (Fisher et al., 2005). In 2014, the definition of epilepsy was revised by the ILAE Task Force with consultation from the international epilepsy community to redefine the operational definition for clinical purposes (Fisher et al., 2013). The report broadens the definition and clearly defines epilepsy as a disease in contrast to the traditional reference to epilepsy as a disorder or representing a multitude of brain disorders (Fisher et al., 2014). The following is the official new definition for seizures and epilepsy:

Epilepsy is a disease of the brain defined by any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring > 24 hours apart;
2. One unprovoked (or reflex) 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;
3. Diagnosis of an epilepsy syndrome.

Epilepsy is considered to be *resolved* for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years (Fisher et al., 2014).

1.4.1 Classification

Since 1960, the ILAE has been classifying epileptic seizures and syndromes, with publications in 1981 for the classification of seizures, and 1989 for the classification of epilepsies and epileptic syndromes (Berg et al., 2010). Several revisions to terminology and concepts as recommended by the Commission on Classification and Terminology of the ILAE (CCTILAE) from 2005 to 2009 were published by Berg et al. (2010), noting that significant advances in basic and clinical neurosciences have resulted in greater insight into epilepsy and seizures, necessitating regular changes to previous classification systems. Standard classification of epilepsy is not only important for clinical and research communication, but also for diagnoses and descriptions relating to specific medications and treatment (CCTILAE, 1981).

The 1981 International Classification of Epileptic Seizures (ICES) is based on clinical features using electroencephalograms (EEGs) and video recordings as analyzed by expert members of the CCTILAE (CCTILAE, 1981). Seizures are classified into categories of partial (focal and local), generalized (convulsive or nonconvulsive) and unclassified epileptic seizures, with further detailed sub-classification within these categories (CCTILAE, 1981). Partial seizures are recognized by the exclusive initial activation of neurons in a single cerebral hemisphere, whereas generalized seizures activate neurons simultaneously in both hemispheres. The further classification of partial seizures is based primarily on the extent of impaired consciousness, while generalized seizures commonly impair consciousness and are thus further classified mainly according to differences in EEG characteristics such as patterns of electrical activity (CCTILAE, 1981).

The 1989 International Classification of Epilepsies and Epileptic Syndromes (ICE) was created to supplement ICES (CCTILAE, 1989). Similar to ICES, classifications in ICE were decided through the study of clinical features, EEGs and video recordings. An epileptic syndrome is characterized by a specific collection of signs and symptoms and is determined according to criteria such as the type of seizures, severity, age of onset, etiology, and other electroclinical characteristics. ICE consists of four categories: localization-related (focal, local, and partial), generalized, undetermined (focal and generalized), and special syndromes. Syndromes are further subdivided according to idiopathic, symptomatic, and cryptogenic conditions (CCTILAE, 1989). However within the past decade, the CCTILAE has recommended the replacement of these terms to reflect etiology with “genetic”, “structural and metabolic”, and “unknown cause” (Berg et al., 2010). Thurman et al. (2011) note that this broader classification is more flexible to different study purposes and future advances in etiological research.

A revised classification system for seizures was created in 2006 by the Core Group of the Task Force on Classification and Terminology of the ILAE and is summarized in Table 1.1 (Engel, 2006). The updated system reclassifies seizure types into self-limited epileptic seizures and status epilepticus. There are three main categories for self-limited epileptic seizures: generalized onset, focal onset, and neonatal seizures. Generalized onset seizures are further subdivided into five categories: seizures with tonic and/or clonic

manifestations, absences, myoclonic seizure types, epileptic spasms, and atonic seizures. Focal onset seizures are characterized by differences in the structure, site, and spread of seizure-induced disruption in neuronal function (Engel, 2006). Therefore, they are subdivided into the four categories: local, with ipsilateral propagation to, with contralateral spread to, and secondarily generalized seizures. The unique features of neonatal seizures enable further classification. Status epilepticus is further classified into nine categories according to the associated mechanisms of initiation, spread and termination, as well as factors affecting maturation and future structural or functional brain disturbances (Engel, 2006).

In the 2011 ILAE Epidemiology Commission Report on “Standards for Epidemiologic Studies and Surveillance of Epilepsy”, Thurman et al. (2011) suggested a new matrix for classifying seizures that was flexible to cases where information is unavailable or unclear, particularly EEG data. The proposed system classifies seizures according to two criteria: onset (generalized, focal, and undetermined) and predominant ictal features (motor, nonmotor, and unknown).

Although the classification of epilepsy syndromes was recommended by Berg et al. (2010) to reflect etiology, both Engel (2006) and Berg et al. (2010) acknowledge that updating the classification of syndromes is still a work in progress and that age at onset is another example of how epilepsy syndromes can be organized. The classification of all recognized epilepsy syndromes according to age of onset and related conditions are outlined in Table 1.2.

Table 1.1: Epilepsy seizure classification.
Reproduced with permission from Table 1 in Engel (2006), Copyright © 2006 John Wiley and Sons (Appendix C).

| |
|---|
| Self-limited epileptic seizures |
| I. Generalized onset |
| A. Seizures with tonic and/or clonic manifestations |
| 1. Tonic-clonic seizures |
| 2. Clonic seizures |
| 3. Tonic seizures |
| B. Absences |
| 1. Typical absences |
| 2. Atypical absences |
| 3. Myoclonic absences |
| C. Myoclonic seizure types |
| 1. Myoclonic seizures |
| 2. Myoclonic atstatic seizures |
| 3. Eyelid myoclonia |
| D. Epileptic spasms |
| E. Atonic seizures |
| II. Focal onset (partial) |
| A. Local |
| 1. Neocortical |
| a. Without local spread |
| i Focal clonic seizures |
| ii Focal myoclonic seizures |
| iii Inhibitory motor seizures |
| iv Focal sensory seizures with elementary symptoms |
| v Aphasic seizures |
| b. With local spread |
| i Jacksonian march seizures |
| ii Focal (asymmetrical) tonic seizures |
| iii Focal sensory seizures with experiential symptoms |
| 2. Hippocampal and parahippocampal |
| B. With ipsilateral propagation to: |
| 1. Neocortical areas (includes hemiclonic seizures) |
| 2. Limbic areas (includes gelastic seizures) |
| C. With contralateral spread to: |
| 1. Neocortical areas (hyperkinetic seizures) |
| 2. Limbic areas (dyscognitive seizures with or without automatisms [psychomotor]) |
| D. Secondarily generalized |
| 1. Tonic-clonic seizures |
| 2. Absence seizures |
| 3. Epileptic spasms (unverified) |
| III. Neonatal seizures |
| Status epilepticus |
| I. Epilepsia partialis continua (EPC) |
| A. As occurs with Rasmussen syndrome |
| B. As occurs with focal lesions |
| C. As a component of inborn errors of metabolism |
| II. Supplementary motor area (SMA) status epilepticus |
| III. Aura continua |
| IV. Dyscognitive focal (psychomotor, complex partial) status epilepticus |
| A. Mesial temporal |
| B. Neocortical |
| V. Tonic-clonic status epilepticus |
| VI. Absence status epilepticus |
| A. Typical and atypical absence status epilepticus |
| B. Myoclonic absence status epilepticus |
| VII. Myoclonic status epilepticus |
| VIII. Tonic status epilepticus |
| IX. Subtle status epilepticus |

Table 1.2: Epilepsy syndrome classification.
Reproduced with permission from Table 3 (Electroclinical syndromes and other epilepsies) in Berg et al. (2010), Copyright Wiley Periodicals, Inc. © 2010 International League Against Epilepsy (Appendix D).

| |
|--|
| <p>Electroclinical syndromes arranged by age at onset^a</p> <p>Neonatal period</p> <ul style="list-style-type: none"> Benign familial neonatal epilepsy (BFNE) Early myoclonic encephalopathy (EME) Ohtahara syndrome <p>Infancy</p> <ul style="list-style-type: none"> Epilepsy of infancy with migrating focal seizures West syndrome Myoclonic epilepsy in infancy (MEI) Benign infantile epilepsy Benign familial infantile epilepsy Dravet syndrome Myoclonic encephalopathy in nonprogressive disorders <p>Childhood</p> <ul style="list-style-type: none"> Febrile seizures plus (FS+) (can start in infancy) Panayiotopoulos syndrome Epilepsy with myoclonic atonic (previously atatic) seizures Benign epilepsy with centrotemporal spikes (BECTS) Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE) Late onset childhood occipital epilepsy (Gastaut type) Epilepsy with myoclonic absences Lennox-Gastaut syndrome Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)^b Landau-Kleffner syndrome (LKS) Childhood absence epilepsy (CAE) <p>Adolescence – Adult</p> <ul style="list-style-type: none"> Juvenile absence epilepsy (JAE) Juvenile myoclonic epilepsy (JME) Epilepsy with generalized tonic-clonic seizures alone Progressive myoclonus epilepsies (PME) Autosomal dominant epilepsy with auditory features (ADEAF) Other familial temporal lobe epilepsies <p>Less specific age relationship</p> <ul style="list-style-type: none"> Familial focal epilepsy with variable foci (childhood to adult) Reflex epilepsies <p>Distinctive constellations</p> <ul style="list-style-type: none"> Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS) Rasmussen syndrome Gelastic seizures with hypothalamic hamartoma Hemiconvulsion-hemiplegia-epilepsy <p>Epilepsies that <i>do not</i> fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)</p> <p>Epilepsies attributed to and organized by structural-metabolic causes</p> <ul style="list-style-type: none"> Malformations of cortical development (hemimegalencephaly, heterotopias, etc.) Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.) Tumor Infection Trauma Angioma Perinatal insults Stroke Etc. <p>Epilepsies of unknown cause</p> <p>Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se</p> <ul style="list-style-type: none"> Benign neonatal seizures (BNS) Febrile seizures (FS) |
| <p>^aThe arrangement of electroclinical syndromes does not reflect etiology.</p> <p>^bSometime referred to as Electrical Status Epilepticus during Slow Sleep (ESES).</p> |

1.4.2 Prevalence and Incidence

According to the WHO, epilepsy is among the top three conditions reported in primary health care settings around the world (Wiebe et al., 2009). With a substantial global burden of disease, the prevalence of epilepsy was estimated to be 65 million people worldwide in 2010 (Thurman et al., 2011). The WHO estimates that in developed countries, the incidence is approximately 40 to 70 new cases each year per 100,000 persons, while the incidence rate in developing countries is approximately double (World Health Organization, 2012).

Although the reported rates of disease vary across studies due to differences in case definitions and research methods, in Canada the prevalence of epilepsy is approximately 600 cases per 100,000 persons. For children and adolescents, the incidence in Canada has been reported to range between 21 and 118 cases per 100,000 persons, paralleling rates in the United States and other industrialized countries (Wiebe et al., 2009).

The negative impact of epilepsy is expressed through increased economic costs, greater prevalence of psychosocial outcomes, higher rates of injury, poorer quality of life, and higher rates of mortality than in the general population (Wiebe et al., 2009).

1.4.3 Etiology

Following the classification scheme recommended by the CCTILAE in relation to the subcategories of epileptic syndromes, there are currently three main types of causes defined by the ILAE, namely, genetic, structural and metabolic, and syndromes with unknown cause (Berg et al., 2010). Often the cause of epilepsy and seizures is multifactorial (Bell and Sander, 2001), involving complex factors such as the environment, genetics, comorbidity, and other physiologic functions (Hart and Sander, 2008). Multiple precipitating factors also influence the likelihood of epileptic seizures, such as head injuries, sleep deprivation, substance abuse, and stress. The etiology of epilepsy varies by risk factors such as age and type of seizures. In infants, epilepsy may result from hypoxia, perinatal intracranial trauma, disruptions in metabolism, infection, and brain malformations (Hart and Sander, 2008). The cause of epilepsy is harder to determine in children and adolescents, however, with approximately 70% of seizures

considered idiopathic (Cowan et al., 1989) and attributed to a genetic predisposition (Hart and Sander, 2008). Adult onset epilepsy involves the same causes, in addition to brain tumours and cerebrovascular disease as the most common causes over the age of 30 (Hart and Sander, 2008). However, in developing nations, parasitic, bacterial, and viral infections are the most important etiological factors (Senanayake and Román, 1993).

The complex pathophysiologic processes leading to the development of epileptic seizures and epilepsy may be induced by etiological risk factors causing mutations in ion-channels, focal lesions, neurogenesis, neuronal loss, structural reorganization of neuronal circuitry, and changes in the neuronal microenvironment (Chang and Lowenstein, 2003). Since most cases of epilepsy are idiopathic, the exact molecular, chemical and genetic mechanisms are unclear (Chang and Lowenstein, 2003).

1.4.4 Clinical Aspects of Childhood Epilepsy

The manifestation of epilepsy and epileptic seizures varies according to individual differences in brain maturity, neuronal activity, confounding disease, medications, and several other factors (Fisher et al., 2005). However, following the ICES (CCTILAE, 1981) and the ICE (CCTILAE, 1989), common signs and symptoms have been used to categorize different types of epileptic seizures and syndromes. This classification system details identifiable clinical aspects of epilepsy, such as the impairment of consciousness at seizure onset during a complex partial seizure (Engel, 1991).

At the onset of a seizure, normal sensory, motor and autonomic functions are typically interrupted (Fisher et al., 2005). Sensory distortions may arise as single sensations such as visual hallucinations or as a complex experience of multiple sensory systems. Changes in the nervous system can be expressed as impaired consciousness and behaviour, as well as changes in emotional state such as fear and elation. Distortions in memory manifest as both positive and negative symptoms, whereas cognitive deficits can negatively affect abilities such as attention and speech. As described previously in Section 1.4, epilepsy is officially diagnosed in three circumstances: when a patient experiences at least two unprovoked seizures that occur > 24 hours apart, when the recurrence rate of further

unprovoked seizures is high, and when patients are diagnosed with an epilepsy syndrome (Fisher et al., 2014).

The years between the ages of 2 and 12 have been described as a phase where the development of cognitive and social skills is crucial. The effects on development define the categories of “benign”, “intermediate”, and “catastrophic” epilepsy in childhood. Benign epilepsy involves mild infrequent seizures without cognitive and psychosocial effects. Catastrophic epilepsy involves a high frequency of seizures and associated injuries with permanent effects on cognitive and social development. It is often resistant to medication and symptoms can cause significant social barriers such as the need to continually wear protective equipment. Some benign epilepsies are clearly identifiable, such as benign rolandic epilepsy with typical features, genetic etiology, and excellent prognosis. However, as benign occipital epilepsy demonstrates, they may also be complex with variable features, unknown etiology, and indeterminate prognosis. Intermediate epilepsies include childhood absence epilepsy, epilepsies characterized by cryptogenic partial seizures, and generalized epilepsy with febrile seizures plus (GEFS+) (Camfield and Camfield, 2002). The clear categorization of these epilepsies into “benign” and “catastrophic” is complicated by the variation in response to medication, as well as presence and absence of cognitive and learning problems. Catastrophic childhood epileptic syndromes include continuous spike-wave in slow sleep (CSWS) disorder, Landau-Kleffner syndrome, Lennox-Gastaut syndrome, and Myoclonic-astatic epilepsy (Camfield and Camfield, 2002).

1.4.5 Prognosis and Treatment

Prognosis in epilepsy depends on factors such as etiology, patient age, seizure type, number of seizures, and other characteristics that influence treatment (Bell and Sander, 2001). With no cure for epilepsy, medical treatment is primarily designed to control and eliminate seizures (Kohrman, 2007). However, it is now widely accepted that optimizing HRQL is an equally important goal (Speechley, 2013).

Bell and Sander (2001) detail four groups that help to categorize prognosis. “Excellent prognosis” is defined by few seizures and a high potential for spontaneous remission.

“Good prognosis” describes seizures that are controlled by AEDs and remission that is usually permanent. “AED-dependent prognosis” is when the long-term use of AEDs is required to suppress seizures, whereas “bad prognosis” is when intensive AED treatment is unable to control seizures. In the clinical setting, these prognostic groups are no longer in common use due to difficulties in its practical application (Bell and Sander, 2001).

Through treatment but without the long-term use of AEDs, approximately 70% of patients become seizure-free. However, AEDs are required for seizure control in approximately 10% to 15% of patients, and 15% to 20% of patients are unable to suppress seizures even with intensive AED therapy. Despite the approval of over 15 anti-seizure medications by the US Food and Drug Administration, the use of a single medication at a time is preferred in treating epilepsy to reduce the number of adverse side effects (Kohrman, 2007).

Common side effects of AED use in children include hyperactivity, somnolence, weight changes, and skin rashes (Greenwood, 2000, Kohrman, 2007). AEDs typically function by increasing the inhibition and reducing the excitability of membranes (Engel, 1991). The general effect on cerebral function is therefore nonspecific and leads to adverse side effects (Engel, 1991). Newer medications are not always more effective than older drugs, however, they often have fewer known side effects (Kohrman, 2007). Alternative therapies for treating epilepsy include the ketogenic diet, vagus nerve stimulation, experimental implantable devices, and surgery (Kohrman, 2007).

1.5 Overview of Thesis

The remaining chapters of this thesis are organized as follows:

Chapter 2 briefly describes the concept and measurement of severity and single-item rating scales, followed by a review of the psychometric properties of existing scales for the measurement of the severity of seizures, syndromes, and epilepsy. Chapter 3 provides relevant definitions and an overview of psychometric properties of measurement scales. This chapter also describes the research methodology including data source, study population, measures, and data analysis strategies specific to each objective. Chapter 4 reports the sample characteristics and results of the current study, while Chapter 5 presents a detailed discussion of the study results, strengths and limitations of the study, and future directions for the GASE Scale.

CHAPTER 2

LITERATURE REVIEW

2.1 The Concept and Measurement of Severity

There are many ways to define severity for both clinical and health research goals. Stein and colleagues (1987) explain that severity is not a fixed concept and that different types of severity represent distinct constructs and characteristics. They describe severity as a broad abstract construct that can represent characteristics of a biological defect, amount of illness or disability, impact on quality of life, and social, emotional or financial burden. To help define the concept of severity, a framework was developed that outlines three inter-related constructs related to intrinsic biological severity: physiological or morphological severity, functional severity, and burden of illness. These types of severity interact to form the larger overall concept of severity of chronic illness (Stein et al., 1987).

Measuring severity involves specifying a dimension of illness along a spectrum and using proxies to quantify the clinical manifestations of interactions among biological, genetic, and environmental determinants. To quantify aspects of the framework, proxies measuring physiological and morphological severity use laboratory and anatomical reports while measures of functional severity assess aspects of health related to regular daily function, such as the number of days spent in bed or cognitive disability due to disease. The burden of illness on families and society incorporates the financial, emotional, and social dimensions of severity (Stein et al., 1987).

Severity may derive from different aspects of life and health depending on the perspective of the clinician, patient, or family. Therefore, the objectives and perspective of a study, the type of illness or disability, time frame, and the population of interest will determine the criteria for defining and measuring severity. Severity can be measured through direct observations of symptoms and behaviours or indirectly using existing records and third party judgements. This variety is reflected in the many different severity

scales developed for different types of disease depending on the study objectives, population, and design (Stein et al., 1987).

2.2 Single-item Rating Scales

Single-item rating scales are widely used in research and clinical applications as an alternative to multi-item measures. While multi-item measures contain several items to evaluate the different dimensions of a construct, single-item measures represent an entire concept in a single, global question and are open to consider every dimension influencing the assessment of a phenomenon (Gardner et al., 1998, Patrician, 2004). Common single-item scaling methods include the visual analog scale (VAS), the unipolar adjectival scale, the bipolar Likert scale, and graphical representational scales such as the face scale which uses pictures to show varying degrees of unhappiness, pain or distress (Streiner and Norman, 2008). As they are easy to administer, reduce costs, and require less time to complete, single-item measures impose minimal burden on patients and physicians (Patrician, 2004). However, since the objectives and requirements of a study determine which type of measure to use, in situations where researchers are interested in differentiating the main dimensions under evaluation or identifying a detailed source of change in longitudinal studies, multi-item measures are more suitable (Youngblut and Casper, 1993, Patrician, 2004).

Despite thorough debate over the utility of single-item rating scales, there is evidence that in certain circumstances multi-item measures are not always better (Gardner et al., 1998). Single-item measures were reported to effectively assess health status (DeSalvo et al., 2006), quality of life (Zimmerman et al., 2006), psychological well-being (Youngblut and Casper, 1993, Zimmerman et al., 2006), medication adherence (Kalichman et al., 2009), and other non-health related concerns such as job satisfaction (Wanous et al., 1997). Clinicians' ratings on single-item scales have also demonstrated validity in many domains of health, including sedation (Weinert and McFarland, 2004), quality of life and side effects of chemotherapy (Coates et al., 1983a, Coates et al., 1983b, Coates et al., 1990), anxiety with myocardial infarction (De Jong et al., 2005), bladder condition (Coyne et al., 2006), physical activity (Iwai et al., 2001), dental anxiety (Neverlien, 1990), severity of dyspepsia symptoms (Veldhuyzen van Zanten et al., 2006), quality of

life and health in epilepsy (Stavem et al., 2000, Stavem et al., 2001), and severity of seizures (Carpay et al., 1996).

2.3 Measurement of Severity of Seizures and the Severity of Epilepsy

An ongoing challenge for clinicians and researchers is the measurement of the severity of epilepsy. Although multiple measurement tools have been developed, there is no universally accepted standard severity scale (Thurman et al., 2011). The objectives of a study typically inform the choice of particular measure to use and studies often employ more than one measure.

In clinical trials measuring the efficacy of new AEDs, the frequency and severity of seizures are important outcome measures (Baker et al., 1998a). However, the majority of existing scales emphasize only the assessment of the severity of seizures. These ratings scales are similar in the method of evaluation used, usually an interview or questionnaire, but they prioritize different clinical characteristics and sources for assessment, such as the clinician's viewpoint or the patient's perspective (Thurman et al., 2011).

The ILAE "Standards for Epidemiologic Studies and Surveillance of Epilepsy" (Thurman et al., 2011) provides a table that identifies common examples of standardized "epilepsy-related severity assessment instruments" developed for clinical trials. Three categories of measures are listed. There are six "Seizure Severity Measures": the Seizure Frequency Scoring System (SFSS); the Veterans Administration Seizure Frequency and Severity Rating Scale (VA); the National Hospital (Chalfont) Seizure Severity Scale (NHS3); the Occupational Hazard Scale (OHS); the Liverpool Seizure Severity Scale (LSSS); and the Hague Seizure Severity Scale (HASS). There is one "Syndrome Severity Measure" listed, namely the Epilepsy Syndrome Severity Scores- Child (ESSS-C). There is only one measure listed as an "Epilepsy Severity Measure", the Global Assessment of Severity of Epilepsy (GASE) Scale.

The following review outlines four of the measures listed by the ILAE that are specific to the assessment of the severity of epilepsy seizures, syndromes, and overall illness. Two

instruments that were designed for a specific purpose, that is, the SFSS assessing patients undergoing surgery (Rodgers et al., 2012) and the OHS assessing the degree of social impairment affecting work suitability (Cramer and French, 2001) are not described here. Other scales that evaluate specific forms of epilepsy such as the Early Childhood Epilepsy Severity Scale (E-Chess) (Humphrey et al., 2008) assessing childhood tuberous sclerosis are not reviewed here either. The Seizure Severity Questionnaire (SSQ) is also included in this review under the heading of “Measures of Severity of Seizures” for its assessment of the severity of seizures.

2.4 Measures of Severity of Seizures

2.4.1 Veterans Administration Seizure Frequency and Severity Rating Scale (VA)

Developed by the Veterans Administration Cooperative Study Group in 1978 and revised in 1985, the VA Scale was designed for use in clinical trials to compare the effects of anti-epileptic drugs (AEDs). Over more than a decade, 1100 patients with newly diagnosed epilepsy were recruited to participate in two multicenter studies (Cramer, 2001) assessing the efficacy of four common anticonvulsant drugs in the USA (Wijsman et al., 1991). The VA Scale is an interviewer-administered assessment (Baker et al., 1998a) that relies on the recall and diaries of patients to inform the severity score (Cramer, 2001). Clinicians interview patients together with individuals who have observed the seizures. The scale is composed of three sections each focusing on one of the three types of partial-onset seizures: simple, complex, and secondarily generalized. Incorporating both the levels of frequency and the severity of seizures, the sections contain similar questions. Each section score is scored based on seizure type and frequency, followed by modifications according to the circumstances surrounding a seizure such as a warning sign. Section scores are then combined into a final composite score (Cramer, 2001). The composite score enabled a simple evaluation and comparison of AED outcomes in the VA Cooperative studies (Wijsman et al., 1991).

Validity and Reliability. Although the developers of the VA Cooperative Studies reported results comparing scores on the VA Scale for patients using the four most commonly

used AEDs, they did not report any results of specific psychometric testing for the VA Scale (Cramer, 2001).

An independent assessment of the inter-rater reliability of the composite VA score as an indicator of clinical severity was conducted in the Netherlands using 24 consecutive patients 15 years of age and older selected at random from out-patient clinics with two successive interviews conducted separately by the patient's clinician and one of the study authors using the VA Scale. The results indicated moderate inter-rater reliability (Wijsman et al., 1991). Further validity testing of the composite score conducted in 47 consecutive patients produced results indicating acceptable construct validity (Wijsman et al., 1991).

Responsiveness. The responsiveness of the VA Scale is unclear, as the initial VA Cooperative studies comparing the treatment effects of four AEDs did not agree on the sensitivity of the scale. Developers were unable to determine whether the finding of no significant difference among treatment groups was due to the scale's inability to detect change or the general equivalence among the AEDs. However, the second VA trial reported a significant difference in scores between patients taking carbamazepine (CBZ) and valproate (VPA) (CBZ mean: 6.2 versus VPA mean: 2.0, $p = 0.04$) (Cramer and French, 2001).

Summary. Although clinicians completed each interview within the 20 minute time frame for regular consultation during both prospective studies (Wijsman et al., 1991), the scoring system was found to be complex, thus limiting its widespread use (Cramer, 2001). While the VA Scale is recognized as an adequate tool for overall assessment based on a review of the evidence, caution has been advised regarding the extent to which the scale can be used to measure changes in seizure severity based on its lack of sensitivity reported by the initial VA Cooperative Studies (Cramer and French, 2001).

2.4.2 National Hospital (Chalfont) Seizure Severity Scale (NHS3)

The Chalfont Seizure Severity Scale, first described by Duncan and Sander (1991), was designed to evaluate the severity of seizures in AED clinical trials. Consisting of

weighted scores for 11 clinical features affecting the severity of seizures, the Chalfont scale is a patient- and observer-based scale that can accommodate evaluation of patients with several types of seizures. When administered by health professionals, the scale can be completed within a few minutes. Content of the scale was determined through interviews with 50 recruited patients and their families at an epilepsy clinic in the United Kingdom (Duncan and Sander, 1991). Although the age and sex of patients were not described by Duncan and Sander (1991), Baker et al. (1998a) indicated that the 1996 revised version of the Chalfont scale renamed the National Hospital Seizure Severity Scale (NHS3) was intended for adults.

Based on the results of a study on the AED tiagabine (Duncan and Sander, 1991), suggesting poor responsiveness to change, there were substantial revisions to create the NHS3 (O'Donoghue et al., 1996).

Similar to the approach of the VA Scale, the NHS3 involves responses from patients and relatives who have witnessed the seizures (Baker et al., 1998a). However, unlike the VA scale, evaluated seizures are not restricted to three types and a single 7-item system is used for assessment (Cramer, 2001). The NHS3 is adapted from the Chalfont scale with fewer seizure-related factors and a simpler scoring system where all seven items have equal weight except for a question on warnings prior to seizures (O'Donoghue et al., 1996).

Validity and Reliability. The NHS3 was found to have sufficient inter-rater and test-retest reliability for use in AED trials when data were analyzed for groups of individuals, but not for single patient data based on a study of 87 consecutive adult patients (45 males and 42 females) with a median age of 31 years (range: 27 to 44 years), accompanied by their relatives from an epilepsy clinic at a tertiary referral centre (O'Donoghue et al., 1996).

There is also evidence of construct validity of the NHS3 based on two experiments ($n_1 = 80$ and $n_2 = 50$) that asked patients to rank the severity of five sample seizure types presented on cards for comparison with a ranking determined by the NHS3 (weighted kappa = 0.82 signifying very good agreement) (O'Donoghue et al., 1996).

Responsiveness. Studies using the NHS3 did not provide evidence to support the responsiveness of the scale, which suggests that the drugs either did not affect the severity of seizures or the scale was incapable of detecting change (Cramer, 2001).

Summary. Despite improvement from the original Chalfont scale, the NHS3 has been noted to have several limitations primarily in scoring and point assignment. The 1 to 4 point rating scale for each item has been criticized as arbitrary and simplistic, thus exposing the scale to over and under-rating. The potential to report rare injuries and the same type of seizure more than once also contributes to overestimated scores. Further, in determining the overall impact of injury, the scale assigns points to only the most severe injury experienced by the patient without consideration for the frequency of injuries and falls (Cramer and French, 2001). The lack of evidence supporting the responsiveness of the scale is another crucial limitation of the NHS3 (Cramer, 2001).

2.4.3 Liverpool Seizure Severity Scale (LSSS)

The Liverpool Seizure Severity Scale (LSSS) was designed as a patient-reported scale with two subscales to summarize the severity of seizures from the perspective of the patient during AED treatment evaluation. In the original design, the first subscale “percept” contained 9 questions assessing the patients’ sense of control over seizures, while the second subscale “ictal” contained 10 questions assessing the severity of the ictal and post-ictal experience (Baker et al., 1991). The number of items in the LSSS has repeatedly changed over the course of several AED studies, and while the original scale used a 4-point Likert scale for each question, updated versions of the LSSS use a 5-point Likert scale to improve the sensitivity of the scale in detecting potential treatment effects of AEDs (Smith et al., 1995). The “percept” subscale was also eliminated from future versions of the LSSS (Cramer and French, 2001).

Validity and Reliability. Assessment of early versions of the LSSS produced mixed results for both validity and reliability. Initial tests supported the validity and reliability of the “ictal” subscale (Baker et al., 1991, Wagner et al., 1995), but consistently suggested poor validity and reliability of the “percept” subscale (Baker et al., 1991, Wagner et al., 1995, Rapp et al., 1998).

Subsequent modifications to improve the LSSS required patients with multiple seizure types to complete the questionnaire separately for their most severe seizures designated as “major”, and their least severe seizures designated as “minor”. Although modifications improved the test-retest and internal consistency reliability for both “ictal” and “percept” subscales, investigators recommended future testing of the validity and responsiveness of the scale (Baker et al., 1998b).

Despite past revisions to the LSSS, Scott-Lennox et al. (2001) argued that the scale was unusable so they re-developed the scale to address limitations of complexity and length, the scale’s inability to account for the episodic nature of epilepsy, variation due to unclear definitions of “major” and “minor” seizures, and the ineffective “percept” subscale. After modifying the scale, investigators re-analyzed archival LSSS data from two studies evaluating Lamotrigine (LTG) therapy: Adjunctive Lamictal [Lamotrigine] in Epilepsy: Response to Treatment (ALERT) and a double-blind randomized control study (LAM30/31). The revised LSSS (LSSS 2.0) eliminated the “percept” subscale and generated a single “most severe” “ictal” score instead of the two “major” and “minor” seizure type ratings. Further adjustments enabled researchers to assign a value to previously “undefined” scores and reduce the amount of missing data for clinical research assessments. When the original LSSS scoring system was compared with the LSSS 2.0 in a test for reliability, the Cronbach’s alpha coefficient exceeded 0.7 for “major”, “minor”, and “most severe” data in the ALERT study as well as for “most severe” in the LAM30/31 study, thus supporting the internal consistency of the new scoring system. Construct validity was further confirmed by known-groups validity in data from both studies. The baseline scores for seizure types rated by physicians varied significantly ($F = 2.37$ to $F = 10.06$, 2 d.f.) and patients with simple or generalized complex seizures scored high while patients with simple partial seizures scored lower, indicating that the LSSS 2.0 is capable of differentiating patients with different types of seizures (Scott-Lennox et al., 2001).

Responsiveness. A randomized, placebo-controlled, double-blind, cross-over study involving 81 patients (33 males and 48 females) with a mean age of 34 years (range: 15 to 67 years) found that following treatment with LTG, the “percept” subscale was

unresponsive to changes in severity ($t = -0.28$, CI: -1.0 to 0.43 , $p = 0.443$) (Smith et al., 1993), which was later confirmed by other studies (Smith et al., 1993, Wagner et al., 1995, Rapp et al., 1998). Although the “ictal” subscale detected statistically significant difference in mean scores ($t = -1.06$, CI -1.90 to -0.22 , $p = 0.017$) (Smith et al., 1993), it was not considered large enough to be clinically significant (Baker et al., 1998a).

In the analysis of archival data measured at baseline and week 16 from the ALERT study (Scott-Lennox et al., 2001), the LSSS 2.0 appeared to be sensitive to changes in a patient’s condition of epilepsy following LTG therapy, which is known to be effective in reducing the frequency of seizures (Bryant-Comstock et al., 2001). Four physician-rated aspects of seizure severity (global rating of epilepsy status, overall severity of seizures, time to recovery, and severity of injuries) detected statistically significant change ($p < 0.05$), which was reflected by a similar change in seizure severity as scored by the LSSS 2.0 (Scott-Lennox et al., 2001). Additionally, the mean change (\pm SD) in LSSS 2.0 scores for patients receiving LTG therapy at week 16 (9.2 ± 23.4 , $n = 467$) was significantly higher ($p = 0.0002$) than the mean change in LSSS 2.0 scores for patients who had discontinued therapy before week 16 (0.8 ± 23.8 , $n = 87$) and paralleled the significant improvement ($p < 0.006$) in other physician-rated aspects of seizure severity (Bryant-Comstock et al., 2001).

Although it is unclear which version of the LSSS was employed by researchers in an assessment of the AED zonisamide, results of the 19 week study in 281 adults indicated statistically significant change between LSSS scores at baseline and week 19 (Dupont et al., 2010). However, clinical relevance was questioned due to small observed effects of the LSSS (Schmidt, 2010).

Summary. Despite improvements to the scale (Scott-Lennox et al., 2001) and some evidence of responsiveness to change, further testing is required to verify the test-retest and inter-rater reliability specific to the revised scoring system. Evidence to support the clinical significance of change detected by the scale is also needed before recommendation as a reliable assessment tool in clinical trials (Schmidt, 2010).

2.4.4 Hague Seizure Severity Scale (HASS)

The Hague Seizure Severity Scale (HASS) is an adaptation of the LSSS developed for use in the treatment of childhood epilepsy and measures the severity of seizures in children by parent report using self-administered questionnaires (Cramer, 2001). Containing 13 questions, the contents of HASS were suggested and modified by both parents and child neurologists (Carpay et al., 1996).

Validity and Reliability. In a study of 80 children (46 males and 34 females) with a mean age of 9.6 years (range: 4 to 16 years) from outpatient child neurology departments and university hospitals in the Netherlands, HASS questionnaires were mailed to participants along with a follow-up questionnaire to 18 participants 2 weeks after completion of the first survey. Assessment of reliability indicated high internal consistency (Cronbach's alpha of 0.85) and high test-retest reliability (Pearson correlation coefficient of 0.93), while the distribution of HASS scores supported the scale's discriminant validity. HASS scores were also significantly correlated with the frequency of seizures (Spearman rank correlation coefficient of -0.33, $p = 0.004$) (Carpay et al., 1996).

Reliability of the HASS is further supported by a 2-year prospective longitudinal study, assessing the changes in 28 children (14 males and 14 females) with a mean age of 6 years (range: 7 months to 15 years) with medically intractable epilepsy who did not undergo surgical intervention. Kwan and Brodie (2000) define patients who continue to experience seizures as having intractable epilepsy. Children were recruited through the Dutch Collaborative Epilepsy Surgery Programme (DuCESP) and assessed in an outpatient clinic in the Netherlands. Across the 4 time points, children were relatively stable with no significant change in motor impairment, motor development, and perceived restrictions on social activity throughout the duration of the study. HASS scores also did not show statistically significant change of seizure severity from baseline (mean score range: 29-28) (van Empelen et al., 2007).

In a study involving 117 children (67 males and 50 females) with a mean age of 9.7 years (range: 4 to 16 years) from outpatient child neurology departments in the Netherlands, investigators compared HASS scores with a neurologist completed Visual Analogue

Scale (VAS). Despite both scales showing large variability in severity scores within each seizure type, significant differences were found between three subgroups that sorted types of seizures by the degree of severity: minor (absences and simple partial seizures), intermediate (complex partial seizures), and major (generalized tonic-clonic seizures), thus supporting the construct validity. A statistically significant correlation (Pearson's correlation coefficient of 0.45, $p < 0.001$) was also found between HASS and VAS scores. However, after stratifying for seizure type, correlations decreased ($0.10 \leq r \leq 0.26$) and statistical significance was lost. A significant correlation found between HASS scores and seizure frequency (Pearson correlation coefficient of -0.28, $p < 0.05$) also decreased to $r < 0.14$ following stratification. Unlike HASS scores, VAS scores were not correlated with seizure frequency and were significantly correlated with the duration of epilepsy, schooling level, and mono- or poly-therapy. The substantial difference in ratings was not considered an indication of the validity of either rating scale but rather attributed to different factors impacting neurologists' and parents' perspectives (Carpay et al., 1997).

Responsiveness. In a prospective longitudinal study on the consequences of hemispherectomy, HASS was used to measure the change in severity of seizures following surgery at an outpatient clinic in the Netherlands. For a period of two years, 12 children (3 males and 9 females) with a mean age of 5.9 years (range: 0.3 to 11.1 years) at the time of surgery were evaluated once prior to hemispherectomy and three times after the procedure. Group mean scores assessed 6 months and 2 years after surgery showed significant decrease in severity from baseline with scores of 30.52 (SD 2.9, range 27 to 39) for before surgery, 14.8 (SD 0.8, range 13 to 15, $p < 0.01$) for 6 months, and 13.25 (SD 0.7, range 13 to 15, $p < 0.01$) at 2 years. Significant change was also detected by other measures of seizure frequency (Engel classification (Engel et al., 1993)), gross motor activity (Gross Motor Function Classification Scale), functional skills and caregiver assistance (Pediatric Evaluation of Disability Inventory), and perceived restrictions on social activity (Hague Restrictions in Childhood Epilepsy Scale) (van Empelen et al., 2004). Given that epilepsy surgery effectively reduces seizure activity in children with pharmaco-resistant seizure disorders, the significant reduction in severity

detected by HASS is consistent with change in several other measures in the study and provides evidence to support its responsiveness (van Empelen et al., 2004).

Significant change in HASS scores as well as frequency of seizures 3 months prior to treatment with methylphenidate and 1 month after treatment was also reported in a study testing the safety and efficacy of methylphenidate used to treat ADHD in 22 children (mean age: 11 years) with epilepsy (Santos et al., 2013). These findings provide further evidence to support the responsiveness of the scale.

Summary. There is adequate evidence to support the effective measurement properties of the HASS for use as a parent-report measure in childhood epilepsy. Research on the clinical significance of change detected by the HASS would further strengthen its acceptance as a useful measure of seizure severity.

2.4.5 Seizure Severity Questionnaire (SSQ)

Acknowledging the limitations of previous seizure severity scales, the Seizure Severity Questionnaire (SSQ) was developed to assess treatment response in clinical trials (Cramer et al., 2002). As opposed to the LSSS 2.0 assessing the most severe seizure type currently experienced by the patient, the SSQ evaluates the most frequent seizure type and excludes questions that prevent the universal assessment of seizures, such as elements relating only to certain types of seizures and treatment effects. Other questionnaires, patient experience, and the expertise from epileptologists were consulted in the selection of content for the scale, as well as face and content validity (Cramer et al., 2002).

The initial structured interview completed in less than 35 to 50 minutes contained 22 items that were categorized into warning, activity and recovery phases, along with questions on overall seizure severity and bothersomeness. The recovery phase was further divided into cognitive, emotional, and physical aspects of recovery. Items were scored by duration in minutes or by a 7-point Likert scale which were then combined into a total Summary Score (Cramer et al., 2002).

Following pilot testing of the initial SSQ, the questionnaire was revised to contain 24 items (Borghs et al., 2014). Similar to the original questionnaire, items were divided into three categories of aura/warning, ictal, and postical events, as well as global questions assessing the overall seizure severity and bothersomeness. However, the phrasing of questions and response format were simplified to collect only “yes” or “no” answers and scores on the 7-point Likert scale. The revised SSQ also eliminated the final Summary Score, a question on the severity of the warning sign, and an item addressing nocturnal seizures (Cramer et al., 2002, Borghs et al., 2014).

Validity and Reliability. In the pilot study, 91 adult patients (41 males and 50 females) with a mean age of 39 years (range: 17 to 77 years) were recruited from three centres in the United Kingdom and the United States. A total of 87 accompanying relatives or friends also provided information as observers to seizures. Patients and their observers were both interviewed by two interviewers independently and between 2 to 48 days following the first interview, 63 patients were re-interviewed. Results for the Summary Score showed moderate inter-rater ($r = 0.76$) and test-retest reliability ($r = 0.74$). However, the item-level assessment produced greater variability and reduced reliability for individual items. Items related to duration and the severity of cognitive effects, as well as procedural flaws were criticized for the poor reliability (Cramer et al., 2002).

Comparing SSQ scores to other common scales revealed a low correlation with the VA scale ($r = 0.24$), and a moderate correlation with the NHS-3 ($r = 0.31$) and the LSSS ($r = 0.48$). When compared with each other, the different constructs targeted by each scale were reflected in poor correlations between all scales (Cramer et al., 2002).

A study in the United States collected data from 775 postal questionnaires to assess quality of life, and scores from the Centre for Epidemiologic Studies Depression Scale (CES-D), the SSQ, and the Sheehan Disability Scale (SDS). Results showed that individuals with severe, moderate and no symptoms of depression reported significantly different SSQ subscale scores ($p < 0.0001$ to $p \leq 0.05$), and provided evidence that the SSQ was able to discriminate between different degrees of severity among respondents with and without depression (Cramer et al., 2003).

Despite the need for further scale development, the initial SSQ was described in several clinical research studies using the scale as an outcome assessment tool to demonstrate AED efficacy and correlation with other measures of quality of life (Cramer et al., 2003, Sancho et al., 2010, Schmidt, 2010, Cramer et al., 2012, Borghs et al., 2012).

Although the revised SSQ was analyzed for sensitivity to change (Borghs et al., 2014), there are no published reports available that describe the specific validity and reliability of the newly revised scale.

Responsiveness. In a review of measures evaluating the effect of AEDs on the post-ictal state (Schmidt, 2010), the initial SSQ detected changes in severity following treatment with the AED lacosamide in phase II/III clinical trials (Chung et al., 2007, Halász et al., 2009). Data pooled from two randomized control trials with a total of 823 patients showed that patients allocated to the lacosamide treatment reported large mean improvements in severity detected by all subscales of the SSQ (Schmidt, 2010). Other studies assessing the long-term effects of lacosamide treatment using pooled data from three Phase III clinical trials reported statistically significant mean improvement of SSQ subscales after one year of lacosamide treatment (Cramer et al., 2012), as well as substantial reductions in seizure severity detected by the SSQ (Borghs et al., 2012).

In a 6-month study involving 54 hospitals in Spain and 261 enrolled patients (122 males and 139 females) with a mean age of 40.8 years, the initial SSQ measured the mean change in seizure severity in regular clinical practice for patients with refractory partial epilepsy. Patients were also assessed using the Hamilton Anxiety Rating Scale (HAM-A), the Hamilton Depression Rating Scale (HAM-D), the Medical Outcomes Study—Sleep Scale (MOS-Sleep), the Quality of Life in Epilepsy Inventory-31 (QOLIE-31), and the Morisky-Green test. When compared with baseline, both the 3 and 6 month change in SSQ scores were statistically significant ($p < 0.0001$). Although all of the rating scales showed a change in scores from baseline, changes detected by the SSQ were not directly compared with changes from the other rating scales (Sancho et al., 2010).

To assess the revised SSQ, data from baseline to week 48 was pooled from two open-label extensions of lacosamide clinical trials ($n = 308$ and $n = 376$). Patients were

grouped according to the type of seizure at baseline: complex partial seizures (CPS) or secondarily generalized partial seizures (SGPS), and individuals with $\geq 50\%$ reduction in seizure frequency of the baseline seizure type were further classified as “responders”. For individuals with SGPS, the difference in mean change on the SSQ total score between responders and nonresponders was -0.94, while the difference for individuals with CPS was -0.47. The difference between SGPS- and CPS-specific scores (-0.47) indicated that patients with more severe seizures (SGPS) experienced a greater reduction in seizure frequency (Borghs et al., 2014). A study on the minimally important change thresholds for the SSQ determined that a 0.48-point change (range: 0.34 to 0.50) in the SSQ total score reflected clinically meaningful change (Cramer et al., 2014). Therefore, the results provided adequate evidence to support the responsiveness of the revised SSQ to change according to seizure type (Borghs et al., 2014).

Summary. Although the revised version of the SSQ shows evidence to support its ability to detect clinically meaningful change, there is only some preliminary evidence of validity and reliability established for the original version of the SSQ. Prior to use of the SSQ as an endpoint in clinical trials of AEDs, further research was recommended (Nixon et al., 2013).

2.5 Measure of Severity of Epilepsy Syndromes

2.5.1 Epilepsy Syndrome Severity Scores- Child (ESSS-C)

In contrast to measures evaluating the severity of seizures, the Epilepsy Syndrome Severity Scores-Child (ESSS-C) is a measure for the severity of epilepsy syndromes. The scale assigns a standard severity rating for each pediatric epilepsy syndrome to be used with other measures in evaluating the complete severity of seizure condition (Dunn et al., 2004).

The ESSS-C was developed with feedback from 18 pediatric neurologists to rate the severity of 36 pediatric epilepsy syndromes listed by the ILAE. Experts anonymously rated syndromes on a 10-point scale based on medical treatment response, seizure severity, and long-term prognosis in four rounds of testing. Final scores for each epilepsy syndrome were compiled into a single reference table (Dunn et al., 2004). During

development, syndromes with the highest and lowest ratings obtained unanimous or near unanimous ratings from neurologists. Although all scores were generally consistent, syndromes with middle range scores were more variably rated. Ratings were only unanimous for three syndromes: early myoclonic encephalopathy, early infantile epileptic encephalopathy with suppression burst, and simple febrile convulsion (Dunn et al., 2004).

The difficulty in obtaining unanimous scores for all syndromes was partly attributed to the Delphi technique used to establish severity scores. Additionally, the rarity of certain syndromes, and individual variability in response to medical treatment, seizure severity, and long-term prognosis posed a barrier to obtaining consensus. Individual physician bias and differences in prioritization for different outcomes also influenced syndrome ratings. The developers state that obtaining additional information on the rationale behind experts' scores would have provided further insight into the variability of certain syndrome scores. Other limitations to the ESSS-C concern future revisions to the ILAE classifications, as well as having only 12 of 18 enrolled experts complete the study (Dunn et al., 2004).

To date, there have been no published studies testing the psychometric properties of the ESSS-C.

2.6 Measure of Severity of Epilepsy

2.6.1 Global Assessment of Severity of Epilepsy Scale (GASE)

The Global Assessment of Severity of Epilepsy (GASE) Scale is a single-item measure developed by a panel of experts in pediatric neurology, epidemiology and neuropsychology to provide a more efficient measurement tool applicable to both clinical and research needs (Speechley et al., 2008). Designed as a clinician-report measure, the GASE Scale assesses the overall severity of a child's epilepsy at the time of clinical assessment. The clinician is asked: "Taking into account all aspects of this patient's epilepsy, how would you rate its severity at his/her last visit?". It uses a 7-point Likert response scale with clinical descriptors ranging from "extremely severe", to "not at all severe". Ratings measure the overall severity of a patient's epilepsy by considering all clinical aspects. Following assessment for clarity, relevance, usability, and face and

content validity, researchers conducted further testing for validity and reliability (Speechley et al., 2008).

Validity and Reliability. Preliminary construct validation tested for convergent validity by comparing scores on the GASE Scale and seven clinical aspects of epilepsy identified by the experts as factors influencing the clinical assessment. The seven aspects are: frequency of seizures, intensity of seizures, falls or injuries during seizures, duration/severity of the post-ictal period, total dose/number of AEDs, side effects of AEDs, and interference of epilepsy or drugs with daily life activities. Each aspect was rated on a 7-point Likert scale where “1” represented “none, never, or mild” and “7” represented “extremely frequent, severe, or high” (Speechley et al., 2008).

In the first test for validity, fifteen pediatric neurologists across Canada assessed between 1 and 20 (mean: 9) of their patients on the GASE Scale and the seven clinical aspects. A total of 134 children with epilepsy and a mean age of 8.7 years (SD: 5.6 years) participated in the study. The Spearman rank-order correlation coefficients assessing the association between the GASE Scale scores and each of the seven clinical aspects were statistically significant ($p = 0.001$) and ranged from 0.49 to 0.87, with seizure frequency as the most strongly correlated aspect. Signifying the strength of the relationship, the seven clinical aspects together accounted for 80.9% of the variation in the GASE Scale with frequency of seizures accounting for the most variance in severity of epilepsy at 77.5% ($p < 0.001$) (Speechley et al., 2008).

When two pediatric neurologists independently rated 65 clinical case scenarios describing real patients with varying degrees of severity, age (mean: 7.3 years, range: 0 to 18 years), and sex (37 males and 28 females), neurologists fully agreed on the severity of 29 cases (45%) using the GASE Scale, but differed by one point for 27 cases (42%) and two points in 9 cases (13%). The weighted κ value of 0.85 (95% CI: 0.79 to 0.90) indicated “almost perfect agreement” and high inter-rater reliability (Speechley et al., 2008).

High test-retest reliability was also found when two neurologists evaluated a random sample of 24 case scenarios from the initial 65 total cases after a 3-week interval. Perfect agreement was observed between times 1 and 2 in 13 cases (54%) for rater 1, and 15

cases (63%) in rater 2. However, a one-point difference in ratings was obtained in 10 cases (42%) for rater 1 and 9 cases (37%) for rater 2. Rater 1 further experienced a two point difference in a single case (4%). The weighted κ value for agreement in rater 1 was 0.90 (95% CI: 0.82 to 0.98) and 0.95 (95% CI: 0.91 to 0.98) for rater 2, while the Spearman rank correlation coefficient between times 1 and 2 was reported as 0.94 (95% CI: 0.89 to 0.96) (Speechley et al., 2008).

The GASE Scale has also been tested for its validity in the adult population. After adapting the tool for use as a patient self-report measure, construct validity was assessed in 250 adult patients (mean age: 40.9, SD:14.9; 45.3% male) from the cross-sectional Neurological Disease and Depression Study (NEEDS) in Calgary, Canada. The seven response categories remained unchanged, while the phrasing of the question was adjusted for direct use by patients: “Taking into account all aspects of your epilepsy, how would you rate its severity now?”. Statistically significant ($p < 0.05$) Spearman’s rank correlations were reported between the GASE Scale ratings and clinical and self-reported outcomes of seizure frequency ($r = -0.36$), number of AEDs ($r = -0.37$), AED side effects ($r = 0.35$), and responses from the Patient Health Questionnaire (PHQ9) ($r = 0.33$), Hospital Anxiety and Depression Scale (HADS) (HADS Anxiety: -0.18 ; HADS Depression: -0.32), and the Global Assessment of Epilepsy Related Disability (GAERD) Scale ($r = 0.57$). The GAERD Scale was developed as a similar single-item 7-point Likert scale to evaluate the disability due to seizures in adult patients with epilepsy (Wiebe et al., 2013). Researchers noted that although it was statistically significant, GASE Scale ratings did not correlate strongly with type of seizure ($r = 0.10$). After adjusting for clinical and demographic characteristics using multiple linear regression, the strongest predictors of the severity of epilepsy were disability due to epilepsy and AED side effects. This study further supports the scale’s construct validity and value as an effective clinical assessment tool (Wiebe et al., 2013).

Responsiveness. Responsiveness of the GASE Scale has not been assessed. A primary objective of the current study is to assess the responsiveness of the GASE Scale for clinical and research applications.

Summary. In addition to preliminary results supporting the construct validity and reliability of the GASE Scale, other key advantages include the 2 minute completion time and simple format. The scale also addresses the need for a global assessment of illness severity, which is important for decisions in therapy change, invasive treatments, and counselling, as well as assessing the impact of interventions. Further, the patient-specific rating enables cross-sectional comparison of patients and the assessment of the severity of epilepsy within patients over time (Speechley et al., 2008).

Although preliminary evidence suggests the usefulness of the GASE Scale in evaluating the severity of epilepsy, the scale requires further testing of measurement properties. As noted by researchers, estimates may have been inflated due to the methodology of preliminary tests, and clinician ratings reflect only one of several relevant perspectives including parents and patients themselves. Therefore, the developers indicate that the next step is to compare GASE scores with more empirical and objective clinical patient data, along with other common measures of epilepsy-related clinical aspects in research studies and systematic tests of construct validity, reliability, and responsiveness to change in patients over time (Speechley et al., 2008).

2.7 Summary of Measurement Scales

Although there are various measurement tools available to assess epilepsy-related severity, each scale possesses limitations preventing its widespread use. Based on a review of common scales assessing the severity of seizures and epilepsy, suggestions were made to create a simple, broad and more flexible instrument that could incorporate all of the complex factors affecting the severity of epilepsy, including elements not assessed by current scales (Cramer, 2001).

Table 2.1 provides an overview of the measurement properties for the existing severity scales described in this chapter. As reported by the ILAE, problems in the ease of use, sensitivity to changes, and subjectivity of assessments pose barriers toward the acceptance of a single standard epilepsy severity scale (Thurman et al., 2011). The majority of these scales have been shown in preliminary testing and some clinical trials to possess adequate face and content validity as well as sufficient reliability in inter-rater

and test-retest assessments (Cramer and French, 2001). However, none of the scales completely satisfy the psychometric requirements of outcome methods. Instrument flaws, complex scoring methods, and insufficient responsiveness testing are major concerns for the usefulness of these measures in assessing the severity of epilepsy and clinically relevant change (Cramer, 2001). Further, existing scales are often not practical for use in clinical or research settings due to the time commitment required to complete. Although only the HASS, ESSS-C, and GASE Scale were designed for the assessment of epilepsy in children (Baker et al., 1998a), measurement scales intended for adults may be adapted for use in children.

The ILAE “Standards for Epidemiologic Studies and Surveillance of Epilepsy”, reports that standardized measures assessing the severity of seizures fail to measure the total impact of epilepsy (Thurman et al., 2011). The use of scales evaluating the severity of seizures as standard outcome measures in AED trials was also not recommended due to the lack of evidence for clinical utility (Mohanraj and Brodie, 2003). Since statistically significant change may not translate into change that is clinically meaningful to patients (Cramer et al., 2014), investigators must determine the amount of change on scales that is necessary to be considered useful to patients. Researchers propose that scales evaluate information from multiple sources to ensure all aspects of the patient’s epilepsy are examined (Cramer and French, 2001). A combination of several measures may also provide a more comprehensive evaluation of the multidimensional nature of epilepsy (Dunn et al., 2004, Wagner et al., 2009).

Table 2.1: Summary of the assessment of validity, reliability, and responsiveness for the severity scales reviewed in this chapter. A “+” indicates that there is evidence to support the psychometric property, while “-“ indicates that there is evidence that does not support it. Unclear or flawed results are designated by “?”, while “0” indicates that no information was found. Where data are available for a scale that has undergone revisions, results reflect the assessment of the most recent version of the scale. Several investigators have indicated the lack of adequate testing for many of the measurement properties (Cramer, 2001, Cramer and French, 2001, Mohanraj and Brodie, 2003, Nixon et al., 2013). Therefore, the evidence to support specific psychometric properties as indicated in this table may only represent partial supporting evidence. See Section 2.4 to 2.6 for details. The table design is adapted from Terwee et al. (2007).

| | Content validity | Internal consistency ($\alpha \geq 0.7$) | Construct validity ($\kappa \geq 0.7$ or as determined by investigators) | Inter-rater reliability (ICC ≥ 0.7) | Test-retest reliability (ICC/Pearson's $r \geq 0.7$) | Responsiveness | Clinical significance of detected change |
|----------------------------------|------------------|--|---|---|---|----------------|--|
| Seizure Severity Measures | | | | | | | |
| VA Scale | + | ? | + | + / ? | 0 | ? | 0 |
| NHS3 | + | + | + | + / ? | + / ? | 0 | 0 |
| LSSS | + | + | + | + / ? | + / ? | + | 0 |
| HASS | + | + | + / ? | 0 | + | + | 0 |
| SSQ | + | 0 | + / - / ? | + / ? | + / ? | + | + |
| Syndrome Severity Measure | | | | | | | |
| ESSS-C | + | N/A | 0 | 0 | 0 | 0 | 0 |
| Epilepsy Severity Measure | | | | | | | |
| GASE | + | N/A | + | + | + | TBD | TBD |

CHAPTER 3

METHODS

3.1 Assessing the Psychometric Properties of Measurement Scales

Ensuring the quality of information collected by health measurement tools is essential to the appropriate design and selection of instruments used in both research and clinical assessment. Psychometric properties such as validity, reliability, and responsiveness provide insight into the accuracy and consistency of data collected by tools designed to measure subjective constructs such as quality of life, depression, or severity of illness. Validity refers to the degree to which an instrument measures what it was designed to measure, including subtypes of face, content, criterion, and construct validity. Reliability refers to the degree to which an instrument maintains the same results upon repeated application in similar conditions, including subtypes of test-retest, internal consistency, intra-rater, and inter-rater reliability (Streiner and Norman, 2008, pp.167-83, 247-74). Responsiveness refers to an instrument's ability to detect change over time and is further divided into internal and external responsiveness (Husted et al., 2000).

This study assesses the construct validity, stability, and responsiveness of the GASE Scale. The following subsections describe construct validity, stability, and responsiveness in further detail.

3.1.1 Construct Validity

Construct validity is the extent to which an instrument corresponds to a proposed interpretation of scores based on an underlying theory of the phenomenon under study (Aronson et al., 2002, Porta, 2008). It is important because many attributes cannot be observed or measured directly, such as anxiety or pain. The measurement of these factors relies on hypothesized manifestations that can be observed, such as an increased heart rate in patients experiencing anxiety (Streiner and Norman, 2008, p.257). In the absence of a criterion measure for comparison, researchers assess construct validity. Hypothetical constructs are used to examine the logical relationships between measures and other

relevant variables, methods, and patterns of scores. Therefore, there are many different approaches in assessing the construct validity of an instrument depending on the study objectives and population and it is a continuous process of examination with no single best method (Aaronson et al., 2002). Common statistical methods include using group differences, correlation analyses, structural equation modelling, and factor analysis (Cronbach and Meehl, 1955, Smith, 2005). For example, the two forms of construct validation: convergent and divergent evaluate the correlation between measures and either related or unrelated variables, respectively (Streiner and Norman, 2008, pp.262-3). A challenge in construct validation arises in interpreting findings where the results of a measure may reveal similar scores for two groups that were expected to differ. Since construct validation assesses both the theory and the measure, Streiner and Norman (2008, pp.259) describe three possible explanations for such results: the instrument is effective, but the theory is incorrect; the theory is correct, but the instrument cannot discriminate between the two groups; or both the theory and the measure are defective. In such instances, further studies would be required to clarify the results.

3.1.2 Stability

Validation of measurement instruments also involves ensuring the reliability of test scores. Reliability refers to the amount of random and systematic error associated with a measurement. It reflects the degree to which an instrument maintains the same results upon repeated application with different examiners and at different times. One aspect of reliability is the stability of an instrument over time. Test-retest reliability often assesses stability of test scores from two different occasions when patients are unlikely to have changed. Generally, the time interval for observations is between 2 to 14 days (Streiner and Norman, 2008, pp.167-207). To quantify reliability, there are several forms of the reliability coefficient, namely the Pearson correlation, intra-class correlation (ICC), and kappa coefficient. Despite frequent use of kappa and the Pearson correlation, the ICC is considered superior and preferred for continuous scales (Guyatt et al., 2008, pp.257, Streiner and Norman, 2008, pp.183-8). Although there are no universally applicable conventions to interpret ICC values, a minimum test-retest coefficient of 0.7 is generally considered adequate for use in research (Guyatt et al., 2008, pp.257, Streiner and

Norman, 2008, pp.193-4). Streiner and Norman (2008, pp.182-3) describe three possible explanations for low coefficients of reliability: the scale is reliable, but the attribute itself has changed over time; the attribute did not change, but the scale is unreliable; or test scores recorded at the second occasion were influenced by the first administration of the test.

It is important to establish stability of an instrument before testing for responsiveness to change, in order to increase confidence that changes detected are due to real change in the attribute being tested and not due to measurement error.

3.1.3 Responsiveness

Responsiveness is widely accepted as the ability of a measure to detect change (Aaronson et al., 2002). However, there is little agreement on the specific kind of change and no standard definition for responsiveness. Although the terms “responsiveness” and “sensitivity” are often used interchangeably, Liang (2000) argues that “sensitivity to change” is a broader term referring to any degree of change irrespective of clinical relevance or meaning to patients, while responsiveness is “the ability of an instrument to measure a meaningful or clinically important change in a clinical state” (Liang, 2000). While Streiner and Norman (2008, p.282) support the definition proposed by Liang, in a review listing sixteen variations of the definition for responsiveness, Beaton et al. (2001) recommended a simpler definition proposed by de Bruin et al. (1997): “Accurate detection of change when it has occurred”. Aaronson et al. (2002) suggest that “meaningful” change is a separate aspect of how data are interpreted. Despite disagreement over the concept and definition, as well as the interpretation and appropriate statistical methods used to assess responsiveness, researchers agree on the importance of establishing responsiveness for common measures used to detect change. Knowledge about the responsiveness of an instrument has value in both research and clinical practice where the accurate measurement of change in aspects of health status can be a primary outcome of clinical trials, influence treatment decisions, and help to monitor patients’ health over time. The selection of instruments, sample size estimation, and prioritization of outcomes also benefit from information on instrument responsiveness (Deyo et al., 1991).

As there is no consensus on the preferred statistical measure of responsiveness, investigators frequently report multiple statistics within a single study (Aaronson et al., 2002, Streiner and Norman, 2008, p.283). Husted et al. (2000) note that the various statistical strategies assess either internal or external responsiveness. They define internal responsiveness as “the ability of a measure to change over a particular pre-specified time frame”, while external responsiveness is “the extent to which changes in a measure over a specified time frame relate to corresponding changes in a reference measure of health status” (Husted et al., 2000).

Assessment of internal responsiveness involves distribution-based methods (Lydick and Epstein, 1993) where change is often detected in a measure in the context of pre-post clinical trials or treatments known to be efficacious. Common statistics include the paired t-test, Cohen’s effect size (ES), Guyatt’s Responsiveness Statistic (GRS), and the standardized response mean (SRM). Both Husted et al. (2000) and Zou (2005) favour the SRM as the most appropriate statistic, in part due to its independence from sample size and no need for an external criterion for change. Assessment of external responsiveness involves anchor-based methods (Lydick and Epstein, 1993) where changes are often compared with a criterion measure or other related constructs. Common methods include the receiver operating characteristic (ROC) curve, correlation analyses, and regression models. These statistical approaches and their respective limitations are discussed in greater detail by Deyo et al. (1991), Stratford et al. (1996), Husted et al. (2000), Liang (2000), Beaton et al. (2001), Stratford and Riddle (2005), Zou (2005), Norman (2008), and Streiner and Norman (2008, pp.282-95).

The interpretation of responsiveness statistics is also complicated by disagreement over the magnitude of change considered important. The Minimally Important Difference, Cohen’s thresholds for the SRM, probability of change statistic, and the reliable change index are some ways in which researchers calculate whether documented change is adequate. Understanding this change is further complicated by potential biases related to “response shift” and “implicit theories of change” (Streiner and Norman, 2008, p.279).

3.2 Data Source and Study Population

The data for this thesis are from the Health-Related Quality of Life in Children with Epilepsy Study (HERQULES). HERQULES was a two-year prospective cohort study that primarily assessed the health-related quality of life (HRQL) and risk factors in children with new onset epilepsy in Canada (Speechley et al., 2012). Using a two-stage clustered sampling strategy between April 2004 and April 2007, 53 (74%) out of a total of 72 practicing paediatric neurologists listed under the Canadian Association of Child Neurology (CACN) recruited the parents of children with epilepsy (median: 9 families per physician) meeting the inclusion criteria of the study. The study sample included new cases of epilepsy in children (range: 4 to 12 years old) with ≥ 2 unprovoked seizures. The children had not received past confirmation of the diagnosis and were seeing a paediatric neurologist for the first time. Participating parents possessed sufficient English language skills and were the primary caregivers of the children for a minimum of 6 months. Patients were excluded from the study if they were diagnosed with other progressive or degenerative neurological disorders and other co-morbid non-neurological disorders presumed to have an impact on quality of life (Speechley et al., 2012).

At four designated time points (baseline, 6, 12, and 24 months following the diagnosis of epilepsy), a mailed parent-report questionnaire collected information on HRQL and a series of child and family characteristics, while a clinician-report form collected information on clinical characteristics of the child's epilepsy. Of a total of 456 parents mailed questionnaires, 374 (82%) completed the baseline questionnaire and 283 parents (62%) returned all 4 completed questionnaires. Compared with those who completed the study ($n = 283$), children who were lost to follow-up ($n = 91$) were not significantly different ($p > 0.05$) in mean age, sex, severity of epilepsy, behavior problems or levels of health-related quality of life. Older parents who were married, had more education, and a higher income were more likely to complete and return all questionnaires, however (Speechley et al., 2012). The baseline time point was defined as the closest time to diagnosis following recruitment of parents into the study and it was intended to record the immediate impact of diagnosis on HRQL and associated factors. Together, the specific time intervals were selected to avoid missing potential fluctuations in scores while

ensuring enough time to detect changes in the measures and with minimal burden on participants. Further details of the HERCULES study methodology and results are described by Speechley et al. (2012).

3.3 Measurement

3.3.1 Parent Questionnaire

In the HERCULES study, the mailed parent questionnaire documented parents' perceptions of HRQL in children with epilepsy in the first two years following diagnosis as well as several family characteristics. HRQL was measured using the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) and the Child Health Questionnaire (CHQ) (Speechley et al., 2012).

In the current study, two questions from the CHQ (Fig. 3.1) and QOLCE (Fig. 3.2) sections are used to evaluate the responsiveness of the GASE Scale scores and to assess the association between the parents' perception of current child health and the child's severity of epilepsy as evaluated by the GASE Scale.

8.12. Compared to one year ago, how would you rate your child's health now? (check one box only)

| | | | | |
|------------------------------------|--|-------------------------------------|---------------------------------------|-----------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Much better now than 1 year ago | Somewhat better now than 1 year ago | About the same now as 1 year ago | Somewhat worse now than 1 year ago | Much worse now than 1 year ago |

Figure 3.1: HERCULES study CHQ question 8.12 assessing the parents' perception of change in child health.

1.15. Compared to other children his/her age, how do you think your child's health has been in the past 4 weeks?
Please consider your child's epilepsy as part of his/her health when you answer this question.

| | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Excellent | Very Good | Good | Fair | Poor |

Figure 3.2: HERCULES study QOLCE question 1.15 assessing the parents' perception of current child health.

3.3.2 Physician Report Form

In the HERQULES study, the physician form collected information on the clinical characteristics of the child's epilepsy. The two-page clinician-report form documented the patient's date of birth, last visit to the neurologist, age of first seizure, family history of epilepsy, whether the patient was attending school, type of seizure(s), epilepsy syndrome, CSE, exclusive nocturnal seizures, epilepsy medication information, major co-morbid conditions such as behavioural, cognitive, and motor problems, as well as neurological deficits, and the severity of epilepsy. The type of seizure was classified according to the ILAE's 1981 classification of seizures (ICES), while the type of epilepsy and epilepsy syndrome were classified according to the ILAE's 1989 classification of epilepsies and epileptic syndromes (ICE) (Speechley et al., 2003). In particular, the overall severity of epilepsy was measured using the GASE Scale and specific information was collected on seven core clinical aspects of epilepsy (Speechley et al., 2008).

Several questions on the physician form were adapted from the Canadian Epilepsy Data Registry (CEDAR Visit Form), and the physician form used to test both the Quality of Life in Epilepsy for Adolescents questionnaire (QOLIE-AD-48) and the Impact of Child Neurologic Handicap Scale (ICNH) (Speechley et al., 2003).

Appendix A contains the physician form used at baseline and Appendix B contains the physician form used at follow-up (6, 12, and 24 months).

In the current study, scores from the GASE Scale are compared with data gathered from other questions in the physician form to evaluate the construct validity, stability, and responsiveness of the GASE Scale.

3.3.2.1 The GASE Scale

The GASE Scale is a global rating scale assessing the overall individual severity of childhood epilepsy at time of clinical assessment. It consists of a single-item, 7-point Likert scale with the clinical descriptors: "not at all severe", "a little severe", "somewhat severe", "moderately severe", "quite severe", "very severe", and "extremely severe" (Fig. 3.3). By considering all clinical aspects, clinicians are asked to assess the overall severity

of a child's epilepsy (Speechley et al., 2008). A detailed description of the development and results of previous validity and reliability testing is provided in Chapter 2 section 2.6.1.

Taking into account all aspects of this patient's epilepsy, how would you rate its severity at his/her last visit? Please check one answer.

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

Figure 3.3: The Global Assessment of Severity of Epilepsy (GASE) Scale: a single-item, 7-point global rating scale assessing the overall severity of epilepsy in children.

3.3.2.2 Clinical Aspects of Epilepsy

Seven core clinical aspects of epilepsy were included in the physician form to document the frequency of seizures, intensity of seizures, falls or injuries during seizures, severity of the post-ictal period (conceptually defined as the abnormal condition immediately after an epileptic seizure and return to baseline (Fisher and Engel, 2010)), amount of AEDs, side effects of AEDs, and the interference of epilepsy or drugs with daily activities. These aspects were rated on a 7-point Likert scale with descriptors for 1 representing “none or never” and 7 representing “extremely frequent, severe or high”. The seven aspects were selected by an expert panel of three paediatric neurologists and two experienced epilepsy research coordinators. The expert panel had independently reviewed and agreed to these clinical aspects of a patient's epilepsy as key contributing factors in the clinical assessment of the severity of epilepsy (Speechley et al., 2008).

3.3.2.3 Other Clinical Characteristics of Epilepsy

In addition to the seven core clinical aspects of epilepsy, the current study also evaluates information on the reporting of convulsive status epilepticus (CSE), exclusive nocturnal seizures, and the total number of AEDs (recorded as a numerical quantity, in contrast to the Likert scale response described above for “amount of AEDs”).

3.4 Data Analysis

All statistical analyses were conducted using Statistical Analysis System (SAS) software Version 9.3 (SAS Institute Inc., Cary, NC, US).

3.4.1 Construct Validity of the GASE Scale

Objective 1: Hypotheses and Procedure

To evaluate the construct validity of the GASE Scale, a priori hypotheses were created to predict the correlations between GASE scores and neurologists' ratings of clinical characteristics of epilepsy contributing to the overall diagnosis of severity. Data recorded at Times 1, 2, 3, and 4 (baseline, 6, 12, and 24 months post-diagnosis, respectively) were analyzed at each time point. In this study, the clinical descriptors of the GASE Scale were specified using numerical values (1 to 7), with "not at all severe" designated as "1" and "extremely severe" designated as "7".

a) GASE scores will be correlated with several clinical aspects of epilepsy rated by neurologists. These correlations are predicted to be at least moderate ($r \geq 0.3$).

In the first test of construct validity, each of 7 clinical aspects of epilepsy (frequency of seizures, intensity of seizures, falls or injuries during seizures, severity of post-ictal period, amount of AEDs, side effects of AEDs, and interference of epilepsy or drugs with daily activities) was predicted to independently correlate at least moderately (≥ 0.3) with GASE scores. Of these 7 clinical aspects, the frequency of seizures was further predicted to possess the strongest correlation with GASE scores. Correlations between GASE scores and each clinical aspect of epilepsy were tested using Spearman rank-order correlation, 95% confidence intervals (CI) and a P-value < 0.05 for statistical significance. Correlations were interpreted using Cohen's classification for effect size. A correlation of 0.10 to 0.30 was regarded as weak; 0.30 to 0.50 was regarded as moderate; and > 0.50 was regarded as strong (Cohen, 1988, pp.79-80). Multiple linear regression was additionally used to assess the specific relationship between GASE scores and the 7 core clinical aspects of epilepsy, while adjusting for the effects of the other aspects. The coefficient of determination (R^2) and the associated 95% CI was used to assess the

proportion (%) of total variation in GASE scores explained by the 7 clinical aspects of epilepsy.

b) GASE scores will be correlated at least moderately ($r \geq 0.3$) with the “total number of AEDs” reported by neurologists.

In the second test of construct validity, the total number of AEDs was predicted to correlate at least moderately (≥ 0.3) with GASE Scale scores. Spearman rank-order correlation, 95% CI and a P-value < 0.05 for statistical significance was calculated and also interpreted using Cohen’s criteria for effect size (Cohen, 1988, pp.79-80).

c) and d) GASE scores will indicate more severe epilepsy for children who have experienced CSE than those who have not and GASE scores will indicate less severe epilepsy for children whose seizures are exclusively nocturnal.

In the third and fourth tests of construct validity, children who had experienced CSE were predicted to have higher GASE scores than children who had not, while children with exclusively nocturnal seizures were predicted to have lower GASE scores than children with daytime seizures. For both tests, independent-samples t-tests compared mean GASE scores for patients with and without these specific epilepsy conditions.

e) GASE scores will be correlated with parents’ perception of child health. The correlation will be at least moderate ($r \geq 0.3$) with GASE scores indicating more severe epilepsy associated with parents reporting children’s health as poorer.

In the fifth and final test of construct validity in this study, neurologists’ ratings using GASE were predicted to correlate at least moderately (≥ 0.3) with parents’ perception of child health as rated by the QOLCE question (Figure 3.2) asking parents: “Compared to other children his/her age, how do you think your child’s health has been in the past 4 weeks? Please consider your child’s epilepsy as part of his/her health when you answer this question.” Responses to this QOLCE question are assigned a numerical value from 1 to 5, with “1” designated as “Poor” and “5” designated as “Excellent”. Spearman rank-order correlation, 95% CI and a P-value < 0.05 for statistical significance were calculated and interpreted using Cohen’s criteria for effect size (Cohen, 1988, pp.79-80).

3.4.2 Stability of the GASE Scale

Objective 2: Hypothesis and Procedure

Since there is no gold standard for the assessment of overall severity of epilepsy, seven key clinical aspects of epilepsy were determined to be the most objective clinical indicators of stable severity of epilepsy as recorded in the Physician Form based on physician's most recent interviews with patients and parents. The following seven external criteria were used to compare with the GASE Scale to assess stability and change over time: frequency of seizures, intensity of seizures, falls or injuries during seizures, severity of the post-ictal period, CSE, exclusive nocturnal seizures, and number of AEDS currently. The selection of these clinical aspects was informed by a paediatric neurologist and epileptologist. To ensure a sufficiently short time frame where patients' status was less likely to have changed (Streiner and Norman, 2008, pp.182), the 6 month time interval from Time 2 (6 months post-diagnosis) to Time 3 (12 months post-diagnosis) was chosen for this analysis. At Time 2, about 6 months had elapsed since diagnosis, allowing time for more stable diagnoses and for patients to adjust to treatment.

a) In patients for whom neurologists' reports of key clinical aspects of epilepsy and a composite score indicate stability in the patient's epilepsy over a period of 6 months, GASE scores will remain stable over the same time period.

For each clinical aspect and the composite score combining all aspects, the patient sample was divided into two sub-groups: "stable" and "changed". Patients were classified as "stable" if ratings for the clinical criteria showed zero change from Time 2 to Time 3. Stability for the clinical aspect of CSE was further restricted to patients who had not experienced the condition at either time point. Patients were classified as "changed" if ratings for the clinical criteria were different at Time 2 and Time 3.

For each "stable" sub-sample, the distribution, intra-class correlation coefficient (ICC) and its 95% CI, and paired t-test were calculated for GASE scores from Time 2 to Time 3.

The distribution of raw change scores for each "stable" sub-sample was calculated by subtracting Time 3 scores from Time 2 scores. The detailed point change and direction of

change (positive or negative) were assessed. A positive change score indicated an increase in severity of epilepsy as rated by the GASE Scale.

The ICC estimate quantifies the reliability of measurements over time (Shrout and Fleiss, 1979). It can be defined as the proportion of total variability explained by the variability among patients (Deyo et al., 1991). In addition to the strength of the correlation between GASE scores at Time 2 to Time 3, it also assesses variation of the slope and intercept. The approach calculating ICC from an analysis of variance described by Deyo et al. (1991, pp. 149-50) was used for this analysis, with 95% CI obtained on the basis of F-distribution.

The ICC ranges between 0 to +1, with 1 indicating perfect reliability and 0 suggesting poor reliability (Deyo et al., 1991). Although there are no universally applicable conventions to interpret ICC values, a general rule is that ICC should exceed 0.7 for adequate reliability (Guyatt et al., 2008, pp.257, Streiner and Norman, 2008, pp.193-4). The paired t-test was additionally used to test whether mean GASE scores for the stable sub-group at Time 2 were statistically different at Time 3 at the 5% significance level.

b) In patients whose parents' reports of child health status indicate stability in the patient's epilepsy over a period of 6 months, GASE scores will remain stable over the same time period.

Following the same method used for the clinical criteria, the patient sample was divided into two sub-groups according to the parents' reports of child health, as rated by the QOLCE question (Figure 3.2) asking parents: "Compared to other children his/her age, how do you think your child's health has been in the past 4 weeks? Please consider your child's epilepsy as part of his/her health when you answer this question." Patients were classified as "stable" if their parents' ratings showed zero change from Time 2 to Time 3. The remaining patients were classified as "changed" for having different scores at the two time points. In the "stable" sub-sample, the ICC of the GASE scores, and the 95% CI were calculated for Time 2 to Time 3. The paired t-test was additionally used to test whether GASE scores for the stable sub-group were statistically different ($p > 0.05$) at the two time points.

3.4.3 Responsiveness of the GASE Scale

Objective 3: Hypotheses and Procedure

Since there is no consensus on the best statistical measure of responsiveness, multiple statistics (distribution-based and anchor-based methods) were adopted to assess the responsiveness of the GASE Scale.

Distribution-based methods (internal responsiveness):

a) The GASE Scale will be able to detect statistically significant changes in the severity of epilepsy over time (from baseline to 6, 12, and 24 months post-diagnosis).

In the assessment of internal responsiveness, the GASE Scale was predicted to detect statistically and clinically relevant changes in the severity of epilepsy over the course of the study. Data from Time 1 (baseline) was used as a reference to compare with data from Times 2, 3, and 4 (6, 12, and 24 months post-diagnosis, respectively).

Responsiveness detected by the GASE Scale over the 4 time points was tested using the standardized response mean (SRM). The SRM evaluates the magnitude of change over time and is accepted as the most appropriate statistic for assessing internal responsiveness when a gold standard is not available (Zou, 2005). At each time point compared to baseline, the mean change in GASE score was divided by the standard deviation of the respective change in scores. The standard deviation reflects the variability of the change scores, with lower variability relative to mean change resulting in a larger SRM coefficient (Husted et al., 2000). To interpret the SRM, the probability of change statistic (p) was also calculated based on the cumulative normal distribution. The probability of change ranges between 0.5, indicating no ability to detect change, and 1.0 indicating perfect ability (Zou, 2005). A probability of greater than 0.5 would suggest that the scale is able to detect changes thereby providing evidence to support the utility of the GASE Scale in detecting changes in the severity of epilepsy in children.

Anchor-based methods (external responsiveness):

b) Change in severity of epilepsy reported using the GASE Scale over a period of 12 months will be correlated with neurologists' reports of changes in key clinical aspects of epilepsy and a composite score of the aspects over the same time period.

The seven key clinical aspects of epilepsy and their composite score that were described previously to assess the stability of the GASE Scale in Objective 2 were used in this analysis: frequency of seizures, intensity of seizures, falls or injuries during seizures, severity of the post-ictal period, CSE, exclusive nocturnal seizures, and number of AEDS currently. For the GASE Scale and each of the clinical aspects of epilepsy, change scores were calculated by taking the difference between Time 1 and Time 3 data, where change was most likely to occur for patients in the study. Correlations between change scores for the GASE Scale and for each of the clinical aspects or the composite score were then determined using Spearman rank-order correlation (without assuming normality of the data), 95% CI, and a P-value < 0.05 for statistical significance. As with the test of construct validity, correlations were interpreted using Cohen's classifications for effect size (Cohen, 1988, pp.79-80).

c) Change in severity reported using the GASE Scale over a period of 12 months will be correlated with changes in parents' perceptions of child health status over the same time period.

Since parents are the observers most familiar with their child's epilepsy, this test of responsiveness used the parents' perception of change in child health as an external reference measure of health status. Two questions from the Parent Questionnaire provided information on the parents' perception of change and it was predicted that these opinions would correlate with changes reported using GASE scores. CHQ Question 8.12 (Figure 3.1) asked parents: "Compared to one year ago, how would you rate your child's health now?". Responses were assigned a numerical value from 1 to 5, with "1" designated as "Much better now than 1 year ago" and "5" designated as "Much worse now than 1 year ago". QOLCE Question 1.15 (Figure 3.2) asked parents: "Compared to

other children his/her age, how do you think your child's health has been in the past 4 weeks? Please consider your child's epilepsy as part of his/her health when you answer this question." Responses were assigned numerical values from 1 to 5, with "1" representing "Poor" and "5" representing "Excellent". For analysis of the QOLCE question, change scores were calculated from the difference of scores between Time 1 and Time 3. For the CHQ question only Time 3 data were used since the question specifies a comparison point of one year ago. Correlations between GASE change scores and parents' perception of change were determined using Spearman rank-order correlation, 95% CI, and a P-value < 0.05 for statistical significance. Cohen's classifications for effect size were also used to interpret correlations (Cohen, 1988, pp.79-80).

d) In patients for whom neurologists' reports of key clinical aspects of epilepsy and the composite score indicate change in the patient's epilepsy over a period of 12 months, common responsiveness statistics will show that GASE scores also change over the same time period.

The seven key clinical aspects of epilepsy from the Physician Form and their composite score that were previously used to assess the stability of the GASE Scale in Objective 2 were used to assess change in the patient's epilepsy over a period of 12 months: frequency of seizures, intensity of seizures, falls or injuries during seizures, severity of the post-ictal period, CSE, exclusive nocturnal seizures, and number of AEDS currently.

As conducted in the assessment of stability, for each of the seven clinical indicators or the composite score combining all aspects, the patient sample was divided into two sub-groups: "stable" and "changed". Patients were classified as "stable" if ratings for the clinical criteria showed zero change from Time 1 to Time 3. The remaining patients were classified as "changed" for ratings that were different at Time 1 and Time 3.

For each "changed" sub-sample, Cohen's Effect Size (ES), Guyatt's Responsiveness Statistic (GRS), and a paired t-test were calculated to compare GASE scores at Time 1 with Time 3. The Area under the Receiver Operating Characteristic Curve (AUROC) and 95% CI were additionally assessed to determine the probability of GASE change scores

to differentiate and agree with the “stable” and “changed” classifications determined by the clinical criteria.

The ES quantifies the magnitude of difference in mean scores by dividing the difference between mean scores at Time 1 to Time 3 with the standard deviation of baseline scores, thereby transforming the score change into a standard measure of change. This is expressed mathematically as: $(M_1 - M_3) / SD_{\text{Baseline}}$, where M_1 represents the mean of scores from Time 1; M_3 represents the mean of scores from Time 3; and SD_{Baseline} is the standard deviation of the scores from Time 1. Related to ES, GRS divides the mean change in scores from Time 1 to Time 3 by the standard deviation of the change for the stable patients. This is expressed mathematically as: $(M_1 - M_3) / SD_{\text{Stable}}$, where M_1 represents the mean of scores from Time 1; M_3 represents the mean of scores from Time 3; and SD_{Stable} is the standard deviation of the change in stable patients. As suggested by Guyatt, the GRS expresses responsiveness as a function of the variability in score changes for stable patients, instead of the standard deviation of baseline scores (Deyo et al., 1991). ES and GRS were interpreted using Cohen’s conventions for ES: 0.2 was regarded as small; 0.5 was regarded as moderate; and 0.8 was regarded as large (Streiner and Norman, 2008, pp. 153).

By comparing the mean GASE scores at Time 1 with Time 3 for each “changed” subsample, the paired t-test was additionally used to test whether Time 1 GASE scores were significantly different at Time 3 at the 5% significance level.

The ROC is commonly used to evaluate the discriminative accuracy of measurement scales and can be interpreted as an estimate of the probability of concordance (SAS Institute Inc., 2006). Using the sensitivity (true positive rate) and specificity (false positive rate) of score changes, the AUROC assesses the probability of the measurement scale to correctly classify patients as “stable” or “changed” (Deyo et al., 1991). In the context of this study, the seven clinical aspects and composite score acted as the external reference for true stability and change. Therefore, the AUROC analysis assessed whether the GASE Scale identified patients as “stable” (no change in GASE score from Time 1 to Time 3) or “changed” (any change in GASE score from Time 1 to Time 3) in accordance

with classifications determined by the clinical aspects or composite score. To interpret this probability, an AUROC of 0.50 to 0.70 was classified as low; 0.70 to 0.90 was classified as moderate; and greater than 0.90 was classified high (Streiner and Norman, 2008, pp. 161).

e) In patients whose parents' reports of child health indicate change in the patient's epilepsy over a period of 12 months, common responsiveness statistics will show that GASE scores also change over the same time period.

As with the previous assessments involving parents' perception of child health, two questions from the Parent Questionnaire provided information on the parents' perception of change. CHQ Question 8.12 (Figure 3.1) asked parents: "Compared to one year ago, how would you rate your child's health now?" Responses were assigned a numerical value from 1 to 5, with the following designations: 1 = "Much better now than 1 year ago"; 2 = "Somewhat better now than 1 year ago"; 3 = "About the same now as 1 year ago"; 4 = "Somewhat worse now than 1 year ago"; and 5 = "Much worse now than 1 year ago". QOLCE Question 1.15 (Figure 3.2) asked parents: "Compared to other children his/her age, how do you think your child's health has been in the past 4 weeks? Please consider your child's epilepsy as part of his/her health when you answer this question." Responses were assigned numerical values from 1 to 5, with the following designations: 1 = "Excellent"; 2 = "Very good"; 3 = "Good"; 4 = "Fair" and 5 = "Poor". For analysis of the QOLCE question, change scores were calculated from the difference of scores between Time 1 and Time 3. For the CHQ question only Time 3 data were used since the question specifies a comparison point of one year ago.

For both questions from the Parent Questionnaire, the patient sample was divided into two sub-groups: "stable" and "changed". Patients were classified as "stable" if ratings for the QOLCE question showed zero change from Time 1 to Time 3, while a rating of 3 ("About the same now as 1 year ago") on the CHQ question classified patients as "stable". The remaining patients not classified as "stable" were classified as "changed". For each "changed" sub-sample, ES, GRS, and a paired t-test were calculated to compare GASE scores at Time 1 with Time 3. AUROC and the 95% CI were additionally

measured to determine the probability of GASE change scores to discriminate and agree with the “stable” and “changed” classifications determined by the perception of parents.

ES and GRS were interpreted using Cohen’s conventions for ES: 0.2 was regarded as small; 0.5 was regarded as moderate; and 0.8 was regarded as large (Streiner and Norman, 2008, pp. 153). To interpret the AUROC, 0.50 to 0.70 was classified as low; 0.70 to 0.90 was classified as moderate; and greater than 0.90 was classified high (Streiner and Norman, 2008, pp. 161).

CHAPTER 4

RESULTS

4.1 Sample Characteristics

Table 4.1 shows the characteristics of the sample. Of a total of 456 parent questionnaires mailed in HERQULES, 374 (82%) were completed and returned at Time 1 (baseline), 335 (73%) returned at Time 2 (6 months post-diagnosis), 304 (67%) returned at Time 3 (12 months post-diagnosis) and 282 (62%) returned the final questionnaire at Time 4 (24 months post-diagnosis). At Time 1, the mean age of children was 7.5 (SD: 2.3) years and 52% were male, while parents had a mean age of 37.7 (SD: 6.1%) years and only 7.2% were male. The majority of parents were married (79.6%), biological parents (94.1%) and working full or part-time (67%). Just over one half (53.4%) of parents had completed college or university and approximately 45% of parents had an annual household income of \$70,000 or more. At Time 4, the majority of parents who were retained throughout the duration of the study were married (82.5%), working full or part-time (76.9%), had completed college or university (63.3%), and had an annual household income of \$70,000 or more (54%).

Table 4.2 and Figure 4.1 show the descriptive statistics for GASE scores reported by neurologists at all four time points. At Time 1, the mean GASE score was 2.57 (SD: 1.19), indicating somewhere between “a little severe” and “somewhat severe” on the GASE Scale. By Time 4, the mean GASE score had decreased to 1.7 (SD: 1.06), indicating somewhere between “not at all severe” and “a little severe”.

4.2 Results

4.2.1 Construct Validity of the GASE Scale

Objective 1: Results

- a) **GASE scores will be correlated with several clinical aspects of epilepsy rated by neurologists. These correlations are predicted to be at least moderate ($r \geq 0.3$).**

The strength of the association between the physician-rated GASE scores and the seven clinical aspects of epilepsy was estimated by the Spearman correlation coefficient and is summarized in Table 4.3. All correlations were statistically significant at $p = 0.001$, except at Time 1 for the side effects of AEDs ($p = 0.0128$) and the amount of AEDs ($p = 0.20$). In most cases, the seven clinical aspects were moderately correlated with the GASE Scale. Over time, there was a general increase in the size of the correlations between each clinical aspect and GASE scores. At every time point, three clinical aspects were consistently correlated the highest with the GASE Scale: frequency of seizures, intensity of seizures, and interference of epilepsy or drugs with daily activities. Although intensity of seizures showed the strongest correlation with GASE scores at Time 1, frequency of seizures demonstrated the strongest correlation with GASE scores at Time 2. The frequency of seizures was also strongly correlated with GASE scores at Times 3 and 4 along with the interference of epilepsy or drugs with daily activities. In the multiple linear regression analysis adjusting for the effects of the other clinical variables, the seven clinical aspects gradually accounted for more variation in GASE scores over time (from 28% at Time 1 to 70% at Time 4) (Tables 4.4a-d). The intensity of seizures explained the most variation in GASE scores at Time 1. However, at Times 2, 3, and 4, the frequency of seizures and interference of epilepsy or drugs with daily activities accounted for the most variance when all clinical aspects were included in the model. The following paragraphs describe the results of this analysis in further detail (Table 4.3).

At Time 1, GASE scores demonstrated a moderate correlation with the following clinical aspects of epilepsy: interference of epilepsy or drugs with daily activities, intensity of seizures, frequency of seizures, and falls or injuries during seizures, with correlations ranging from 0.34 to 0.30. A weak correlation was observed with the severity of the post-ictal period, side effects of AEDs, and the amount of AEDs, with correlations between 0.14 and 0.07, with the correlation for amount of AEDs not being statistically significant. Time 1 results indicate that higher severity of epilepsy was correlated with more frequent, severe or high interference of epilepsy or drugs with daily activities, intensity and frequency of seizures, and falls or injuries during seizures. Higher severity of epilepsy was only weakly correlated with more frequent, severe or high severity of the post-ictal period and side effects of AEDs.

At Time 2, GASE scores demonstrated at least moderate correlations with four of the seven clinical aspects of epilepsy: frequency of seizures, interference of epilepsy or drugs with daily activities, intensity of seizures, and side effects of AEDs, with correlations ranging from 0.51 to 0.30. The frequency of seizures additionally showed a strong correlation with GASE scores ($r = 0.51$; 95%CI: 0.42 to 0.58; $p < 0.001$). A weak correlation was observed between GASE scores and falls or injuries during seizures, amount of AEDs, and the severity of the post-ictal period, with correlations ranging between 0.28 and 0.24. Time 2 results indicate that those with epilepsy of higher severity had higher frequency of seizures, interference of epilepsy or drugs with daily activities, intensity of seizures, and side effects of AEDs. Additionally, these patients only had a weak association with higher falls or injuries during seizures, amount of AEDs, and the severity of the post-ictal period.

At Time 3, GASE scores demonstrated at least a moderate correlation with five of the seven clinical aspects of epilepsy: frequency of seizures, interference of epilepsy or drugs with daily activities, intensity of seizures, side effects of AEDs, and falls or injuries during seizures, with correlations ranging from 0.49 to 0.31. A weak correlation was observed between GASE scores and severity of the post-ictal period, and the amount of AEDs, with correlations of 0.24 and 0.23. Time 3 results indicate that those with epilepsy of higher severity had higher frequency of seizures, interference of epilepsy or drugs with daily activities, intensity of seizures, side effects of AEDs, and falls or injuries during seizures. These patients were only weakly associated with higher severity of the post-ictal period and the amount of AEDs.

At Time 4, all seven clinical aspects were at least moderately correlated with GASE scores, with correlations ranging from 0.60 to 0.37. The frequency of seizures, interference of epilepsy or drugs with daily activities, and the intensity of seizures demonstrated a strong correlation, while a moderate correlation was observed with the side effects of AEDs, falls or injuries during seizures, amount of AEDs, and severity of the post-ictal period. Time 4 results indicate that those with epilepsy of higher severity had more severe states of all seven clinical aspects.

The multiple linear regression analysis adjusted for the effects of the seven core clinical aspects of epilepsy and is summarized in Tables 4.4a-d. At Time 1, the seven core clinical aspects together accounted for $R^2 = 28\%$ (95% CI: 19% to 35%; $p < 0.001$) of the total variation in GASE scores, with intensity of seizures having the strongest independent effect in the physician-rated severity of epilepsy relative to the other factors in the model (Regression coefficient: 0.24; $p < 0.001$). At Time 2, the seven clinical aspects together accounted for $R^2 = 43\%$ (95% CI: 32% to 50%; $p < 0.001$) of the total variation, with frequency of seizures having the strongest independent effect relative to the other aspects in the model (Regression coefficient: 0.28; $p < 0.001$). Similarly at Time 3, the clinical aspects together accounted for $R^2 = 44\%$ (95% CI: 34% to 51%; $p < 0.001$) of the total variation, with frequency of seizures having the strongest independent effect relative to the other factors in the model (Regression coefficient: 0.35; $p < 0.001$). By Time 4, the seven clinical aspects accounted for $R^2 = 70\%$ (95% CI: 63% to 75%; $p < 0.001$) of the total variation in GASE scores, with frequency of seizures again having the strongest independent effect relative to the other six clinical aspects (Regression coefficient: 0.47; $p < 0.001$).

b) GASE scores will be correlated at least moderately ($r \geq 0.3$) with the “total number of AEDs” reported by neurologists.

Table 4.5 shows the correlation between GASE scores and the total number of AEDs at all four time points. At Time 1, more severe GASE scores were only weakly correlated with a higher total number of AEDs ($r = 0.18$; 95% CI: 0.08 to 0.28; $p < 0.001$). However, at Times 2 ($r = 0.32$; 95% CI: 0.22 to 0.41; $p < 0.001$), 3 ($r = 0.36$; 95% CI: 0.26 to 0.45; $p < 0.001$) and 4 ($r = 0.37$; 95% CI: 0.27 to 0.46; $p < 0.001$), GASE scores indicating higher severity were moderately correlated with a higher total number of AEDs.

c) GASE scores will indicate more severe epilepsy for children who have experienced CSE than for those who have not.

Results of the subgroup analysis for CSE are presented in Table 4.6. At all four time points, there was no significant difference in mean GASE scores between patients with

and without CSE occurrence since the previous visit ($p > 0.05$). This indicates that the overall severity of epilepsy as rated by the GASE Scale did not differ between patients with or without CSE at baseline, 6, 12, and 24 months post-diagnosis.

d) GASE scores will indicate less severe epilepsy for children whose seizures are exclusively nocturnal.

Results of the subgroup analysis for exclusive nocturnal seizures are presented in Table 4.7. At Times 1, 2, and 4, the independent-samples t-test found a significant difference ($p < 0.05$) in mean GASE scores between patients with exclusive nocturnal seizures and those whose seizures were not exclusively nocturnal, but the mean scores were not significantly different at Time 3. This indicates that the overall severity of epilepsy as rated by the GASE Scale was higher for patients whose seizures were not exclusively nocturnal at three of the four times assessed.

e) GASE scores will be correlated with parents' perception of child health. The correlation will be at least moderate ($r \geq 0.3$) with GASE scores indicating more severe epilepsy associated with parents reporting children's health as poorer.

Parents' perception of child health was rated by the QOLCE question asking parents: "Compared to other children his/her age, how do you think your child's health has been in the past 4 weeks? Please consider your child's epilepsy as part of his/her health when you answer this question." The strength of the association between the physician-rated GASE scores and the parents' perception of child health was estimated by the Spearman correlation coefficient and is presented in Table 4.8. GASE scores showed a weak correlation with parents' perception of child health at Times 1 ($r = -0.17$; 95% CI: -0.27 to -0.07; $p = 0.0013$) and 2 ($r = -0.23$; 95% CI: -0.33 to -0.12; $p < 0.001$), indicating that more severe GASE scores were only weakly associated with the parents' perception of poorer child health at baseline and 6 months post-diagnosis. However, a consistent increase in the strength of the association resulted in moderate correlations at Times 3 ($r = -0.31$; 95% CI: -0.41 to -0.20; $p < 0.001$) and 4 ($r = -0.34$; 95% CI: -0.45 to -0.23; $p < 0.001$), indicating that GASE scores indicative of more severe epilepsy were moderately

associated with the parents' perception of poorer child health at 12 and 24 months post-diagnosis.

4.2.2 Stability of the GASE Scale

Objective 2: Results

a) In patients for whom neurologists' reports of key clinical aspects of epilepsy and a composite score indicate stability in the patient's epilepsy over a period of 6 months, GASE scores will remain stable over the same time period.

Overall distribution of GASE change scores from Time 2 to Time 3

As summarized in Table 4.9a, a total of 311 children had GASE severity ratings for Time 2 and Time 3. The mean change was -0.14 (95% CI -0.26 to -0.03) with change ranging from -4 points to +4 points on the GASE Scale. Of the 311 children, 157 (50.5%) showed identical GASE scores at the two time points, indicating no change in severity. While 62 (20%) children experienced an increase in GASE scores (1-point increase: 46, 2-point increase: 14, 3-point increase: 1, and 4-point increase: 1 individual), 92 (29.5%) children experienced a decrease in GASE scores (1-point decrease: 66, 2-point decrease: 20, 3-point decrease: 5, and 4-point decrease: 1 individual).

Distribution of GASE change scores from Time 2 to Time 3 in sub-samples of patients with no change in the clinical aspects of epilepsy and composite score

As summarized in Table 4.9b and c, the results indicate that for all "stable" sub-samples, the majority of patients (48.8% to 73.3%) did not change in the severity of epilepsy as rated by the GASE Scale. The highest percentage of patients not showing a change in GASE scores was for the composite score: of the 101 patients showing stability on all seven clinical aspects taken together, 74 (73.3%) did not experience change in GASE scores. As predicted, GASE scores were generally stable in patients for whom neurologists reported stability in the key clinical aspects of epilepsy and the composite score. Although GASE change scores varied as much as a ± 4 -point change from Time 2 to Time 3, the change values were centred around zero change with only a small number

of patients with larger change scores.

For patients classified as stable on the basis of each of the clinical aspects individually, there were more children with decreasing severity of epilepsy over time rather than increasing, indicating that while physicians' rating of the individual clinical aspects themselves did not change, they tended to record more improvement than deterioration in the overall severity of epilepsy. Detailed descriptions of the distribution (Table 4.9b) and direction (Table 4.9c) of GASE scores for each "stable" sub-sample are provided below.

Frequency of seizures

Of the 321 patients with ratings for the frequency of seizures at Time 2 and Time 3, 176 (58%) showed no change in frequency of seizures. Of these children, two thirds showed no change in the severity of epilepsy as rated by the GASE Scale, while one quarter showed a 1-point change and the remaining small proportion showed a 2 or 3-point change. In terms of the direction of GASE change, about 13% experienced an increase in severity, with the vast majority experiencing only a 1-point increase, and 21% experienced a decrease in severity, again with most experiencing only a 1-point decrease.

Intensity of seizures

Of the 319 patients with ratings for the intensity of seizures at Time 2 and Time 3, 170 (53%) showed no change in intensity of seizures. Of these children, two thirds showed no change in the severity of epilepsy as rated by the GASE Scale, while one quarter showed a 1-point change and the remaining small proportion showed a 2, 3, or 4-point change. In terms of the direction of GASE change, approximately 17% experienced an increase in severity, with the majority experiencing only a 1-point increase, and 19% experienced a decrease in severity, again with most experiencing only a 1-point decrease.

Falls or injuries during seizures

Of the 321 patients with ratings for falls or injuries during seizures at Time 2 and Time 3, 252 (78.5%) showed no change in falls or injuries during seizures. Over one half of these children showed no change in severity of epilepsy as rated by the GASE Scale, while one third showed a 1-point change and the remaining small proportion showed a 2, 3, or 4-

point change. In terms of the direction of GASE change, about 19% experienced an increase in severity, with the vast majority experiencing only a 1-point increase, and 26% experienced a decrease in severity, again with most experiencing only a 1-point decrease.

Severity of the post-ictal period

Of the 321 patients with ratings for the severity of the post-ictal period at Time 2 and Time 3, 203 (63.2%) showed no change in the severity of the post-ictal period. Over one half of these children showed no change in severity of epilepsy as rated by the GASE Scale, while about one third showed a 1-point change and the remaining proportion showed a 2, 3, or 4-point change. In terms of the direction of GASE change, approximately 16% experienced an increase in severity, with the majority experiencing a 1-point increase, and 25% experienced a decrease in severity, again with most experiencing only a 1-point decrease.

CSE

Of the 322 patients with ratings for CSE at Time 2 and Time 3, 295 (91.6%) did not have CSE at both time points. Approximately one half of these children showed no change in severity of epilepsy as rated by the GASE Scale, while over one third showed a 1-point change and the remaining proportion showed a 2, 3, or 4-point change. In terms of the direction of GASE change, 21% experienced an increase in severity, with the vast majority experiencing a 1-point increase, and 30% experienced a decrease in severity, again with most experiencing only a 1-point decrease.

Exclusive Nocturnal Seizures

Of the 319 patients with ratings for exclusive nocturnal seizures at Time 2 and Time 3, 292 (91.5%) showed no change in exclusive nocturnal seizures. One half of these children showed no change in severity of epilepsy as rated by the GASE Scale, while just over one third showed a 1-point change and the remaining small proportion showed a 2, 3, or 4-point change. In terms of the direction of GASE change, about 20% experienced an increase in severity, with the majority experiencing a 1-point increase, and 30% experienced a decrease in severity, again with most experiencing only a 1-point decrease.

Number of AEDs currently

Of the 318 patients with ratings for number of AEDs currently at Time 2 and Time 3, 268 (84.3%) showed no change in the number of AEDs currently. Just over one half of these children showed no change in severity of epilepsy as rated by the GASE Scale, while over one third showed a 1-point change and the remaining proportion showed a 2, 3, or 4-point change. In terms of the direction of GASE change, 19% experienced an increase in severity, with most experiencing a 1-point increase, and 29% experienced a decrease in severity, again with the majority experiencing a 1-point decrease.

Composite score

Of the 310 patients with ratings for all seven clinical aspects of the composite score at Time 2 and Time 3, 101 (32.6%) showed no change in any of the aspects. Of these children, three quarters showed no change in severity of epilepsy as rated by the GASE Scale, while one fifth showed a 1-point change and the remaining small proportion showed a 2 or 3-point change. In terms of the direction of GASE change, about 16% experienced an increase in severity, with the majority experiencing a 1-point increase, and 11% experienced a decrease in severity, again with most experiencing a 1-point decrease.

Stability statistics: ICC, 95% CI, and paired t-test comparing GASE scores from Time 2 with Time 3.

Results summarized in Table 4.9d show the stability statistics for GASE scores in the “stable” sub-samples of patients, classified using the individual clinical aspects of epilepsy and the composite score. For each classification, the ICC was greater than 0.50 and ranged between 0.52 and 0.64. Overall severity of epilepsy as rated by the GASE Scale was most stable when correlated with frequency of seizures (ICC 0.64; 95% CI 0.54 to 0.72) and the least stable when correlated with CSE (ICC 0.52; 95% CI 0.43 to 0.59). This indicates that relative to the other clinical aspects, the frequency of seizures appears to be most strongly related to a physician’s overall assessment of stability in the severity of epilepsy using the GASE Scale. Results of the paired t-test show that only

intensity of seizures, falls or injuries during seizures, and the composite score did not have statistically different GASE scores at Times 2 and 3 ($p > 0.05$), suggesting that other factors in addition to the selected clinical criteria may influence the assessment of stability in the severity of epilepsy.

b) In patients whose parents' reports of child health status indicate stability in the patient's epilepsy over a period of 6 months, GASE scores will remain stable over the same time period.

Results are shown in Table 4.10. In the “stable” sub-sample according to the parents' perception of child health in the past 4 weeks, the ICC for GASE scores from Time 2 to Time 3 was 0.53 (95% CI 0.38 to 0.65) with $t = 1.7$ and $p > 0.05$. GASE scores at the two time points did not differ significantly, providing some evidence that GASE scores remained stable over the 6 month period.

4.2.3 Responsiveness of the GASE Scale

Objective 3: Results

The overall distribution of GASE change scores from Time 1 to Time 3 is summarized in Table 4.11. A total of 331 children in the patient sample had GASE severity ratings for Time 1 and Time 3. The mean change was -0.73 (95% CI -0.86 to -0.59) with change ranging from -5 points to +3 points on the GASE Scale. Of the 331 children, just over one third showed identical GASE scores at the two time points, indicating no change in severity. While 13% of children experienced an increase in GASE scores, just over one half experienced a decrease in GASE scores.

Distribution-based methods (internal responsiveness):

a) The GASE Scale will be able to detect statistically significant changes in the severity of epilepsy over time (from baseline to 6, 12, and 24 months post-diagnosis).

The SRM and probability of change statistic (p) for the GASE Scale at Time 1 (baseline) compared with Time 2, 3, and 4 (6, 12, and 24 months post-diagnosis) are summarized in Table 4.12. According to Cohen's benchmarks for effect size (Cohen, 1988, p.40), the

SRMs comparing mean change in GASE scores from baseline to 6 months (SRM:-0.49, 95% CI -0.61 to -0.37), 12 months (SRM: -0.58, 95% CI -0.71 to -0.45), and 24 months post-diagnosis (SRM: -0.68, 95% CI -0.81 to -0.55) showed a moderate magnitude of change. The corresponding probability of change was significantly greater than 0.5 for all three comparisons with baseline: 6 months (p : 0.69; 95% CI 0.65 to 0.73), 12 months (p : 0.72; 95% CI 0.68 to 0.76), and 24 months post-diagnosis (p : 0.75; 95% CI 0.71 to 0.79), indicating that the GASE Scale has a greater than 50% probability of detecting change. This suggests that the GASE Scale is sensitive in detecting change in the severity of epilepsy in children.

Anchor-based methods (external responsiveness):

b) Change in severity of epilepsy reported using the GASE Scale over a period of 12 months will be correlated with neurologists' reports of changes in key clinical aspects of epilepsy and a composite score of the aspects over the same time period.

As shown in Table 4.13, the mean change in GASE scores from Time 1 to Time 3 demonstrated a moderate correlation with changes in: the composite score, intensity of seizures, frequency of seizures, and severity of the post-ictal period, with correlations ranging from 0.47 to 0.33. Increases in the severity of GASE scores from Time 1 to Time 3 were moderately correlated with increases in the composite score, intensity and frequency of seizures, and severity of the post-ictal period over the same time period.

A weak correlation was observed with changes in falls or injuries during seizures ($r = 0.22$; 95% CI 0.11 to 0.32; $p < 0.001$), indicating that increases in the severity of GASE scores from Time 1 to Time 3 were only weakly associated with increases in falls or injuries during seizures.

The mean change in GASE scores also demonstrated a weak correlation with: the number of AEDs currently, CSE, and exclusive nocturnal seizures, with correlations ranging from 0.10 to -0.01 and these correlations were not statistically significant.

c) Change in severity reported using the GASE Scale over a period of 12 months will be correlated with changes in parents' perceptions of child health status over the same time period.

The mean change in GASE scores from Time 1 to Time 3 demonstrated a weak correlation with change in parents' perception of their child's health. As shown in Table 4.14, the change in parents' perception of child health as measured using the QOLCE question: "Compared to other children his/her age, how do you think your child's health has been in the past 4 weeks? Please consider your child's epilepsy as part of his/her health when you answer this question." showed a weak correlation with change in mean GASE scores ($r = -0.12$; 95% CI -0.23 to 0 ; $p = 0.053$). An increase in severity detected by the physician-rated GASE Scale from Time 1 to Time 3 was only weakly correlated with the parents' perception of a decline in their child's health during the same time period.

The change in parents' perception of their child's health as measured by the CHQ question asking parents: "Compared to one year ago, how would you rate your child's health now?" at Time 3, was also weakly correlated with the mean change in GASE scores from Time 1 to Time 3 ($r = 0.24$; 95% CI 0.12 to 0.35 ; $p < 0.001$). An increase in severity detected by the GASE Scale was only weakly correlated with the parents' perception of their child's worsening health status.

d) In patients for whom neurologists' reports of key clinical aspects of epilepsy and the composite score indicate change in the patient's epilepsy over a period of 12 months, common responsiveness statistics will show that GASE scores also change over the same time period.

For all "changed" sub-samples (clinical aspects and the composite score), GASE scores from Time 1 to Time 3 demonstrated a moderate to large ES and GRS, ranging from 0.56 to 0.84. This suggests that when change is detected in specific clinical criteria, the GASE Scale is responsive to this change. Results are summarized in Table 4.15. The largest ES of 0.77 was found for the change in GASE scores of patients classified as "changed" in the severity of the post-ictal period. However, the largest GRS of 0.84 was found for

GASE change scores of patients from the “changed” sub-samples for both frequency and intensity of seizures. The results indicate that the GASE Scale detected at least a moderate magnitude of change from Time 1 to Time 3 when clinical criteria recorded change in frequency of seizures, intensity of seizures, falls or injuries during seizures, severity of the post-ictal period, CSE, exclusive nocturnal seizures, and number of AEDS currently.

The paired t-test comparing the mean GASE scores at Time 1 with Time 3 showed that for all “changed” sub-samples except for CSE, there was a statistically significant difference ($p < 0.001$) in GASE scores at the two time points. The results indicate that the GASE Scale was responsive to changes in the clinical aspects. The smaller t-statistic for GASE scores in the “changed” CSE sub-sample suggests that other factors may have a greater influence on the assessment of change in the severity of epilepsy using the GASE Scale. CSE does not appear to be a key factor in this assessment. The magnitude and significance of the t-statistic in all sub-samples of “changed” patients (except CSE) were also larger than for patients classified as “stable” in the tests for stability, providing further evidence that GASE scores detected greater change in the Time 1 to Time 3 “changed” sub-samples than the Time 2 to Time 3 “stable” sub-samples.

For all clinical aspects and the composite score, the AUROC consistently demonstrated a low area under the curve and ranged from 0.50 to 0.67. Probability of concordance was highest for patients classified by frequency of seizures with an AUROC of 0.67 (95% CI 0.61 to 0.74), followed by the intensity of seizures (0.63; 95% CI 0.56 to 0.69) and severity of the post-ictal period (0.59; 95% CI 0.53 to 0.65). The results indicate some ability of the GASE Scale to discriminate “stable” and “changed” patients according to select clinical criteria or the composite score.

e) In patients whose parents’ reports of child health indicate change in the patient’s epilepsy over a period of 12 months, common responsiveness statistics will show that GASE scores also change over the same time period.

For the sub-sample classified as “changed” by the parents’ perception of child health, GASE scores from Time 1 to Time 3 demonstrated a moderate to large ES and GRS,

ranging from 0.61 to 0.70. Results are summarized in Table 4.16. The results indicate that the GASE Scale detected at least a moderate magnitude of change from Time 1 to Time 3 when parents reported a change in their child's health. This suggests that when change is perceived by parents, the GASE Scale is responsive to this change.

The paired t-test comparing the mean GASE scores at Time 1 with Time 3 showed that in the "changed" sub-samples for the parents' perception of child health, there was a statistically significant difference ($p < 0.001$) in GASE scores at the two time points. These results indicate that the GASE Scale detected changes in overall severity of epilepsy that were also perceived and reported by parents as changes in child health. Parents' perception of their child's health may also be a factor that was considered by physicians to assess change in the overall severity of epilepsy using the GASE Scale. The magnitude and significance of the t-statistic in the sub-sample of "changed" patients ($t = 7.48$; $p < 0.001$) was also larger than for patients classified as "stable" ($t = 1.7$; $p = 0.09$) in the tests for stability, providing further evidence that GASE scores detected greater change in the Time 1 to Time 3 "changed" sub-sample than the Time 2 to Time 3 "stable" sub-sample.

For GASE scores in the "changed" sub-sample of the parents' perception of child health, the discriminative accuracy was low, with an AUROC of 0.50 (95% CI 0.44 to 0.57) and 0.54 (95% CI 0.47 to 0.61). These results indicate low ability of the GASE Scale to discriminate "stable" and "changed" patients according to the parents' perception of stability and change in their child's health status.

Table 4.1: Demographic characteristics of children and parents at Times 1 (baseline), 2 (6 months post-diagnosis), 3 (12 months post-diagnosis), and 4 (24 months post-diagnosis).

| | TIME 1: N = 373 | TIME 2: N = 335 | TIME 3: N = 304 | TIME 4: N = 282 |
|--|----------------------------|----------------------------|----------------------------|----------------------------|
| CHILDREN | | | | |
| Age, years (mean (SD)) | 7.5 (2.3) | 7.9 (2.4) | 8.5 (2.3) | 9.5 (2.3) |
| Sex, % Male | 52.3 | 51.3 | 50.3 | 51.4 |
| PARENTS | | | | |
| Age, years (mean (SD)) | 37.7 (6.1) | 38.2 (5.8) | 39.1 (5.9) | 40.3 (5.6) |
| Sex, % Male | 7.2 | 5.1 | 5.3 | 7.1 |
| Relationship with child, % | | | | |
| Biological parent | 94.1 | 94.9 | 94.4 | 95.7 |
| Other (step; foster; adoptive; guardian) | 5.9 | 5.1 | 5.6 | 4.3 |
| Work status, % | | | | |
| Working full or part-time | 67.0 | 70.6 | 73.5 | 76.9 |
| Full time homemaker | 21.6 | 19.4 | 18.9 | 15.5 |
| Not working (due to child's health; for 'other' reasons) | 7.6 | 5.8 | 4.6 | 4.3 |
| Other (looking for work out the home; student) | 3.8 | 4.2 | 3.0 | 3.3 |
| Highest level of education, % | | | | |
| < 8 years | 1.9 | 0.6 | 0.3 | 0.4 |
| 8-12 years | 9.4 | 8.3 | 6.3 | 5.3 |
| Completed high school | 22.3 | 21.7 | 19.8 | 19.6 |
| Completed vocational/technical training | 13.1 | 11.0 | 13.9 | 11.4 |
| Completed college/university | 44.5 | 49.8 | 50.8 | 51.6 |
| Completed graduate school | 8.9 | 8.6 | 8.9 | 11.7 |
| Marital status, % | | | | |
| Married | 79.6 | 79.6 | 80.3 | 82.5 |
| Never married | 9.4 | 8.7 | 7.9 | 6.1 |
| Separated or divorced | 9.4 | 10.8 | 10.5 | 10.7 |
| Other (widowed; remarried) | 1.6 | 0.9 | 1.3 | 0.7 |
| Annual household income, % | | | | |
| < \$40,000 | 21.7 | 22.4 | 19.5 | 14.8 |
| \$40,000 to \$69,999 | 30.9 | 27.4 | 23.6 | 26.9 |
| \$70,000 to \$99,999 | 22.6 | 23.1 | 26.4 | 23.6 |
| ≥ \$100,000 | 22.3 | 24.9 | 27.1 | 30.3 |
| Unknown | 2.5 | 2.2 | 3.4 | 4.4 |

Table 4.2: GASE Scale scores at Times 1 (baseline), 2 (6 months post-diagnosis), 3 (12 months post-diagnosis), and 4 (24 months post-diagnosis).

| Time | N | Missing | Mean (SD) | Median |
|--------|-----|---------|-------------|--------|
| Time 1 | 376 | 11 | 2.57 (1.19) | 2 |
| Time 2 | 343 | 44 | 1.97 (1.12) | 2 |
| Time 3 | 340 | 47 | 1.86 (1.04) | 2 |
| Time 4 | 322 | 65 | 1.70 (1.06) | 1 |

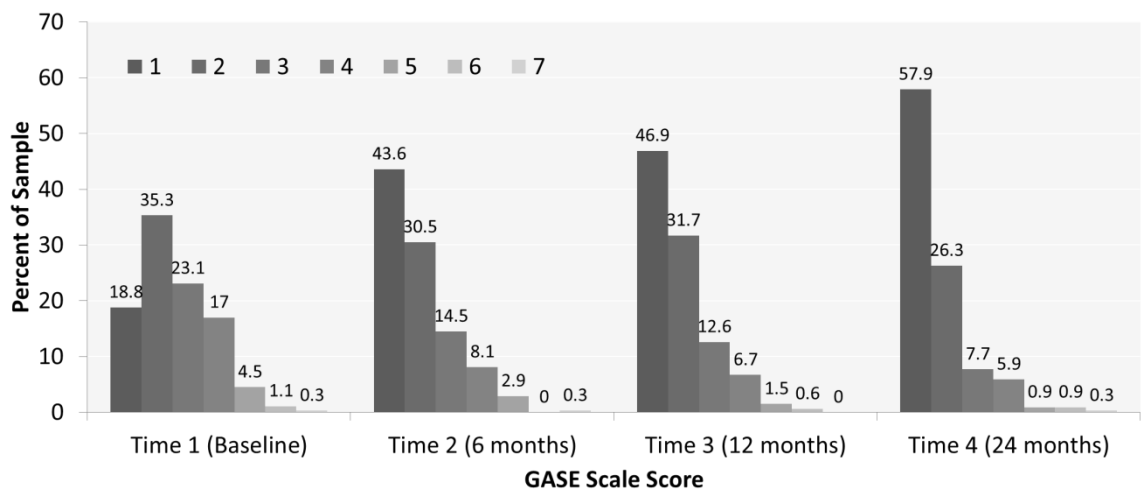


Figure 4.1: Distribution of GASE Scale scores at Times 1 (baseline), 2 (6 months post-diagnosis), 3 (12 months post-diagnosis), and 4 (24 months post-diagnosis).

Table 4.4a: Results for Objective 1a. Multiple-linear regression analysis showing the coefficient of determination for each model (R^2) and regression coefficients of the cross-sectional association between GASE scores and seven clinical aspects of epilepsy at Time 1 (baseline).

| | Regression coefficients | | | | | | |
|---|-------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 | Model 7 |
| Intercept | 1.85* | 1.14* | 1.05* | 1.09* | 0.89* | 0.86* | 0.90* |
| Frequency of seizures | 0.22* | 0.17* | 0.17* | 0.16* | 0.16* | 0.17* | 0.10* |
| Intensity of seizures | Not included | 0.32* | 0.26* | 0.29* | 0.28* | 0.26* | 0.24* |
| Falls or injuries during seizures | Not included | Not included | 0.16* | 0.17* | 0.15* | 0.18* | 0.15* |
| Severity of the post-ictal period | Not included | Not included | Not included | -0.05 | -0.04 | -0.05 | -0.07 |
| Amount of AEDs | Not included | Not included | Not included | Not included | 0.15 | -0.04 | -0.09 |
| Side effects of AEDs | Not included | Not included | Not included | Not included | Not included | 0.22* | 0.17* |
| Interference of epilepsy or drugs with daily activities | Not included | Not included | Not included | Not included | Not included | Not included | 0.23* |
| R^2 | 0.09** | 0.19** | 0.21** | 0.20** | 0.21** | 0.24** | 0.28** |
| Adjusted R^2 | 0.09** | 0.19** | 0.20** | 0.19** | 0.20** | 0.23** | 0.27** |
| 95% CI for R^2 | 0.03, 0.14 | 0.11, 0.25 | 0.13, 0.27 | 0.12, 0.26 | 0.13, 0.27 | 0.15, 0.31 | 0.19, 0.35 |
| n | 372 | 371 | 370 | 367 | 365 | 352 | 345 |
| Missing | 15 | 16 | 17 | 20 | 22 | 35 | 42 |

* Statistically significant at $p < 0.05$. ** Statistically significant at $p < 0.0001$.

Table 4.4b: Results for Objective 1a. Multiple-linear regression analysis showing the coefficient of determination for each model (R^2) and regression coefficients of the cross-sectional association between GASE scores and seven clinical aspects of epilepsy at Time 2 (6 months post-diagnosis).

| | Regression coefficients | | | | | | |
|---|-------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 | Model 7 |
| Intercept | 1.07* | 0.87* | 0.79* | 0.81* | 0.44* | 0.39* | 0.42* |
| Frequency of seizures | 0.49* | 0.39* | 0.39* | 0.38* | 0.34* | 0.34* | 0.28* |
| Intensity of seizures | Not included | 0.22* | 0.16* | 0.18* | 0.15 | 0.15 | 0.17* |
| Falls or injuries during seizures | Not included | Not included | 0.14 | 0.14 | 0.13 | 0.11 | 0.07 |
| Severity of the post-ictal period | Not included | Not included | Not included | -0.02 | -0.03 | -0.07 | -0.10 |
| Amount of AEDs | Not included | Not included | Not included | Not included | 0.28* | 0.18* | 0.13* |
| Side effects of AEDs | Not included | Not included | Not included | Not included | Not included | 0.18* | 0.10 |
| Interference of epilepsy or drugs with daily activities | Not included | Not included | Not included | Not included | Not included | Not included | 0.24* |
| R^2 | 0.31** | 0.34** | 0.34** | 0.34** | 0.38** | 0.41** | 0.43** |
| Adjusted R^2 | 0.31** | 0.33** | 0.34** | 0.33** | 0.38** | 0.40** | 0.42** |
| 95% CI for R^2 | 0.22, 0.38 | 0.24, 0.41 | 0.24, 0.41 | 0.24, 0.41 | 0.29, 0.45 | 0.32, 0.48 | 0.34, 0.50 |
| n | 342 | 341 | 341 | 340 | 340 | 339 | 338 |
| Missing | 45 | 46 | 46 | 47 | 47 | 48 | 49 |

* Statistically significant at $p < 0.05$. ** Statistically significant at $p < 0.0001$.

Table 4.4c: Results for Objective 1a. Multiple-linear regression analysis showing the coefficient of determination for each model (R^2) and regression coefficients of the cross-sectional association between GASE scores and seven clinical aspects of epilepsy at Time 3 (12 months post-diagnosis).

| | Regression coefficients | | | | | | |
|---|-------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 | Model 7 |
| Intercept | 0.91* | 0.84* | 0.72* | 0.75* | 0.57* | 0.46* | 0.41* |
| Frequency of seizures | 0.55* | 0.49* | 0.50* | 0.48* | 0.43* | 0.42* | 0.35* |
| Intensity of seizures | Not included | 0.10 | 0.05 | 0.11 | 0.10 | 0.05 | 0.03 |
| Falls or injuries during seizures | Not included | Not included | 0.18 | 0.24* | 0.21* | 0.20* | 0.24* |
| Severity of the post-ictal period | Not included | Not included | Not included | -0.14 | -0.12 | -0.10 | -0.17 |
| Amount of AEDs | Not included | Not included | Not included | Not included | 0.17* | 0.01 | -0.01 |
| Side effects of AEDs | Not included | Not included | Not included | Not included | Not included | 0.33* | 0.25* |
| Interference of epilepsy or drugs with daily activities | Not included | Not included | Not included | Not included | Not included | Not included | 0.26* |
| R^2 | 0.32** | 0.33** | 0.33** | 0.34** | 0.35** | 0.41** | 0.44** |
| Adjusted R^2 | 0.32** | 0.32** | 0.33** | 0.33** | 0.35** | 0.40** | 0.43** |
| 95% CI for R^2 | 0.24, 0.40 | 0.24, 0.41 | 0.25, 0.41 | 0.25, 0.42 | 0.26, 0.43 | 0.32, 0.48 | 0.34, 0.51 |
| n | 338 | 336 | 336 | 336 | 335 | 333 | 332 |
| Missing | 49 | 51 | 51 | 51 | 52 | 54 | 55 |

* Statistically significant at $p < 0.05$. ** Statistically significant at $p < 0.0001$.

Table 4.4d: Results for Objective 1a. Multiple-linear regression analysis showing the coefficient of determination for each model (R^2) and regression coefficients of the cross-sectional association between GASE scores and seven clinical aspects of epilepsy at Time 4 (24 months post-diagnosis).

| | Regression coefficients | | | | | | |
|---|-------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 | Model 7 |
| Intercept | 0.46* | 0.41* | 0.17 | 0.19 | -0.07 | -0.10 | 0.01 |
| Frequency of seizures | 0.80* | 0.71* | 0.69* | 0.68* | 0.61* | 0.56* | 0.47* |
| Intensity of seizures | Not included | 0.13* | 0.03 | 0.12 | 0.10 | 0.09 | 0.12 |
| Falls or injuries during seizures | Not included | Not included | 0.36* | 0.43* | 0.41* | 0.37* | 0.14 |
| Severity of the post-ictal period | Not included | Not included | Not included | -0.17* | -0.18* | -0.13 | -0.22* |
| Amount of AEDs | Not included | Not included | Not included | Not included | 0.26* | 0.14* | 0.07 |
| Side effects of AEDs | Not included | Not included | Not included | Not included | Not included | 0.20* | 0.11* |
| Interference of epilepsy or drugs with daily activities | Not included | Not included | Not included | Not included | Not included | Not included | 0.42* |
| R^2 | 0.56** | 0.57** | 0.59** | 0.59** | 0.63** | 0.65** | 0.70** |
| Adjusted R^2 | 0.56** | 0.57** | 0.58** | 0.59** | 0.63** | 0.64** | 0.69** |
| 95% CI for R^2 | 0.49, 0.63 | 0.49, 0.64 | 0.51, 0.65 | 0.51, 0.65 | 0.56, 0.69 | 0.58, 0.70 | 0.63, 0.75 |
| n | 322 | 321 | 321 | 321 | 321 | 321 | 321 |
| Missing | 65 | 66 | 66 | 66 | 66 | 66 | 66 |

* Statistically significant at $p < 0.05$. ** Statistically significant at $p < 0.0001$.

Table 4.5: Results for Objective 1b. Spearman rank correlations of GASE scores with the total number of AEDs reported by neurologists at Time 1 (baseline), 2 (6 months post-diagnosis), 3 (12 months post-diagnosis), and 4 (24 months post-diagnosis).

| | Time 1 | Time 2 | Time 3 | Time 4 |
|---------------------|---------------|---------------|---------------|---------------|
| Spearman Rho | 0.18 | 0.32 | 0.36 | 0.37 |
| 95% CI | 0.08, 0.28 | 0.22, 0.41 | 0.26, 0.45 | 0.27, 0.46 |
| P-value | 0.0005 | < 0.0001 | < 0.0001 | < 0.0001 |

Table 4.6: Results for Objective 1c. Comparison of mean GASE scores for patients with and without neurologist-reported convulsive status epilepticus (CSE) at Time 1 (baseline), 2 (6 months post-diagnosis), 3 (12 months post-diagnosis), and 4 (24 months post-diagnosis).

| | Time 1 | | Time 2 | | Time 3 | | Time 4 | |
|----------------|---------------|------|---------------|------|---------------|------|---------------|------|
| CSE | No | Yes | No | Yes | No | Yes | No | Yes |
| N | 358 | 18 | 327 | 16 | 325 | 14 | 303 | 11 |
| Mean | 2.55 | 2.94 | 1.97 | 2.00 | 1.86 | 2.07 | 1.71 | 1.55 |
| SD | 1.19 | 1.11 | 1.11 | 1.21 | 1.03 | 1.27 | 1.07 | 0.82 |
| Range | 1-7 | 1-5 | 1-7 | 1-5 | 1-6 | 1-4 | 1-7 | 1-3 |
| t Value | -1.36 | | -0.1 | | -0.76 | | 0.51 | |
| DF | 374 | | 341 | | 337 | | 312 | |
| P-value | 0.17 | | 0.9235 | | 0.4463 | | 0.6093 | |

Table 4.7: Results for Objective 1d. Comparison of mean GASE scores for patients with and without neurologist-reported exclusive nocturnal seizures at Time 1 (baseline), 2 (6 months post-diagnosis), 3 (12 months post-diagnosis), and 4 (24 months post-diagnosis).

| | Time 1 | | Time 2 | | Time 3 | | Time 4 | |
|------------------------------|--------|------|--------|------|--------|------|--------|------|
| Exclusive nocturnal seizures | No | Yes | No | Yes | No | Yes | No | Yes |
| N | 291 | 82 | 274 | 66 | 275 | 61 | 263 | 50 |
| Mean | 2.70 | 2.15 | 2.05 | 1.65 | 1.92 | 1.64 | 1.78 | 1.36 |
| SD | 1.22 | 0.98 | 1.16 | 0.83 | 1.08 | 0.82 | 1.12 | 0.63 |
| Range | 1-7 | 1-5 | 1-7 | 1-4 | 1-6 | 1-4 | 1-7 | 1-4 |
| t Value | 3.79 | | 2.61 | | 1.89 | | 2.55 | |
| DF | 371 | | 338 | | 334 | | 311 | |
| P-value | 0.0002 | | 0.0094 | | 0.0599 | | 0.0113 | |

Table 4.8: Results for Objective 1e. Spearman rank correlations for comparison of GASE scores and parents' perception of child health in the past 4 weeks at Time 1 (baseline), 2 (6 months post-diagnosis), 3 (12 months post-diagnosis), and 4 (24 months post-diagnosis).

| | Time 1 | Time 2 | Time 3 | Time 4 |
|---------------------|--------------|--------------|--------------|--------------|
| Spearman Rho | -0.17 | -0.23 | -0.31 | -0.34 |
| 95% CI | -0.27, -0.07 | -0.33, -0.12 | -0.41, -0.20 | -0.45, -0.23 |
| P-value | 0.0013 | < 0.0001 | < 0.0001 | < 0.0001 |

Table 4.9a: Results for Objective 2a. Distribution of GASE change scores from Time 2 (6 months post-diagnosis) to Time 3 (12 months post-diagnosis) (n = 311).

| Change in GASE score from Time 2 to Time 3 | Frequency | Percent |
|---|------------------|----------------|
| -4 | 1 | 0.3 |
| -3 | 5 | 1.6 |
| -2 | 20 | 6.4 |
| -1 | 66 | 21.2 |
| 0 | 157 | 50.5 |
| 1 | 46 | 14.8 |
| 2 | 14 | 4.5 |
| 3 | 1 | 0.3 |
| 4 | 1 | 0.3 |
| Frequency Missing = 76 | | |

Table 4.9b: Results for Objective 2a. Distribution of absolute GASE change scores in the sub-samples of patients exhibiting zero change in clinical aspects of epilepsy and the composite score from Time 2 (6 months post-diagnosis) to Time 3 (12 months post-diagnosis).

| Clinical aspect of epilepsy | Sub-sample with zero change in clinical aspect (T2 to T3) | Absolute change in GASE (from sub-samples with zero change in the clinical aspect) | | | | |
|---|---|---|----------------|---------------|--------------|--------------|
| | | No change | 1-point | 2-point | 3-point | 4-point |
| Frequency of seizures (n = 321) | 176 | 118 (67%) | 46 (26%) | 9 (5%) | 3 (1.7%) | 0 |
| Intensity of seizures (n = 319) | 170 | 110 (64.7%) | 45 (26.5%) | 12 (7%) | 2 (1.2%) | 1 (0.59%) |
| Falls or injuries during seizures (n = 321) | 252 | 140 (55.6%) | 81 (32%) | 24 (9.5%) | 5 (1.98%) | 2 (0.79%) |
| Severity of the post-ictal period (n = 321) | 203 | 120 (59.1%) | 59 (29%) | 19 (9.4%) | 3 (1.48%) | 2 (0.99%) |
| Convulsive Status Epilepticus (n = 322) | 295 (no at both times) | 144 (48.8%) | 109 (37%) | 34 (11.5%) | 6 (2.03%) | 2 (0.68%) |
| Exclusive Nocturnal Seizures (n = 319) | 292 | 148 (50.7%) | 106 (36.3%) | 30 (10.3%) | 6 (2.05%) | 2 (0.68%) |
| Number of AEDs currently (n = 318) | 268 | 139 (52%) | 99 (37%) | 24 (9%) | 5 (1.87%) | 1 (0.37%) |
| Composite score * Frequency + Intensity + Falls + Post-ictal + CSE + ENS + AEDs (n = 310) | 101 | 74 (73.3%) | 19 (18.8%) | 6 (5.9%) | 2 (1.98%) | 0 |

* Frequency = Frequency of seizures; Intensity = Intensity of seizures; Falls = Falls or injuries during seizures; Post-ictal = Severity of the post-ictal period; CSE = Convulsive status epilepticus; ENS = Exclusive nocturnal seizures; AEDs = Number of AEDs currently.

Table 4.9c: Results for Objective 2a. Distribution and direction of change in GASE scores for the sub-samples of patients exhibiting zero change in clinical aspects of epilepsy and the composite score from Time 2 (6 months post-diagnosis) to Time 3 (12 months post-diagnosis).

| Clinical aspect of epilepsy | Sub-sample with zero change in clinical aspect (T2 to T3) | Direction of change in GASE scores (from sub-samples with zero change in the clinical aspect) | | | | | | | | |
|---|---|--|------------|---------|---------|---------|------------|---------|---------|---------|
| | | No change | Increase | | | | Decrease | | | |
| | | | 1-point | 2-point | 3-point | 4-point | 1-point | 2-point | 3-point | 4-point |
| Frequency of seizures (n = 321) | 176 | 118 (67%) | 22 (12.5%) | | | | 36 (20.5%) | | | |
| | | | 20 | 2 | 0 | 0 | 26 | 7 | 3 | 0 |
| Intensity of seizures (n = 319) | 170 | 110 (64.7%) | 28 (16.5%) | | | | 32 (18.8%) | | | |
| | | | 22 | 5 | 0 | 1 | 23 | 7 | 2 | 0 |
| Falls or injuries during seizures (n = 321) | 252 | 140 (55.6%) | 47 (18.7%) | | | | 65 (25.9%) | | | |
| | | | 34 | 11 | 1 | 1 | 47 | 13 | 4 | 1 |
| Severity of the post-ictal period (n = 321) | 203 | 120 (59.1%) | 33 (16.3%) | | | | 50 (24.6%) | | | |
| | | | 25 | 7 | 0 | 1 | 34 | 12 | 3 | 1 |
| Convulsive Status Epilepticus (n = 322) | 295 (no at both times) | 144 (48.8%) | 62 (21%) | | | | 89 (30%) | | | |
| | | | 46 | 14 | 1 | 1 | 63 | 20 | 5 | 1 |
| Exclusive Nocturnal Seizures (n = 319) | 292 | 148 (50.7%) | 58 (19.9%) | | | | 86 (29.5%) | | | |
| | | | 44 | 12 | 1 | 1 | 62 | 18 | 5 | 1 |
| Number of AEDs currently (n = 318) | 268 | 139 (52%) | 51 (19%) | | | | 78 (29%) | | | |
| | | | 40 | 10 | 0 | 1 | 59 | 14 | 5 | 0 |
| Composite score * Frequency + Intensity + Falls + Post-ictal + CSE + ENS + AEDs (n = 310) | 101 | 74 (73.3%) | 16 (15.8%) | | | | 11 (10.9%) | | | |
| | | | 10 | 4 | 2 | 0 | 9 | 2 | 0 | 0 |

* Frequency = Frequency of seizures; Intensity = Intensity of seizures; Falls = Falls or injuries during seizures; Post-ictal = Severity of the post-ictal period; CSE = Convulsive status epilepticus; ENS = Exclusive nocturnal seizures; AEDs = Number of AEDs currently.

Table 4.9d: Results for Objective 2a. Results of the tests of stability (ICC and t-test) for GASE scores from Time 2 (6 months post-diagnosis) to Time 3 (12 months post-diagnosis) using the sub-samples of patients classified by external criteria (clinical indicators or composite score) as “stable” during the same time period.

| External clinical indicator | STABILITY | | |
|--|----------------------|--------------------|-----|
| | ICC (95% CI) | T-Test | n |
| Frequency of seizures | 0.64 (0.54, 0.72) | 2.43 (p = 0.02) | 176 |
| Intensity of seizures | 0.60 (0.50, 0.69) | 0.62 (p = 0.54) | 170 |
| Falls or injuries during seizures | 0.53 (0.44, 0.61) | 1.64 (p = 0.10) | 252 |
| Severity of post-ictal period | 0.54 (0.43, 0.63) | 2.03 (p = 0.04) | 203 |
| Convulsive status epilepticus (no at both times) | 0.52 (0.43, 0.59) | 2.27 (p = 0.02) | 295 |
| Exclusive nocturnal seizures | 0.55 (0.46, 0.62) | 2.40 (p = 0.02) | 292 |
| Number of AEDs currently | 0.53 (0.42, 0.60) | 2.40 (p = 0.02) | 268 |
| Composite score * Frequency + Intensity + Falls + Post-ictal + CSE + ENS + AEDs | 0.61 (0.47, 0.72) | 1.42 (p = 0.16) | 101 |

* Frequency = Frequency of seizures; Intensity = Intensity of seizures; Falls = Falls or injuries during seizures; Post-ictal = Severity of the post-ictal period; CSE = Convulsive status epilepticus; ENS = Exclusive nocturnal seizures; AEDs = Number of AEDs currently.

Table 4.10: Results for Objective 2b. Results of the tests of stability (ICC and t-test) for GASE scores from Time 2 (6 months post-diagnosis) to Time 3 (12 months post-diagnosis) using the sub-samples of patients classified by external criteria (parents’ perception of their child’s health) as “stable” during the same time period.

| External clinical indicator | STABILITY | | |
|---|----------------------|----------------------|-----|
| | ICC (95% CI) | T-Test | n |
| Parents’ perception of child health in past 4 weeks (Time 3 – Time 2) | 0.53 (0.38, 0.65) | 1.70 (p = 0.0918) | 115 |

Table 4.11: Distribution of GASE change scores from Time 1 (baseline) to Time 3 (6 months post-diagnosis) (n = 331).

| Change in GASE score from Time 1 to Time 3 | Frequency | Percent |
|---|------------------|----------------|
| -5 | 1 | 0.3 |
| -4 | 5 | 1.5 |
| -3 | 25 | 7.6 |
| -2 | 50 | 15.1 |
| -1 | 90 | 27.2 |
| 0 | 117 | 35.4 |
| 1 | 38 | 11.5 |
| 2 | 4 | 1.2 |
| 3 | 1 | 0.3 |
| Frequency Missing = 56 | | |

Table 4.12: Results for Objective 3a. Responsiveness indices, Standardized Response Mean (SRM) and probability of change statistic (*p*) for the GASE scores at Time 1 (baseline) compared with Time 2 (6 months post-diagnosis), Time 3 (12 months post-diagnosis), and Time 4 (24 months post-diagnosis).

| GASE Scale Change Score | SRM (95% CI) | <i>p</i> (95% CI) |
|--------------------------------|----------------------|--------------------------|
| Time 2-Time 1 | -0.49 (-0.61, -0.37) | 0.69 (0.65, 0.73) |
| Time 3-Time 1 | -0.58 (-0.71, -0.45) | 0.72 (0.68, 0.76) |
| Time 4-Time 1 | -0.68 (-0.81, -0.55) | 0.75 (0.71, 0.79) |

Table 4.13: Results for Objective 3b. Spearman rank correlations for change in mean GASE scores and change in external criteria (clinical aspects of epilepsy or composite score) rated by neurologists from Time 1 (baseline) to Time 3 (12 months post-diagnosis).

| Change in clinical aspects vs. changes in GASE scores (T3-T1) | Spearman Rho | 95% CI | P-value |
|---|---------------------|---------------|----------------|
| Frequency of Seizures | 0.42 | 0.32, 0.50 | < 0.0001 |
| Intensity of seizures | 0.45 | 0.36, 0.53 | < 0.0001 |
| Falls or injuries during seizures | 0.22 | 0.11, 0.32 | < 0.0001 |
| Severity of the post-ictal period | 0.33 | 0.23, 0.42 | < 0.0001 |
| Convulsive status epilepticus | -0.01 | -0.12, 0.09 | 0.80 |
| Exclusive nocturnal seizures | -0.01 | -0.12, 0.10 | 0.81 |
| Number of AEDs currently | 0.10 | -0.01, 0.20 | 0.08 |
| Composite score * Frequency + Intensity + Falls + Post-ictal + CSE + ENS + AEDs | 0.47 | 0.38, 0.56 | < 0.0001 |

* Frequency = Frequency of seizures; Intensity = Intensity of seizures; Falls = Falls or injuries during seizures; Post-ictal = Severity of the post-ictal period; CSE = Convulsive status epilepticus; ENS = Exclusive nocturnal seizures; AEDs = Number of AEDs currently.

Table 4.14: Results for Objective 3c. Spearman rank correlations for change in mean GASE scores and change in the parents' perception of child health from Time 1 (baseline) to Time 3 (12 months post-diagnosis).

| Parents' perception of change vs. GASE score change | Spearman Rho | 95% CI | P-value |
|--|---------------------|---------------|----------------|
| Parents' perception of child health in the past 4 weeks (Time 3-Time 1) | -0.12 | -0.23, 0 | 0.053 |
| Parents' perception of child health compared to 1 year ago (Time 3) | 0.24 | 0.12, 0.35 | < 0.0001 |

Table 4.15: Results for Objective 3d. Results for the tests of responsiveness (ES, GRS, t-test) for GASE scores from Time 1 (baseline) to Time 3 (12 months post-diagnosis) using sub-samples of patients classified by external criteria (clinical indicators or the composite score) as “changed”. The full patient sample was used to calculate AUROC of the GASE scores.

| | RESPONSIVENESS | | | | | |
|---|-----------------------|------|-----------------------|-----|----------------------|-----|
| | “Changed” Sub-samples | | | | Full Patient Sample | |
| External clinical indicator | ES | GRS | T-Test | n | AUROC (95% CI) | n |
| Frequency of seizures | 0.72 | 0.84 | 11.21 (p < 0.0001) | 259 | 0.67 (0.61, 0.74) | 326 |
| Intensity of seizures | 0.70 | 0.84 | 10.49 (p < 0.0001) | 242 | 0.63 (0.56, 0.69) | 325 |
| Falls or injuries during seizures | 0.76 | 0.79 | 6.69 (p < 0.0001) | 98 | 0.55 (0.48, 0.63) | 326 |
| Severity of post-ictal period | 0.77 | 0.69 | 9.39 (p < 0.0001) | 162 | 0.59 (0.53, 0.65) | 326 |
| Convulsive status epilepticus | 0.67 | 0.69 | 1.35 (p = 0.22) | 7 | 0.50 (0.25, 0.74) | 318 |
| Exclusive nocturnal seizures | 0.68 | 0.60 | 3.23 (p = 0.004) | 23 | 0.51 (0.39, 0.62) | 327 |
| Number of AEDs currently | 0.60 | 0.56 | 4.88 (p < 0.0001) | 94 | 0.52 (0.45, 0.59) | 325 |
| Composite score * Frequency + Intensity + Falls + Post-ictal + CSE + ENS + AEDs | 0.60 | 0.59 | 9.63 (< 0.0001) | 284 | 0.53 (0.40, 0.67) | 302 |

* Frequency = Frequency of seizures; Intensity = Intensity of seizures; Falls = Falls or injuries during seizures; Post-ictal = Severity of the post-ictal period; CSE = Convulsive status epilepticus; ENS = Exclusive nocturnal seizures; AEDs = Number of AEDs currently.

Table 4.16: Results for Objective 3e. Results for the tests of responsiveness (ES, GRS, t-test) for GASE scores from Time 1 (baseline) to Time 3 (12 months post-diagnosis) using sub-samples of patients classified by external criteria (parents' perception of their child's health) as "changed". The full patient sample was used to calculate AUROC of the GASE scores.

| | RESPONSIVENESS | | | | | |
|--|-----------------------|------|----------------------|-----|----------------------|-----|
| | "Changed" Sub-samples | | | | Full Patient Sample | |
| External clinical indicator | ES | GRS | T-Test | n | AUROC (95% CI) | n |
| Parents' perception of child health in past 4 weeks (Time 3 – Time 1) | 0.62 | 0.70 | 7.48 (p = 0.0001) | 172 | 0.50 (0.44, 0.57) | 274 |
| Parents' perception of child health compared to 1 year ago (Time 3) | 0.69 | 0.61 | 8.42 (p < 0.0001) | 164 | 0.54 (0.47, 0.61) | 271 |

CHAPTER 5

DISCUSSION AND CONCLUSION

5.1 Summary and Interpretation of Findings

This study evaluated the measurement properties of the GASE Scale using data from a prospective cohort study (HERQULES) that followed children with newly diagnosed epilepsy across Canada for two years post diagnosis. The results showed that the GASE Scale reflected many of the core clinical aspects that characterize epilepsy in its assessment of overall severity. It was also moderately capable of detecting stability within a 6 month time frame and responsive to changes in clinical criteria, as well as parents' perception of child health over a period of 12 months.

In the evaluation of construct validity, the moderate to strong correlations of frequency and intensity of seizures and interference of epilepsy or drugs with daily activities with GASE scores suggested that these specific elements contributed most strongly to the physician's assessment of overall severity of epilepsy using the GASE Scale. This finding supported the hypothesis that the correlations between several clinical aspects of epilepsy and GASE scores would be at least moderate ($r \geq 0.3$) and is consistent with preliminary research that tested the relationship between GASE scores and physician-rated clinical aspects (Speechley et al., 2008). Frequency of seizures was also moderately correlated with GASE scores in an adult sample of patients (Wiebe et al., 2013). In general, the current study showed that side effects of AEDs, falls or injuries during seizures, and the total number of AEDs also contributed moderately to the assessment, as predicted in the hypotheses. However, the severity of the post-ictal period and amount of AEDs were less important, particularly during the first year following diagnosis.

Although these two variables were only weakly correlated with GASE scores and did not support the hypothesis, they were moderately correlated with GASE scores at Time 4. As hypothesized, patients with exclusive nocturnal seizures scored significantly lower GASE severity than patients without the condition. However, contrary to the hypothesis, CSE did not appear to influence GASE assessment. Similarly in a recent study, patients with CSE had poorer HRQL independent of clinical features such as GASE severity (Ferro et

al., 2014). The small sample size of patients with CSE at all four time points may have also decreased the power of the analysis to detect a statistically significant difference in GASE scores between patients who had experienced CSE and those who had not.

The magnitude of all correlations of ratings on individual clinical aspects of epilepsy with GASE scores increased over time. Although it is possible that physicians were influenced by the content in the Physician Form for their assessment of GASE severity (response bias), it is also possible that these clinical aspects were more important in the assessment of severity the longer patients had been diagnosed with epilepsy. For example, side effects of AEDs will have less impact on the assessment of severity at the time of diagnosis if physicians have not yet prescribed medication. In addition, it is possible that as the epilepsy syndrome and type of seizures become clearer over time, the clinical features pertaining to each syndrome have a more stable and stronger influence on the overall assessment of severity in the clinician's mind.

During development of the GASE Scale, preliminary validation tests found the frequency of seizures to be the most strongly correlated aspect (Speechley et al., 2008). Frequency of seizures is also recognized as a critical factor in the assessment of epilepsy (Cramer and French, 2001) and it is a central component in other epilepsy-related severity assessment instruments. In support of the hypothesis, the frequency of seizures was the strongest predictor of GASE scores at Times 2, 3, and 4. However, at Time 1, the interference of epilepsy or drugs with daily activities and the intensity of seizures were more strongly correlated with GASE. This discrepancy at Time 1 may reflect uncertainty at the time of diagnosis, where physician-rated assessments of clinical aspects and the GASE score were primarily based on free historical recall from parents rather than on direct clinical observation. By Time 2, physicians were likely more familiar with the presentation of their patient's epilepsy and perhaps better able to focus on precise indicators of severity during a defined time frame. This could have resulted in greater clarity to aid diagnosis as well as a coherent assessment of severity and its elements.

Prior to this study, all clinical aspects assessed were accepted as common characteristics related to the illness and its severity (Camfield and Camfield, 2002, Speechley et al.,

2008). Results of the cross-sectional analysis did not fully support the hypotheses for construct validity since only a few aspects seemed to explain most of the total variation in GASE scores. However, overall results suggest that the GASE Scale incorporated several key aspects of epilepsy that are important to clinicians in their consideration of severity. It was also flexible to changes in the importance of different clinical criteria at different times in the course of the condition. These findings provide some evidence to support the construct validity of the physician-rated GASE Scale in a sample of children with newly diagnosed epilepsy in Canada.

Parents' perception of their child's health did not correlate as predicted at every time point with the physicians' assessment of overall severity of epilepsy. The results suggest that parents' perception of child health and the physicians' assessment of severity of epilepsy became more related over time. A weak correlation at Times 1 and 2 increased to a moderate correlation at Times 3 and 4. Although it has been documented that parents perceive their children's epilepsy differently than physicians (Ryan et al., 2003), another explanation for the weak to moderate correlations is that parents and physicians were asked to rate different constructs. While parents were asked to rate their child's health compared to other children his or her age within the context of a questionnaire focused on assessing HRQL, the GASE asked physicians to specifically rate severity of epilepsy. The physicians' assessment was most likely compared to other children with epilepsy. Therefore, the reference populations were also different. The increase in correlation over time may be attributed to physicians and parents sharing their unique expertise and experience with each other, thereby influencing their own perceptions and broadening their overall understanding of childhood epilepsy (Ryan et al., 2003). Low correlations between parental assessment of HRQL and GASE scores may also be explained by the entirely different nature of the HRQL questions. One question asked about the child's health in the last four weeks, and the other was a transitional question asking about health now compared with one year ago. The latter correlated more strongly with GASE scores (Table 4.14), but the interpretation of these dissimilar constructs is not straightforward.

The minimum ICC value of 0.7 generally considered adequate to demonstrate reliability of an instrument (Guyatt et al., 2008, pp.257, Streiner and Norman, 2008, pp.193-4) was

not met for GASE Scale scores taken 6 months apart in stable patients as classified by the various individual clinical variables. The low to moderate stability of GASE scores was also shown by the t-test results, where a significant difference in mean scores was found for several “stable” sub-samples according to the clinical aspects. Nevertheless, the values of ICC ranged between 0.52 and 0.64, indicating that more than 50% of total variability was explained by the variability among patients. Although these results did not strongly support the hypothesis that GASE scores would remain stable when key clinical aspects of epilepsy indicated stability in patients’ epilepsy over a period of 6 months, the finding that the majority of patients changed by only 1-point on the GASE Scale from Time 2 to Time 3 provided some evidence to support stability in the GASE Scale. This finding further indicated that the “zero change” definition of stability used for this assessment may have been too restrictive. This definition provides a conservative estimate of stability and may not be as representative of the clinical situation when assessed with a single-item scale. Therefore, a broader definition of stability may be more meaningful to clinicians and patients, as well as improve interpretation of the reliability of the GASE Scale.

During development of the GASE Scale, preliminary research showed adequate inter-rater and test-retest reliability using a series of clinical case scenarios (Speechley et al., 2008). In the current study, several factors may have influenced the results and decreased reliability. Typically in reliability assessment, observations are recorded with a shorter time interval, often 2 to 14 days (Streiner and Norman, 2008, pp.182). The interval for the current assessment of stability was limited by the data collection schedule of HERQULES, where the shortest interval was 6 months. During this time, patients with newly diagnosed epilepsy may have experienced many changes, from treatment to management of their daily lives. Therefore, it was not the ideal timeframe to assess reliability of the GASE Scale. To improve the assessment of reliability, Streiner and Norman recommend shortening the retest interval (Streiner and Norman, 2008, pp.197). Another reason for lower ICC values could be the method used for classifying patients as stable according to individual clinical variables. Although the ICC was larger when patients were classified by the composite score, the GASE Scale was designed to encompass all aspects of epilepsy including those that were not tested. Therefore,

stability in one aspect may not necessarily determine stability in overall GASE assessment. Other factors are likely to change even when some clinical aspects remain stable over time. The highest ICC demonstrated by the “stable” sub-sample according to frequency of seizures is consistent with the finding that it is a strong predictor of GASE scores and other epilepsy-related severity measures (Cramer and French, 2001). The observation that physicians tended to record a decrease in severity using GASE even when they rated individual clinical aspects as stable over time, also suggests that other factors independent of the key variables tested in this study influenced how physicians judged overall severity of epilepsy. It is also possible that over time, physicians had recalibrated their understanding and assessment of overall severity of epilepsy (response shift). The internal standards against which they evaluated severity at Time 2 may have been different at Time 3, thereby affecting the measurement of stability (Streiner and Norman, 2008, pp.124-5).

The moderate stability of GASE scores also found in the “stable” sub-sample classified according to the parents’ perception of child health did not fully support the hypothesis, but may be attributed to the weak correlation with GASE scores shown in the assessment of construct validity. As mentioned previously, the viewpoints were different, and the questions evaluated different attributes of health or epilepsy.

As there is no agreement over a standard measure of responsiveness (Streiner and Norman, 2008, pp.283), this study used an aggregate of common statistical indices to assess the GASE Scale. Both distribution-based and anchor-based methods suggested that the GASE Scale was sensitive to changes in the severity of epilepsy in children.

In the comparison of mean change in GASE scores from baseline to 6, 12, and 24 months post-diagnosis, the SRMs indicated that the GASE Scale detected a moderate magnitude of change which corresponded with a greater than 50% probability of detecting change. These findings supported the hypothesis that GASE would detect statistically significant change and suggested that it was responsive to changes in severity of epilepsy at all three time intervals.

In the absence of a gold standard for the assessment of overall severity of epilepsy, seven key clinical aspects of epilepsy were selected as external criteria to compare with the GASE Scale on stability and change over time. The criteria were determined to be the most objective clinical indicators of stable severity of epilepsy as recorded in the Physician Form based on physician's most recent interview with patients and parents. As predicted, comparison of mean change scores in the external criteria and the GASE Scale showed that changes in the composite score, intensity and frequency of seizures, and severity of the post-ictal period were moderately correlated with increases in severity of GASE scores from Time 1 to Time 3, with the highest correlation in the composite score. These clinical aspects were also the most highly correlated with GASE scores at each time point in the cross-sectional analysis. Contrary to the hypotheses, CSE and exclusive nocturnal seizure change scores were the least related with changes in GASE and were not found to be statistically significant. The negligible correlation may be attributed to the finding that GASE scores were not influenced by CSE and that few patients changed in their status of exclusive nocturnal seizures over time.

The parents' perception of change in their child's health was analyzed using two different questions from the Parent's Questionnaire and compared with GASE change scores. Both questions indicated that an increase in severity detected by the GASE Scale was only weakly correlated with the parents' perception of their child's health status as worsening. These results did not support the hypothesis. However, the weak correlations may be due to the same reasons why the correlation between parents' and physicians' perceptions were weak to moderate at certain time points in the cross-sectional analyses. In particular, the parents and physicians had different perspectives and were asked to rate similar but different attributes of health and epilepsy.

In evaluating the magnitude of change detected in each of the "changed" sub-samples according to different clinical aspects and the composite score, the ES and GRS indicated that a moderate to large change was consistently detected by the GASE Scale, in support of the hypotheses. The large magnitude of change was estimated by GRS for the "changed" sub-sample as classified by both frequency and intensity of seizures. Since not all clinical aspects equally influence the overall assessment of severity of epilepsy, the

difference in effect sizes reflects the ability of the GASE Scale to respond to distinct changes in specific clinical elements of epilepsy. This provided sufficient evidence to support the responsiveness of the GASE Scale to changes in clinical aspects of epilepsy in children from Time 1 to Time 3 of this study.

Further supporting the hypothesis that GASE scores would reflect the change in patients indicated by key clinical aspects of epilepsy, the t-test additionally showed a significant difference in GASE scores between the two time points, except when change was classified according to CSE. The low t-statistic corresponds with findings from the assessment of construct validity, where CSE did not appear to influence GASE scores. The small sample size of patients who had experienced change in CSE status ($n = 7$) may have also decreased the power of the analysis to detect change if it had occurred. Overall, the “changed” sub-sample based on the composite score had a smaller effect size than the sub-samples based on the individual clinical aspects. For the composite score, patients were classified as “changed” if any of the individual clinical aspects experienced change in score from Time 1 to Time 3, including any patients for whom there were changes in the number of AEDs currently. The “changed” sub-sample based on the number of AEDs currently showed the lowest magnitude of change in GASE over time and therefore, may have reduced the overall effect size detected by the composite score.

Results for the AUROC suggested some ability of the GASE Scale to discriminate between “stable” and “changed” patients who were classified according to certain clinical criteria and the composite score. However, the low discriminatory accuracy of the GASE in this assessment did not support the hypotheses and may be attributed to the low correlation of these individual clinical aspects with GASE scores and the restrictive definition of “stability” or unspecific definition of “changed” patients. Although the selection of specific clinical criteria was informed by a paediatric neurologist and epileptologist, a more thorough analysis is required to assess other contributing aspects to severity of epilepsy and to establish precise definitions of stability and change in the clinical criteria as well as GASE. Considering the limitations associated with the methodology of this assessment of AUROC, the poor results may not provide clinically valuable information about the validation of the GASE Scale. It is possible that the value

of the AUROC would improve with clinically relevant definitions of stability and minimal amount of change.

In evaluating the magnitude of change detected in the “changed” sub-samples according to the two questions assessing parents’ perception of child health, the ES and GRS indicated that a moderate to large change was detected by the GASE Scale in both sub-samples. The t-test additionally showed a significant difference in GASE scores from the two time points. These results support the hypotheses and provide evidence that when change is perceived by parents, the GASE Scale is responsive to this change. Parents’ perception of their child’s health may also be a factor that was considered by physicians when assessing change in the overall severity of epilepsy using the GASE Scale. However, the minimal ability of the GASE Scale to discriminate between “stable” and “changed” patients according to the parents’ perception of stability and change in their child’s health status as shown in the small AUROC was not consistent with predictions and was likely affected by the same limitations surrounding the analysis of clinical variables and the GASE Scale.

5.2 Study Strengths

This study is characterized by several strengths. The data for this thesis came from a two-year, multi-centre, prospective cohort study with a large sample size, a strong response rate, and high retention rates. Participating children were incident cases of epilepsy and represented diverse types of epilepsy syndromes. This study also addressed some of the limitations of past research on the validation of other measurement scales. Stability was assessed using the ICC statistic rather than the Pearson correlation. Streiner and Norman (2008, pp. 183) indicate that the Pearson correlation is a liberal measure and that the ICC is a better estimate of true reliability. Although no single ideal method exists to assess the various aspects of validity of the GASE Scale, this thesis takes advantage of several common statistics used in validation. While many existing scales relevant to the assessment of epilepsy have not assessed responsiveness to change, the validation of the GASE Scale involved data from four time points, enabling the analysis of the GASE Scale’s ability to detect change over time. Several responsiveness indices (distribution-

and anchor-based methods) were also reported so that results could be compared with other scales tested under similar circumstances. This provides further information for readers to decide whether the scale is effective and how it may respond under different study objectives.

5.3 Study Limitations

The current study also has a few limitations. As a secondary analysis, the data used in this thesis were originally collected with the primary objective to assess HRQL in children with epilepsy and the associated risk factors (Speechley et al., 2012). Therefore, items included in the questionnaires were not developed with the main goal of analyzing the validity of the GASE Scale. Other epilepsy-related severity assessment instruments were not included in the study. As a result, there were no comparisons of the GASE Scale with other common measures of severity of seizures or syndromes. Additionally, only the physicians' and parents' perceptions were evaluated since patients themselves were considered too young to accurately complete questionnaires. Since the GASE Scale was developed to consider all aspects of a patient's epilepsy, clinical criteria only represent the clinical dimension of severity. There are many ways to define severity and although the clinical dimension is important for research and clinical goals, the results of this study show that other factors may also contribute to the physicians' assessment of severity of epilepsy, such as biological, genetic, or environmental influences on severity (Stein et al., 1987). Although ratings from several key clinical factors were compared with GASE scores, the limited number of criteria specific to the severity of epilepsy that was included in HERQULES prevented a broader analysis of construct validity. Another limitation of the secondary analysis is that data were collected at a minimum interval of 6 months which is larger than the ideal time frame for assessing the reliability of scores.

A major challenge in the measurement of the severity of epilepsy is the absence of a standard definition and description of specific elements that affect its assessment. The literature surrounding the measurement of severity of epilepsy advocates for a simple, broad, and flexible instrument that incorporates all of the complex factors affecting severity (Cramer, 2001). Although there are several common aspects used to assess severity of epilepsy, there is no clear definition or outline of the appropriate elements that

represent and form the basis of the overall construct. Therefore, it is difficult to determine whether the GASE Scale (or any other scale) accurately captures the overall severity of epilepsy without first establishing all of the criteria that determine the severity of epilepsy (Aaronson et al., 2002).

In contrast, a standard definition that outlines specific criteria may not be applicable in a sample of real patients because the impact of specific variables influencing the assessment of severity depends on the study objectives, population, and design (Stein et al., 1987). Without a standard definition, combining several measures may provide a broader evaluation of the many variables affecting the severity of epilepsy (Dunn et al., 2004, Wagner et al., 2009).

Validity also varies according to the population and context. As a result, the valid application of the GASE Scale in this study may not be applicable to all other situations (Beaton et al., 2001). As shown in the assessment of construct validity, certain variables had more influence on GASE scores at different time points. In particular, the amount of AEDs was not an important factor at the time of diagnosis for children with epilepsy. Also, it is unclear whether the moderate reliability of GASE scores was due to the moderate stability of the scale or a result of the particular study design. Additionally, in the evaluation of responsiveness to change of GASE scores, a minimal amount of change considered valid and important to patients in one circumstance may not be meaningful to another group of patients (Liang, 2000, Revicki et al., 2008). The clinical significance can also depend on the baseline severity level of the patient as well as other external factors.

Another limitation of this study concerns the definition of stability and change. Although GASE scores were evaluated in sub-samples classified according to clinically important factors, the zero change criteria for stability was determined to be too restrictive to be clinically meaningful. For example, when clinical aspects indicated no change, the majority of patients recorded a ± 1 -point change in GASE scores. As the purpose of this study was to examine whether any amount of change could be detected by the GASE Scale, a minimal important change was not examined. The responsiveness indices

analyzed in this study (SRM, ES, GRS, and paired t-test) could not be used to assess the GASE Scale's ability to detect change to varying degrees (Stratford et al., 1996).

Therefore, the study was able to show that the GASE Scale was sensitive to changes in clinically important factors over time. However, the minimal degree of change on the GASE Scale that would translate into meaningful changes for patients and physicians in the sample of patients from HERQULES was not formally explored.

The design of this study was also prone to several forms of bias. If parents could not accurately remember the condition of their child's health in the past year, recall bias may have affected the parents' assessment of change. Since parents were asked to rate the current state of their child's health compared to the previous year, their perception of change may have also been strongly influenced by the perception of their child's current status, which is described by the implicit theory of change (Norman et al., 1997, Streiner and Norman, 2008, pp. 124-5). During the two years of the study, physicians may have altered their internal definition of overall severity of epilepsy and the aspects influencing their assessment, regardless of actual changing factors affecting the severity of epilepsy (Streiner and Norman, 2008, pp. 124-5). For example, it is possible that after seeing the list of clinical aspects and the GASE Scale on the same page of the Physician Form at Time 1, physicians based their subsequent assessments of severity on those specific clinical criteria. This response shift bias further complicates the analysis of whether or not differences over time in the assessment of GASE scores were due to real change in the contributing factors affecting severity of epilepsy in children or to internal changes in the rater of severity.

5.4 Future Directions

There are several opportunities for future research to continue the ongoing process of the validation of the GASE Scale. Since there are many dimensions that are important in the assessment of severity of epilepsy, the development of a broad definition can help to identify specific factors related to the assessment of severity of epilepsy (Aaronson et al., 2002). Future research could also investigate the different aspects considered by physicians, parents, or patients themselves. This would enable a more thorough

assessment of construct validity, where GASE scores are compared with other external criteria in different populations and situations. Another important research goal is to evaluate the relationship between the GASE Scale and other epilepsy-related severity assessment instruments such as the VA Scale, NHS3, LSSS, HASS, SSQ, and the ESSS-Q. This may involve the inclusion of several measures in a single study evaluating severity in patients with epilepsy. The GASE Scale could also be compared with EEG data, as it is important in the clinical assessment of epilepsy.

As the GASE Scale can be modified to assess adult patients, future researchers could also modify the scale to assess the severity of epilepsy from the perspective of parents and patients themselves. This would facilitate a direct comparison of the physicians', parents' and patients' perspective of overall severity of epilepsy.

To improve confidence in the ability of the GASE Scale to detect true changes over time, future work should also reassess the reliability of the GASE Scale within a shorter time frame and in patients who are stable in other aspects of epilepsy. Other tests related to responsiveness to change can involve studying whether the GASE Scale can detect different degrees of change in external criteria and to define a minimal clinically important difference of the GASE Scale which could add value to the finding that the scale is capable of detecting change. Potential studies in the future can also improve the understanding of the changing contribution of factors affecting the assessment of severity of epilepsy over time and the reasons for this change.

Future uses of the GASE Scale may include evaluating the efficacy of treatments for epilepsy or the impact of AEDs, as well as the diagnosis and monitoring of severity status for patients with epilepsy (Aaronson et al., 2002).

5.5 Conclusions

The validation of measurement tools involves an ongoing process of obtaining repeated evidence to verify its accuracy and reliability in measuring the intended construct in different populations and circumstances (Streiner and Norman, 2008, pp.250-2). Building on previous work to improve confidence in the GASE Scale, this study used different criteria and methods to evaluate construct validity, stability, and responsiveness to change in severity of epilepsy. Overall, this study suggested that the GASE Scale captured many important elements in its assessment of overall severity of epilepsy in children. It was also flexible to changes in the importance of different clinical criteria at different moments in time. In a sample of more than 300 children across Canada with newly diagnosed epilepsy, the GASE Scale demonstrated modest potential to detect stability in patients as well as responsiveness to changes over the first two-years following the diagnosis of epilepsy. The moderate correlations of key clinical aspects with GASE scores showed that the scale did not exclusively evaluate the frequency or intensity of seizures, which are the focus of many common measures of epilepsy. In the past, the frequency of seizures was the standard measure for assessing severity as well as the efficacy of AEDs (O'Donoghue et al., 1996). This was followed by the current trend of using measures that assess the severity of seizures. However, in the past few decades the value of a broad measure of severity of epilepsy has been recognized and is recommended because it can incorporate the complex dimensions of epilepsy that are important to clinicians and patients when describing the impact and severity of disease (Cramer, 2001). When the GASE Scale is used together with other measures of epilepsy and severity, the assessment can provide a more comprehensive evaluation of the multidimensional nature of epilepsy (Dunn et al., 2004, Wagner et al., 2009). This is also beneficial for studies interested in identifying the precise factors affecting assessment of severity, since the GASE Scale is a single-item scale and does not provide additional information on the factors influencing severity of epilepsy.

Despite the evidence supporting the general validity of the GASE Scale, future research is still needed to address the limitations of the current study and to continue the process of validation.

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Appendices

APPENDIX A: Physician Report Form 1

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Study I.D. _____

PHYSICIAN FORM

Health Related Quality of Life in Children with Epilepsy: The First Two Years After Diagnosis Through Parents' Eyes

Patient's Date of Birth (dd/mm/yy): _____ Site #: _____

Please answer the following questions based on information from this patient's most recent visit and return upon completion

1. Date of patient's last visit (dd/mm/yy): _____
2. Date form completed (dd/mm/yy): _____
3. Seizure type(s): _____

4. Epilepsy syndrome: _____
5. Convulsive status epilepticus:
 No
 Yes
6. Exclusive nocturnal seizures:
 No
 Yes
7. Age of first seizure (excluding febrile seizure): _____ yrs
8. Does this patient have any family with epilepsy?
 No
 Yes
9. Number of AEDs currently: _____
10. Number of AEDs total: _____
11. Is this patient of school age?
 No
 Yes → Grade: ____ regular class regular class with resource special class
12. Does the patient have behavioural problems?
 No (normal)
 Yes → Please check one: mild moderate severe
 Diagnosis: _____

PLEASE TURN OVER TO COMPLETE

Study I.D. # _____

13. Does the patient have cognitive problems?

- No (normal)
 Yes → Please check one: borderline mild moderate severe

Diagnosis: _____

14. Does this patient have motor problems?

- No
 Yes → Please check one: mild moderate severe

Diagnosis: _____

15. Other neurological deficits? Please specify: _____

16. Taking into account all aspects of this patient's epilepsy, how would you rate its severity at his/her last visit? Please check one answer.

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

17. Rate the following aspects of this patient's epilepsy at his/her last visit.

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 post-ictal period | | | | | | | |
| Amount of antiepileptic drugs | | | | | | | |
| Side effects of antiepileptic drugs | | | | | | | |
| Interference of epilepsy or drugs with daily activities | | | | | | | |

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APPENDIX B: Physician Report Form 2

Q ___ Months

PHYSICIAN FORM

Study ID _____

Health Related Quality of Life in Children with Epilepsy: The First Two Years After Diagnosis Through Parents' Eyes

Patient's Date of Birth (dd/mm/yy): _____ Site #: _____

Please answer the following questions based on information from this patient's most recent visit and return upon completion

1. Date of patient's last visit (dd/mm/yy): _____ or Date of Telephone F/U (dd/mm/yy) _____
2. Date form completed (dd/mm/yy): _____

If information for 3 thru 7 is unchanged from baseline (diagnosis) visit, please check here and proceed to 8.

3. Seizure type(s): 1) _____ 2) _____
3) _____ 4) _____
4. Epilepsy syndrome: _____
5. Convulsive status epilepticus:
 No
 Yes
6. Exclusive nocturnal seizures:
 No
 Yes
7. Age of first seizure (excluding febrile seizure): _____ yrs

8. Does this patient have any family with epilepsy?
 No
 Yes
9. Number of AEDs currently: _____
10. Number of AEDs total: _____
11. Is this patient of school age?
 No
 Yes → Grade: ___ regular class regular class with resource special class

PLEASE TURN OVER TO COMPLETE

Study ID _____

12. Does the patient have behavioural problems?

- No (normal)
 Yes → Please check one: mild moderate severe

Diagnosis: _____

13. Does the patient have cognitive problems?

- No (normal)
 Yes → Please check one: borderline mild moderate severe

Diagnosis: _____

14. Does this patient have motor problems?

- No
 Yes → Please check one: mild moderate severe

Diagnosis: _____

15. Other neurological deficits? Please specify: _____

16. Taking into account all aspects of this patient's epilepsy, how would you rate its severity at his/her last visit? Please check one answer.

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

17. Rate the following aspects of this patient's epilepsy at his/her last visit.

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 post-ictal period | | | | | | | |
| Amount of antiepileptic drugs | | | | | | | |
| Side effects of antiepileptic drugs | | | | | | | |
| Interference of epilepsy or drugs with daily activities | | | | | | | |

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Curriculum Vitae

Name: Cindy Jauhrur Chan

Post-secondary Education and Degrees: The University of Western Ontario
London, Ontario, Canada
2012-2014 M.Sc.

University of Toronto
Toronto, Ontario, Canada
2006-2012 Hon. B.Sc.

Honours and Awards: Endocrinology & Metabolism, Population Health,
and Education Award (Poster Presentation)
London Health Research Day
2014

Ontario Graduate Scholarship
The University of Western Ontario
2013-2014

Western Graduate Research Scholarship
The University of Western Ontario
2012-2014

Dr. James A. Connie P. Dickson Scholarship in Science and Math
University of Toronto
2011

University College Alumni Scholarship
University of Toronto
2010

Related Work Experience Research Assistant
The University of Western Ontario
2012-2014