A. Specific Aims

It is estimated that 2.3 million residents of the US have epilepsy and seizures disorders. (1) Each year, 180,000 Americans are diagnosed with this disorder. (1) From 1988 through 1992, epilepsy was the first-listed diagnosis for an estimated 466,000 hospitalizations. (2, 3) The annual cost of this disorder to the nation was estimated at approximately $12.5 billion. (1) Persons with epilepsy (PWE) have a disproportionate burden of other comorbid conditions compared to the general population, (4, 5) and a high level of healthcare resource utilization. (6, 7) Among major challenges experienced by PWE is the persistence of seizures in the face of advancement in epilepsy treatment, further aggravated by the excess burden of comorbid conditions. Cognizant of the excess burden resulting from comorbid conditions of epilepsy, Living Well II put forth a priority recommendation to expand research on comorbid conditions of epilepsy. (8)

To increase our understanding of epilepsy comorbidities that predict clinical outcomes and healthcare needs and to describe the public health burden of epilepsy comorbidities, we propose to conduct a population-based, statewide, retrospective cohort study of persons with epilepsy identified from all SC non-federal hospitals and emergency departments, and outpatient physician encounters from 2009 through 2013. The unifying hypothesis guiding this project is that PWE with comorbid conditions have significantly higher seizure frequency, hospitalization, more direct medical cost, and higher mortality experience than PWE without comorbid conditions; and comorbidities are more prevalent among minorities, socioeconomically disadvantaged, and rural, under-served communities.

Our specific aims are as follows:

1) Compare the magnitude and distribution of common comorbid conditions among PWE (Case group) relative to persons with fracture of the extremities and patients with delirium/syncope (Comparative Groups).
   - HA1a: We predict that, compared to trauma patients with fractures of the extremities or patients with delirium/syncope, PWE will have significantly higher rate ratios (RR) of comorbid conditions.
   - HA1b: We predict that among PWE, blacks will have significantly higher RR of comorbid conditions than whites.
   - HA1c: We predict that among PWE, persons residing in rural and underserved counties will have significantly higher RR of comorbid conditions than those residing in urban counties.
   - HA1d: We predict that there is inverse relationship between socioeconomic (SES) gradient and the number of comorbid conditions among PWE, i.e., the lower SEG the higher the counts of comorbid conditions. We will determine SES gradient by payer status and geocoded neighborhood and census tract data.

2) Determine the implications of epilepsy comorbidity on mortality and seizure conditions.
   - HA 2a: We predict that PWE with comorbid condition are more likely to have higher mortality (all cause) rate than those without comorbidity.
   - HA 2b: We predict that PWE with comorbid condition(s) are more likely to have higher occurrences of sudden unexplained death (SUDEP) than those without comorbidity.
   - HA 2c: We predict that PWE with more counts of comorbid conditions are more likely to have higher frequency of seizures.

3) Determine the association of comorbidities and individual characteristics, AEDs, recency of the onset of epilepsy, and type of seizure controlling for potential confounders.
   - HA 3a: We predict that the risk of psychiatric comorbidities is socioeconomic dependent after adjusting for age, duration of epilepsy, race, gender, and other potential confounders.
   - HA 3b: We predict that somatic including injuries, psychiatric, and cognitive comorbidities are more likely to occur among epilepsy patients treated with more than two AEDs and patients with generalized tonic clonic seizure
   - HA 3c: We predict that refractory cases of epilepsy that undergo/had epilepsy surgery have fewer epilepsy comorbidities compared to pre-surgery.

4) Determine the population attributable risk of hospitalizations accounted by epilepsy comorbidities and the direct medical care cost.
   - HA 4a: We predict that PWE with comorbid conditions will have higher rates of hospitalization as compared to the population of persons without comorbidity as measured by population attributable risk in percent.
• HA 4b: We predict that direct medical care cost of PWE with comorbid conditions is significantly higher than those PWE without comorbid conditions.

B. BACKGROUND AND SIGNIFICANCE

B.1. Epilepsy as a public health problem: Epilepsy is one of the most common neurological disorders in the world affecting about 50 million people and accounting for 1% of the global burden of diseases. People in the developing world account for 80% of the global burden and nearly 80-90% may not receive regular treatment.(9) The International League Against Epilepsy (ILAE) has defined epilepsy as “a condition characterized by two or more epileptic seizures, unprovoked by any immediate identified cause”(10) In 2005, ILAE proposed a new definition of epilepsy 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” requiring the occurrence of at least one epileptic seizure to establish the diagnosis.(11) The latter definition recognizes the multidimensional aspects of epilepsy beyond seizures. It has been estimated that there are 2.3 million Americans with epilepsy or seizure disorder, and upwards of 181,000 newly diagnosed each year.(1) The Behavioral Risk Factor Surveillance Systems in Georgia, South Carolina, Tennessee, and Texas and the 2002 National Health Interview Survey have revealed epilepsy lifetime prevalence rates of 1.4 to 2.1%. (12-15) Direct and indirect costs for persons with epilepsy accrue through medical expenses, lost work hours, lost household productivity, and missed school days. (1, 16) The lifetime total costs for all incident cases of epilepsy in a year are estimated to be $11.1 billion (1) and can vary according to many different factors, one of which is seizure frequency. It has been shown that persons with higher seizure frequency experience higher total costs, and accumulate more missed days of work or school. (16) In addition, individuals with epilepsy report lower quality of life than both the general population as well as individuals with some other chronic diseases (6, 13, 17), and the stigma experienced by PWE is second to the stigma experienced persons with AIDS. (18)

B.2. Increased risk of comorbidity with epilepsy: Among the risk factors influencing the clinical trajectory of epilepsy and seizure control, comorbid conditions are of paramount relevance. (19) Comorbid conditions have been associated with worsening of seizures, cognitive decline, poor general health, and higher mortality rate. (19-21) For many categories of comorbid conditions, the effects of the comorbidities were more problematic and have a greater influence on subjective health status than the seizures. (19, 22-24) The most frequently cited comorbidities in this regard are depression and anxiety, which severely compromises patients’ abilities to self-manage their epilepsies and predisposes them to substance abuse and suicide. (21, 23-26) Somatic comorbidities such as stroke, heart disease, arthritis, cancer, migraine, and asthma have been reported to be significantly higher among PWE than the general population.(5, 15) Likewise, injuries subsequent to clinically established epilepsy are prevalent problems because of the unpredictability of seizure that predisposes them to traumatic events despite treatment with antiepileptic drugs (AED) and mental alertness. (27-34) Of all causes, injury accounts for the highest standardized mortality rate among PWE. (35, 36)

Compounding the difficulty with seizures and medication side effects, epilepsy is often accompanied by increased morbidity, both physically and mentally. The 1990 Ontario Health Survey of over 60,000 individuals showed that almost three-quarters of the individuals with self-identified epilepsy reported having one or more other chronic health problems, with an average of almost 3 other chronic health problems. (6) These individuals also had the highest level of hospital, emergency, medical, and psychosocial service resource use, compared to healthy individuals, the general population, and other chronically ill individuals. In a one-year prospective population-based study in the United Kingdom (UK), an approximate 1% sample of the population was followed. Individuals with an ICD-9 diagnosis code of 345 (epilepsy) were found to make considerably greater use of health services than people without epilepsy, even after stratification for gender, age, and social class. (7) A higher percentage of the patients had consults for diseases in all disease groups examined, with the exception of infections, and overall twice the mean annual number of consultations. There were particularly high rates of consults for neoplasms, hematological disorders, and mental health disorders. When individual disorders were analyzed, there was a higher proportion of patients with epilepsy seen for dementia, stroke, and gastrointestinal bleeding, as well as marginally higher proportions for many other conditions. Additionally, there was almost 3 times the annual number of referrals to secondary care. A similar study by these researchers covering 2.6% of the population in the UK done through general practices had similar findings in regard to comorbid disorders. (4) The prevalence ratio of somatic disorders, with the exception of musculoskeletal and connective tissue disorders, were increased in adults with epilepsy, with psychiatric disorders occurring twice as often. Annegers et al. looked at heart disease in the Rochester, MN, epilepsy cohort. (37) While incidence of myocardial infarction was increased, there was no increase in the incidence of
Increased mental health morbidity may accompany epilepsy to a larger degree than in the general population, especially depression. (23) In a large US survey, 40 to 46% of individuals with epilepsy felt that it affected some area of their cognitive function. (38) Individuals with epilepsy are believed to have a 4- to 5-fold higher incidence of depression, and up to a 5-fold higher incidence of suicide than the general population (39) and prevalence of depressive disorders is more than 30% in community based epilepsy samples. (40) These authors feel there is evidence that not only can epilepsy lead to depression, but that depression precedes epilepsy. Additionally, neuropsychological studies have shown even persons with epilepsy who have average intelligence have a lower degree of flexibility of mental processing than controls, which limits their ability to cope with daily obstacles. A cross-section of adolescents with epilepsy reported 23% with symptoms of depression. (41) When individuals at an epilepsy clinic were asked to provide a definition of epilepsy, a majority of them included memory problems and quality of life issues. (42) A study was conducted among 102 individuals who were referred for possible focal resection of their epileptogenic lesion, usually because of an unacceptable degree of seizure control. They were without intellectual disability or significant reading disability, and 85% had no structural abnormality underlying their epilepsy. Ninety-five percent had partial seizures. After testing, it was determined that there were three significant independent predictors of psychopathology: an increased number of stressful life events in the past year, poor adjustment to epilepsy, and financial stress. (43) Other studies have also shown individuals with epilepsy to be at increased risk of suicide. (21, 44-46)

Individuals with epilepsy appear to have an increased risk of injury, with as many as 30% reporting injuries, and evidence of greatly increased deaths from injuries and poisoning compared to the general population. (29, 36, 47) Of adults with epilepsy in the UK who answered questions on injuries sustained from an epilepsy attack, 22.5% reported a head injury in the previous year. (48) In the US, patients with seizures may make up almost 1% of all patients seen in an urban emergency department, with 6% having serious trauma resulting from the seizure. (49) Head injury has been reported as the most common injury due to seizures, and drowning the most common cause of death as a result of an injury due to a seizure. (50) Patients with epilepsy at an outpatient center in Japan who died were found to have accidents as the top cause of death, followed by sudden unexplained death. (51)

B.3. Health outcome in epilepsy and the compounding effect of comorbidity and AED toxicity: The outcome of epilepsy is multidimensional and extensive for both individuals and their families. A study conducted to assess the outcomes of epilepsy in the United Kingdom indicated that epilepsy adversely affects multiple areas of an individual's life, even when the individual feels his/her epilepsy to be well-controlled. (48) Jalava and colleagues (52) in Finland concluded that individuals diagnosed with epilepsy in childhood, but with no other neurological problems, had wide-ranging social problems more than 3 decades later. The occurrence of seizures in childhood appear to have a long-term adverse affect on education and social life, even when individuals have no neurological insult, are in remission, and not on medication. (53)

Despite advances in epilepsy treatment, it is estimated that 40% of people with epilepsy in the U.S. live with persistent seizures. (54-56) This percentage agrees fairly well with a U.K. study in which half of individuals with epilepsy had had a seizure in the past year despite treatment. (57) Even when treatment does reduce or eliminate seizures, it is often accompanied by negative side effects and predisposition to secondary comorbidities. Antiepileptic drugs (AEDs) can lead to osteoporosis, gingival hyperplasia, alterations in reproductive endocrine function, weight loss or gain, hyponatremia, aplastic anemia, liver failure, and glaucoma, all linked with secondary comorbidities of epilepsy. (58) In addition, AEDs are known to have major cognitive side effects, which are increased with polytherapy. (59, 60) In a U.S. survey study of over 1000 individuals with epilepsy, 40% and 38% of those taking antiepileptic drugs felt that the drugs had a large effect on their overall energy level and their school performance, respectively. (38) A smaller British study of epileptic individuals with relatively well controlled seizures on monotherapy also reported 40% complaining chronic of fatigue. (61) Another British study on adults with epilepsy found 56.1% reported drug side effects, especially sedation, concentration, and memory problems. (48)

Persons with epilepsy experience increased mortality over the general population. Most studies investigating mortality in persons with epilepsy in relation to the general population report standardized mortality ratios (SMRs). It has been estimated that persons with epilepsy experience overall SMRs ranging from 1.8-9.3 depending on the population selected, (62-68), with higher SMRs in selected populations. (69) Younger patients tend to have the most increased mortality when compared to the general population, and
persons with epilepsy under 20 years of age have more of their mortality attributable to epilepsy than persons over 20.(62, 70) Some studies have found that males with epilepsy had higher SMRs when compared to the general population than females.(62, 70) Differences in mortality by type of seizure and type of epilepsy have also been reported. Individuals who experience generalized tonic-clonic seizures have increased mortality over other seizure types,(62) and individuals with a known etiology for their epilepsy also have increased mortality.(37, 47) While seizure frequency has been shown to be associated with mortality,(71) Hauser et al. found that even after being seizure-free for 5 years, persons with epilepsy still had a persistent elevated mortality over the general population.(62)

Employment and education, often used as surrogates for SES, have also been examined as one of the outcomes of epilepsy in some. Most studies tend to find lower employment rates among individuals with epilepsy,(72-75) although one study that had lower employment rates reported by individuals with epilepsy found no difference in education between patients and controls.(76) The prospective Finnish study that followed children diagnosed with epilepsy determined that these individuals had significantly lower employment and education levels, even if they had been seizure-free without medication for many years.(77) In the U.K., individuals with well-controlled epilepsy were determined to have high levels of employment, except for those with a history of partial seizures, who were significantly more likely to be employed.(78) In a Swedish study, individuals with no seizures in the past year were not more likely to be unemployed than the general public, but they were more likely to be on a disability pension because of lack of sustainable employment.(79) Also, persons with uncontrolled seizures were significantly more likely to be unemployed. In general, in studies that looked at seizure frequency, persons with more frequent seizures had greater unemployment than those with better seizure control. In one of the few U.S. studies, household incomes of individuals with epilepsy averaged 93% of the U.S. median household income, but they were less likely to be employed or to have graduated from high school or college.(55)

**B.4 Socioeconomic Status, Epilepsy, and Comorbidity:** Epilepsy may affect an individual’s SES, or vice-versa. Likewise, comorbidity may affect the outcome of epilepsy and erode the SES of PWE. In a recent article that illustrated the influence of ‘health, wealth, and culture’ on psychosocial morbidities of epilepsy, Hesdorffer and colleague indicated the mediating influence of socioeconomic deprivation as stressor (allostatic load) leading to augmented disease rates and comorbidity.(80) Studies in Britain and Ireland have shown a greater proportion of individuals with epilepsy in the lower socioeconomic classes than the general public,(72, 73, 81) and a large Canadian study found significantly more individuals with epilepsy with a lower income.(6) However, these studies were unable to make temporal associations. A prospective Finnish study of individuals with seizures diagnosed in childhood found no difference in SES between patients and controls, despite finding differences in education and employment.(82) A prospective study in Sweden, found that income increased similarly both for the patients with seizures and controls during a 10-year follow-up, unless the patient had refractory seizures. However, patients had significantly lower annual income before the study’s index seizure and continuously during follow-up, leading them to surmise that patients may have had increased morbidity prior to the index seizure, and that a lower SES could be a risk factor for seizures.(76) Similarly, a prospective study in England concluded that evidence in their study favored poor SES being a risk factor for the development of epilepsy.(83) Hauser and colleagues(26) found an almost three-fold increased risk of epilepsy among individuals seen for head injuries in a racially-mixed impoverished Bronx community than compared to individuals from the middle-class community of Rochester, Minnesota.

**B.5. Gaps in the literature:** There is a lack of information on the prevalence of the full range of epilepsy comorbidities at the population level. Further, the distributions of comorbidities in population subgroups, the factors that explain the disproportionate burden in some population groups, and implications on the natural evolution of epilepsy at the population level remains poorly described. There have been a limited number of population-based studies conducted on epilepsy comorbidities, most of which have been outside of the US and none used systematically identified a range of epilepsy comorbidities.(4, 84, 85) A few of the population-based studies in the US were based on BRFSS, Health Style Surveys, or confined communities.(20, 24, 86, 87) While their have been a few studies that mentioned the higher prevalence of epilepsy in blacks than whites,(88, 89) there is not any study that compared the prevalence of epilepsy comorbidities between the races despite wide gaps in health status. Further, little is known about epilepsy outcomes attributable to comorbidities and the very few studies that looked into mortality of epilepsy including SUDEP have no direct mention of the risk of death attributable to the burden of comorbidity.(68, 90, 91)
Several studies have identified an extensive list of mental health, cognitive, and somatic problems, including injuries, as intricately linked comorbid conditions. Yet, there is uncertainty if epilepsy comorbidities vary in population subgroups and if such variable impact contributes to disparate epilepsy outcomes. There is limited understanding regarding the influence of socioeconomic deprivation and psychosocial stressors on comorbidities of epilepsy (5, 80). Access to care and affordability of AEDs that are safer and with fewer side effects are largely beyond the reaches of low income rural and poor-neighborhood residents; intractable epilepsy is associated with the development of comorbid physical and mental health conditions. (5) Increased comorbid conditions and negative outcomes among blacks with epilepsy (87) and other chronic diseases (92, 93) have been documented and suggest the need to better understand the intricate relationships of race, poverty, and epilepsy comorbidities. This is particularly disconcerting in light of the wide rift in health outcomes that exist among the races and the monumental task needed to eliminate health disparities in the US population by the year 2020. (94) Other gaps in epilepsy comorbidity include, a) absence of population-based, systematically categorized and well-validated full range of common comorbidities, b) poor understanding of the underlying pathophysiology of epilepsy comorbidities (4, 19), differentiating comorbidities that are due to seizures from those that result from other mechanisms that parallel underlying ictal activity. (95)

Another problem with the study of comorbidity and epilepsy is the ascertainment of the comorbid conditions. Many studies included all illnesses in the resource database or used self-confirmed comorbid diagnosis through surveys. (4, 7, 84) Some studies used selected psychiatric comorbidities or specific chronic health conditions that co-occur with epilepsy. (17, 23, 96) Perhaps the most profound deficiency in the literature is the lack of explanation on the underlying neurobiological mechanisms of epilepsy comorbidities. In most of the studies, associations between comorbid illnesses and epilepsy were based on contemporaneous occurrences with speculations and uncertainties why the associations exist.

B.6. Significance of the study
B.6.a The magnitude of epilepsy in South Carolina: Epilepsy and seizure disorders (ESDs) are important public health problems in SC. According to the Epilepsy Foundation of South Carolina, there are about 60,000 individuals and families in the state affected by this disorder. For a two-year period, January 1, 2002 through December 31, 2003, the SC Epidemiological Study of Epilepsy and Seizure Disorders (SCSESESD) recorded 49,696 unduplicated individuals with epilepsy that received medical care and evaluation via emergency department and hospital inpatient services. This number represents the true positives among 62,834 individuals identified with ICD-9-CM diagnosis of 345.x or 780.3 based on a review of a random sample of 3,884 records. The surveillance data showed the true positivity rate of 345.x diagnosis code (excluding status codes 345.2 and 345.3) is 96% while the true positivity rate of 780.39 code for epilepsy is 74%. (97) Cases were ascertained based on ICD-9-CM diagnosis codes of 345.0 through 345.9 for epilepsy and 780.39 for seizure NOS. We excluded repeat visits and hospitalizations using unique identifiers (SSN and/or name with date of birth). Table 1 is the summary table annotated from our published study from the SC population-based epilepsy surveillance using SC BRFSS. (98) The result obtained from BRFSS is comparable with the number of persons with active epilepsy in the state reported from the SCSESESD.

Comparative analysis based on hospital and ED encounter data for the years 2005-2006 reveal the disproportionate burden of comorbidity among PWE in low income—as approximated by payer status—and racial minorities in SC compared with trauma controls (Table 2). The method employed for this analysis relied on random selection of patients with a primary diagnosis of fracture of the extremities with no secondary diagnosis of ESD (Trauma Controls; N=37,258) and patients with a primary diagnosis of ESD with no diagnosis of fracture of the extremities (ESD Cases; N=33,439). Diseases that we identified as common comorbidities of epilepsy (CCE) are those that were recently proposed by the workgroup on Standards for Epidemiological Surveillance (unpublished report) and are included as Appendix A along with the ICD-9-CM codes of these conditions. Result shows the distribution of these comorbid conditions of Epilepsy by various
patient characteristics. The proportions of patients with ESD diagnosis were significantly more likely to be blacks, Medicaid insured, with comorbid diagnosis, and males. Similarly, patients with ESD had more counts of comorbid diagnosis than trauma controls. The race-specific prevalence rates of ESD were 1.33%, 0.67%, and 0.21% for blacks, whites, and other races respectively. The overall prevalence rate of active epilepsy based on this data is 0.7%, which is some what lower than the self-reported rate of 1.1% shown in Table 1. This discrepancy could be the result of not including private physician office visits or over-reporting in the BRFSS self-report. Nonetheless, the reported prevalence rate for active epilepsy in SC is high enough to warrant public health attention and further investigation.

B.6.b. The burden of comorbidities among PWE in South Carolina: Epilepsy comorbidities pose significant challenges to patients and caregivers in SC. Of the 33,439 ESD patients, 53.8% have one of the CCE compared with 41.6% of the trauma controls. ESD patients not only have higher rates but also have significantly more counts of these conditions than the trauma controls (Table 2). As mentioned in the background review, comorbidities are contributing to poor seizure control and drug side-effects because patients are taking multiple medications to manage their illness in additions to AEDs. Specifically, some categories of comorbid diseases are predominantly common among ESD patients than trauma controls. The associations noted for intellectual disabilities (ID) and Infectious/infestations (HIV/AIDS, neurocystercosis) with ESD are 5 to10-folds higher than in trauma controls (Table 3). This suggests the need to target selected comorbid conditions that co-occur more frequently with epilepsy than comparable controls. Psychiatric and somatic comorbidities, which are also known to be prevalent in the general population, show stronger relationships with ESD, suggesting the occurrences of these conditions are beyond what is expected from random variability in the population.(95) The use of trauma comparison, selected in the same time frame and from the same hospitals/EDs, supports our argument that ESD patients have more burden of comorbidity even when compared with hospital controls.

B.6.c. Vulnerable population and the risk of CCE in SC: Population subgroups that are more susceptible to CCE and the consequences thereof are major concerns in epidemiological analysis not only because of moral arguments but also because of social justice issues—the philosophical base of public health practice. In this regard, vulnerable populations, according to AHRQ, are “those who are made vulnerable by their financial circumstances or place of residence, health, age, personal characteristics, functional or developmental status, ability to communicate effectively, and presence of chronic illness or disability.”(99) Hence, PWE that are

| Table 2. Comparison of Patients with Epilepsy/Seizure patients and Trauma |
|-----------------------------|------------------|------------------|------------------|------------------|------------------|
| Patient Characteristics     | Total (N=70,697) | Epilepsy/Seizure (n=33,439) | Trauma (n=37,258) | P-values        |
| Comorbidity Present         | 33,495 (47.4)    | 53.7             | 46.3             | <0.001          |
| Absent                      | 37,202 (52.6)    | 41.5             | 58.5             |                 |
| Comorbidity Count           |                  |                  |                  |                  |
| Four or more                | 901 (1.3)        | 61.4             | 38.6             | <0.001          |
| Three                       | 3,844 (5.4)      | 58.7             | 41.3             |                 |
| Two                         | 10,894 (15.4)    | 54.4             | 45.6             |                 |
| One                         | 17,856 (25.5)    | 51.8             | 48.2             |                 |
| None                        | 37,202 (52.6)    | 41.5             | 58.5             |                 |
| Age group (Years)           |                  |                  |                  |                  |
| 0-9                         | 5,049 (7.9)      | 53.1             | 46.9             | <0.001          |
| 10-19                       | 6,256 (9.8)      | 39.0             | 61.0             |                 |
| 20-59                       | 36,230 (56.6)    | 50.6             | 49.4             |                 |
| 60-79                       | 7,825 (12.2)     | 45.8             | 54.2             |                 |
| 80 and older                | 8,668 (13.5)     | 31.6             | 68.4             |                 |
| Race                        |                  |                  |                  |                  |
| Black                       | 23,883 (33.8)    | 56.8             | 43.2             |                 |
| White                       | 45,127 (63.8)    | 42.7             | 57.3             |                 |
| Others                      | 1,687 (2.4)      | 35.5             | 64.5             |                 |
| Gender                      |                  |                  |                  |                  |
| Male                        | 35,695 (50.5)    | 48.1             | 51.9             |                 |
| Female                      | 35,002 (49.5)    | 46.5             | 53.5             |                 |
| Payer (Insurance)           |                  |                  |                  |                  |
| Commercial                  | 21,606 (30.6)    | 38.3             | 61.8             |                 |
| Medicare                    | 25,782 (36.5)    | 50.1             | 49.9             |                 |
| Medicaid                    | 11,572 (16.4)    | 61.9             | 38.1             |                 |
| Uninsured                   | 11,737 (16.6)    | 43.3             | 56.7             |                 |

| Table 3. Comparison of Comorbidity Categories between ESD and Trauma Controls |
|-----------------------------|------------------|------------------|------------------|------------------|------------------|
| Type of Disorder            | Epilepsy/Seizure (n=33,439) | Trauma (n=37,258) | Crude Risk Ratio (95% CI) |
| Frequency (Column Percent)  |                  |                  |                  |
| Psychiatric Disorders       | 6,047 (18.7)     | 4,675 (13.1)     | 1.75 (1.67 – 1.82) |
| Somatic Disorders           | 20,693 (61.9)    | 17,586 (47.2)    | 1.66 (1.61 – 1.70) |
| Cognitive/Intellectual      | 925 (2.8)        | 129 (0.3)        | 10.17 (6.41 – 12.31) |
| Nutritional Disorders       | 2,240 (6.7)      | 2,101 (5.6)      | 1.50 (1.41 – 1.60) |
| Infectious/Infestations     | 245 (0.7)        | 60 (0.1)         | 5.75 (4.29 – 7.71) |
| No Comorbidity              | 15,452 (46.2)    | 21,750 (58.4)    | Referent |

(95) The use of trauma comparison, selected in the same time frame and from the same hospitals/EDs, supports our argument that ESD patients have more burden of comorbidity even when compared with hospital controls.
racial minorities, uninsured or Medicaid insured, children under 10, and persons older that 80 are groups that fall in this rubric. Our data presented in Table 2 show, these groups constitute about 53% of the persons with ESD diagnosis. It has been demonstrated that the stress of living with epilepsy in these vulnerable population groups escalates the risk of developing depression and other psychiatric and somatic comorbidities because of the cumulative effect of physical and emotional demand required to adapt to the stressful living situation (allostatic load) (100) A risk protagonist that poses unique challenges in SC is created by the current unfavorable economic scenario, which has severely eroded the social support system for vulnerable population. In addition, state resources may exist but do not extend their services to persons with epilepsy in SC.(101) As a result of this, many PWE are increasingly losing their entitlements and financial subsidies. An example for this is the proposed slashing of Medicaid budget by as much as 23%, which barely supports routine physician office visits, at the lowest pay rate limiting access to specialty care. Further, the uninsured population in the state has now reached 20% while the national average is 15.6%. The uninsured are more likely to be minorities, immigrants, and the working poor who will not be eligible for Medicaid because of income threshold yet unable to afford insurance. Although chronically ill and severely disabled PWE qualify for Medicare, severe reduction in Medicare entitlement is in the making further limiting access to care for PWE. Taken together, the poor economic scenario has delivered a double challenge, erosion of the social safety network and limited access to care to the vulnerable population in the state. Given these unfavorable socioeconomic circumstances, a systematic study of comorbid diseases among PWE is timely and warranted.

B.7 Summary and conceptual framework

Substantial differences exist in the types and number of comorbid conditions that exist among PWE. Currently, there is limited information in the literature to fully explain impacts of these differences on the outcome of epilepsy. In this proposal, we bring together scholarship from multiple disciplines to develop, refine, and test multiple hypotheses about the relationship of the common comorbidities and poor outcomes in epilepsy. The conceptual model (Figure 1) builds upon and extends current knowledge about the strong correlation of some comorbid conditions, such as depression, and negative epilepsy outcomes. This model hypothesizes that the effects of the common comorbidities of epilepsy are causally linked to poor epilepsy outcomes. It further hypothesizes the compounding effect of more counts of comorbid conditions towards accelerated occurrence of negative epilepsy outcomes. These are mediated through internal and external factors, including the severity and type of seizure, access to care, individual vulnerability resulting from personal and socioeconomic factors. These factors mediate the influence of the comorbid conditions of PWE and result in repetitive demands to adapt to internal and external stressors (allostatic load). We also hypothesize that epilepsy comorbidities are sufficient enough to result in severe physiological stress without being mediated through the secondary factors (broken lines). Thus, we are conceptualizing that the increased demand to cope with these stressors contributes to poor outcomes of epilepsy. We intend to measure poor outcome in epilepsy with the following indicators.

1) **Seizure-related conditions**—increased severity of seizures, more frequent attacks, SUDEP, and all-cause mortality.

2) **Direct medical care cost**—we will measure direct medical care cost by rates of hospitalization, frequency of medical encounters, and resource usage (surgery, imaging, etc.). We will also measure the excess risk that is attributable to comorbidities in the population.
We recognize that the relationship between epilepsy comorbidities and epilepsy outcomes could be complex and multifactorial. The proposed conceptual framework is a simplified depiction of the theory driving our current proposal. The methodological rigor and data to be gathered are extensive and cannot be fully integrated in this graphic depiction of the model. Further, it is neither our goal nor the intent of the proposed study to investigate the complex relationships that go beyond the realms of epidemiological and clinical research, specifically basic science investigations and elaborations of gene–environment interactions. This proposed study mainly seeks to increase our understanding on the role of a full range of consistently associated comorbidities of epilepsy(102) in aggravating seizure severity, medical care cost, and contributing to mortality. It further seeks to identify the disproportionate burden of the common comorbidities in population subgroups and the factors contributing to differences in prevalence and the consequences thereof.

To test our hypotheses, we propose to undertake, 1) a multi-level analysis by identifying all PWE from statewide hospital, ED, and outpatient encounter data, 2) capturing those who died from the multiple causes of death data (MCDD) from 2009 through 2014, and 3) detailed pathophysiological and typological analysis of epilepsy and a full range of common comorbidities, which have been recently identified by experts (102), on the subset of PWE with comorbidities (cases) and randomly selected PWE without comorbidities (controls) who were evaluated and treated at the MUSC Comprehensive Epilepsy Center (CEC) the only Level IV tertiary care center for epilepsy in the state. The analyses will be guided by our conceptual model (Figure 1), which postulate that common comorbid conditions of epilepsy lead to worsened outcomes with the risk mediated by severity of illness, seizure type, socioeconomic vulnerability, and access to care with accelerated cumulative deterioration (allostatic load) in physical and emotional wellbeing.

Specifically, the project will conduct high-quality research to, 1) determine the magnitude and distribution of comorbid conditions of epilepsy and the factors accounting for the high prevalence in some population subgroups; 2) determine the association between comorbidities and personal characteristics and number of AEDs; 3) identify the underlying risk factors of common comorbid conditions, especially those recognized with new onset; 4) compare seizure conditions and mortality between persons with and without the common comorbidities of epilepsy; and 5) determine the attributable fraction of hospitalizations and direct medical cost attributable to epilepsy comorbidities.

C. PRELIMINARY STUDIES AND EXPERIENCES RELEVANT TO THE PROPOSED STUDY

C.1 Epidemiological surveillance of epilepsy and seizure disorders in SC: We have been conducting data collection on epilepsy and seizure disorder (ESD) in SC since October 2002 as part of the ongoing SC Epidemiological Study of ESD (SCESESD). SCESESD is a comprehensive epidemiological study designed to estimate the prevalence and incidence of epilepsy in SC and determine the causes and etiologies in a representative sample of patients. Cases of epilepsy are identified from three multiple data sources — statewide hospital discharge, emergency department visits, State Health Plan, Medicaid and Medicare physician office visit encounters.
The study defined epilepsy as a person who experienced two or more usually unprovoked seizures. Operationally, cases were ascertained with ICD-9-CM diagnosis codes of 345.0-345.9, 780.3, 780.2, and 293.0. The medical records of a representative sample of cases ascertained by the selected ICD-9-CM codes were evaluated in consultation with a board-certified neurologist/epileptologist to assess the severity and types of seizure (Please see Appendix B for the project’s medical records abstraction tool which will also be adapted for this proposed study). The risk factors and etiologies of epilepsy were determined from results of clinical and medical history information extracted from clinical records. Venues of care were evaluated through focus group surveys with family members, individuals with epilepsy, and advocacy organizations. Result of this evaluation has been published.(103) Persons with incident onset of ESDs were identified if chart review indicated new onset and if there was no prior diagnosis with epilepsy in the electronic billing record. For global estimate of ESD, the project conducted statewide Behavior Risk Factor Surveillance System (BRFSS) by including a four-question epilepsy/seizure module in the SC annual BRFSS. The first result from 11,549 interviews has been published.(98)

We analyzed the ESD surveillance data for all hospital discharges and ED visits that took place in 2002 and 2003. In this analysis, we counted only one visit or discharge per person per year using unique identifiers—Social Security Number, Last Name, and Date of Birth. Accordingly, there were 23,217 and 26,479 persons with epilepsy who were treated with a primary or secondary diagnosis of epilepsy (Table 1 on page xx). Brief descriptions of the main findings are presented in Table 1. Among the key objectives of SCESESD, validation of sensitivity and specificity of administrative data sources for surveillance of epilepsy was salient. To this end, 4,741 medical records were randomly selected from the three sources and 3,987 (84%) of the records were successfully located and abstracted. After excluding records with incomplete information, 3,299 records were evaluated. Summary of the validation measures is presented in Table 4. This evaluation suggested that the administrative data sources have very high predictive value positive for epilepsy (95.7%) but low sensitivity (28.1%) because of miscoding of epilepsy as seizure. We speculate that this is perhaps the result of trying to avoid labeling patients as epilepsy since the diagnosis of epilepsy penalizes patients for insurance and driving privileges. Conversely, patients coded as seizure were true epilepsy cases 80.6% of the time (2000/2482) and seizures resulting from other causes (provoked seizures) only 19.4% of the time (482/2482). A detailed description on the algorithm developed to establish true epilepsy cases from chart review for seizure unspecified (780.39) code is available on our published report.(104)

The findings of the SCESESD have tremendous potential to advance the current proposed study on comorbidity. It will be a natural extension of the epilepsy surveillance activities to look closely at the prevalence and implications of comorbidities and their relationships with poor outcomes and the differences in population groups. The ground work we laid and the extensive database we developed will be invaluable resources to accelerate the proposed research. Among the resources that could be directly transferred to the comorbidity study are data abstraction tools and manuals, the know-how and expertise in chart reviews, SAS
programs and decision trees for validation studies, as well as lessons learned from incorrect decisions we made. We believe these are tremendous advantage we have in bringing study to fruition.

C.2. The SC Health Outcome Project on Epilepsy (SC HOPE). The objectives of this community-based retrospective-cohort study was to assess the outcomes of epilepsy as a function of socio-economic status (SES) (education, income, occupation) and healthcare system determinants (health insurance status, access to care, provider type) using information from two sources: 1) clinical and demographic information from a well-defined, population-based epilepsy surveillance system, 2) follow-up of a cohort of persons with epilepsy recruited from healthcare establishments in the South Carolina Low Country. Persons eligible to participate in the study were residents of 16 counties in SC, age 10 and older, with clinically established epilepsy with ongoing medication and/or physician follow-up. Patients were identified from hospitals, EDs, and community-based physician referral network consisting of private practice, general practice, neurology practice, and epilepsy specialty clinics. By collecting information from medical charts and telephone interviews on 387 adult and adolescent (ages 11-17 years) participants with 760-year of follow-up data, we were able to establish the relationships of socioeconomic factors (income, education level, employment, etc.), access to healthcare, and perceptions about epilepsy with selected epilepsy outcomes as measured by epilepsy quality of life index, seizure control, and employment. Result showed (Table 5) seizure control was significantly poor with lack of health insurance, perceived stigma, low self efficacy, and low income. The risk of depression was significantly higher among PWE with Medicare, perceived stigma, and low self efficacy. The risk of unemployment was significantly higher among persons with Medicaid insurance; Medicare insured who were 18-64 years old, less than high school educated, and persons with low income.

C.3. Population-based study of risk of epilepsy after hospitalization for TBI. We gained extensive experience by conducting and analyzing statewide, population-based follow-up data on TBI and new onset of seizures as a subproject of the South Carolina TBI Follow-up Registry (SCTBIFR). This study was undertaken to determine the risk of developing posttraumatic epilepsy (PTE) within 3 years after discharge among a population-based sample of older adolescents and adults hospitalized with traumatic brain injury (TBI) in South Carolina (Table 6). It also identified characteristics related to development of PTE within this population. The study relied on taking a stratified random sample of persons aged 15 and older with TBI was selected from the SC nonfederal hospital discharge dataset for four consecutive years. Pertinent data were acquired form medical record review and up to three yearly follow-up telephone interviews. The result showed the cumulative incidence of PTE in the first 3 years after discharge and accounting for loss to follow-up, was 4.4 per 100 persons over 3 years for hospitalized mild TBI, 7.6 for moderate, and 13.6 for severe. Those with severe TBI, posttraumatic seizures prior to discharge, and a history of depression were most at risk for PTE. This higher risk group also included persons with three or more chronic medical conditions at discharge. These results raised the possibility that although some of the characteristics related to development of PTE are non modifiable, other factors, such as depression, might be altered with intervention. This study has been published.\(^{(105)}\)
C.4. Comorbidity patterns and distributions among PWE. We completed preliminary analyses on a research manuscript examining the rate at which common comorbidities of epilepsy (Please refer to Appendix A for the listing) occur among PWE compared to two sets of controls. First control includes persons with a primary diagnosis of syncope (780.2), delirium (293.0) with no mention of epilepsy in the secondary diagnosis fields. Second control includes patients with trauma of the extremities (812.x, 813.x, 820.x-824.x) without a secondary diagnosis of syncope, delirium, seizure and epilepsy. The objectives of the study were, 1) to determine if the comorbidities identified occur beyond what is expected to be random variability in the general population (approximated by trauma controls) or persons with diseases that are differential diagnosis to epilepsy and speculated to have comparable patterns of comorbid conditions (approximated by controls with syncope and delirium); 2) to assess the association between epilepsy and the comorbidities compared with controls; 3) determine if biological gradient could be observed with counts of comorbidities. This study relied on epilepsy and seizure patients as cases (n1=33,439); Syncope/dementia patients as the first set of controls (n2=36,130) and randomly selected second set of trauma controls (n3=37,258). All cases and controls were identified from the statewide hospital discharge and ED visit data sets for 2005-2006 encounters. The contents of the dataset is described elsewhere.(106). We used polytomous logistic regression to accommodate simultaneous comparison with the two sets of controls. The overall prevalence rates of the comorbidities were 53.8%, 51.4%, and 41.6% for epilepsy, syncope/delirium, and trauma respectively (Please see Appendix C for detailed distribution of the analysis on comorbidities). Age and gender distributions were comparable among the groups but significantly higher counts of comorbid diseases were noted among the cases than in the controls. The odds of having three or more comorbid conditions were 2.0-2.25 times higher with epilepsy than with either of the two controls after adjusting for age, gender, race, and payer status. By type of comorbidity, very strong association (OR>4.0) was noted for Intellectual disability and cognitive problems, stroke, and syncope and delirium); 2) to assess the association between epilepsy and the comorbidities compared with controls; 3) determine if biological gradient could be observed with counts of comorbidities. This study relied on epilepsy and seizure patients as cases (n1=33,439); Syncope/dementia patients as the first set of controls (n2=36,130) and randomly selected second set of trauma controls (n3=37,258). All cases and controls were identified from the statewide hospital discharge and ED visit data sets for 2005-2006 encounters. The contents of the dataset is described elsewhere.(106). We used polytomous logistic regression to accommodate simultaneous comparison with the two sets of controls. The overall prevalence rates of the comorbidities were
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C.5. Comorbid Traumatic Brain Injury (TBI) among PWE. We have extensive experience in population-based epidemiological surveillance of TBI. Our central nervous system injury surveillance and follow-up registry has been supported by the CDC from 1995 to 2007 and provided seminal work on TBI. We have published 25 articles on the subject including the risk associated with epilepsy and repetitive TBI.(107, 108) Although PWE are at increased risk for all types of injuries, a profound risk propensity occurs with TBI. This has been stated in several studies. In our recent evaluation of 128,882
unduplicated patients over the course of 11 year period, 4,043 (3.14%) were patients with secondary diagnosis of epilepsy/seizure disorders. Comparison between TBI patients who had epilepsy or seizure and those without (Table 8) reveal the extent to which PWE are affected by TBI. While PWE comprise 1% of the state population, they account for 3.14% of the persons with acute TBI. Assessment of multivariable adjusted odds ratios by epilepsy status indicate that PWE had a 60% increased risk of severe TBI (AIS 5-6), were 2.5 and 2x more likely to have adverse drug effect and fall as the cause of TBI respectively, 3x more likely to have intracranial injury, 80-120% more likely to have incremental number of comorbid conditions, and had 70% increased risk of sustaining polytrauma. Epilepsy/seizure is presumed to be pre-existing since the coding convention precludes assigning 345.x and 780.39 for post traumatic convulsion. A sample of medical record reviewed also indicated that TBI patients with post-traumatic convulsions were not assigned 345.x and 780.39 codes.

C.6 Investigator qualifications and experience

The research team assembled to undertake this proposed study shares many years of experience on studies addressing epidemiologic surveillance, epilepsy, traumatic brain and spinal cord injuries, outcome research, psychosocial and nursing research, clinical psychology, data systems and information technology. (Please see Appendix G for selected published work by the research Team). An experienced clinician and researcher with outstanding track record of national leadership on studies of epilepsy (Dr. Wannamaker) and an epidemiologist with many years of experience in epidemiological surveillance and population health (Dr. Selassie) will provide team leadership and expertise in their respective fields to bring this research to fruition. Given the extensive involvement of clinical evaluation and neuro-pathological assessment, two board certified epileptologists and researchers (Drs. Edwards and Martz) are included as investigators. Given the need for assessment of behavioral and psychological morbidities, a clinical psychologist with strong passion in epilepsy and research in depression and anxiety disorders (Dr. Wagner) is included as investigator. Cognizant of the need for psychosocial assessment and the complex social and family influences on epilepsy in children and adolescents, a pediatric nurse practitioner with extensive years of clinical and research experience and numerous recognitions for patient care (Ms. Smith) is included to address the comorbid conditions of epilepsy common in this population group. This research addresses complex sampling, modeling, and extensive programming and data cleaning. To handle this activity, a statistician and programmer (Mr. Gu) is included to work with Dr. Selassie, who also has many years of statistical and programming experiences. Since the hub of the study is based in a Level IV Comprehensive epilepsy center at MUSC, there is a strong fund of knowledge and expertise at our disposal for case consultation and input on as needed basis. Cognizant of a highly organized and legally mandated healthcare data system is the glue that leads this program to success; we have maintained long-standing relationships and strong partnership with the SC ORS. The unique capacity of ORS as the legally mandated repository of healthcare data system is described in Appendix D on ORS data system. To facilitate unfettered access to this unique data system and conduct the study with a sense of mutual ownership, we designated the ORS as the project’s data coordination center and included a highly skilled statistician and data manager (Mr. Finney) to identify, select and validate the case ascertainment protocol of the study in consultation with Dr. Selassie. The medical chart abstraction will be coordinated through an agency that has legal authority for medical record reviews. To carry out this important task, we have included an epidemiologist from the SC DHEC, Bureau of Chronic Diseases (Ms. Demian). The epidemiological and methodological activities of the study will be led by Dr. Selassie while an ongoing clinical oversight and evaluations will be led by Dr. Wannamaker. These two activities will remain the backbone of the project to assess the influence of comorbid diseases on selected epilepsy outcomes and their associations with epilepsy. The foundation built on two previous epilepsy studies and ongoing surveillance activities will provide the resources developed and experiences gained to bring this study to fruition.

C.6 PRIOR EXPERIENCES OF KEY INVESTIGATORS

1. Anbesaw Selassie, MPH, DrPH, 0.25 FTE (Co-PI), is trained in epidemiology and preventive medicine. He is an Associate Professor in the Division of Biostatistics and Epidemiology (DBE) and Director of the Epidemiology Program at the Medical University of South Carolina (MUSC). Dr Selassie has conducted a significant amount of research on outcomes of trauma, brain and spinal cord injuries, epilepsy, and surveillance methods. His prior work includes research on epidemiology of injuries and outcomes, health inequities, and evaluation of clinical preventive services, health disparities, and infectious disease. He has been the PI for three federally awarded studies: 1) the South Carolina TBI Follow-up Registry
SCTBIFR), 2) South Carolina Health Outcome Project on Epilepsy (SCHOPE), and 3) the SC Epidemiological Study of Epilepsy and Seizure Disorder (SCESESD). Dr Selassie’s recent work provided new national estimates on disabilities from TBI by causes of injury including the rate of disabling injuries from acts of violence (109, 110). He is the designated Consulting Epidemiologist for the SC Department of Disabilities and Special Needs overseeing the SC CNS Injury and Related Disabilities Surveillance and Registry. Dr. Selassie led the Surveillance Workgroup for the National Task Force on Mild Traumatic Brain Injury in the US that was mandated to report the finding to the US Congress. He also served as the reviewer of the Institute of Medicine report on brain and spinal cord injuries. He received the Outstanding Service Award for Children and Youth in South Carolina from SC Department of Health and Environmental Control. Under his leadership, the SC TBI surveillance program has been recognized three times among the best surveillance programs for timeliness and quality of data by the National Center for Injury Prevention and Control, CDC. As the Co-Principal Investigator, he will be responsible for the day-to-day administrative and technical activities. He will liaise with the CDC and will represent the project at official meetings.

2. Braxton B. Wannamaker, MD, 0.20 FTE, (Co-PI). Dr. Wannamaker is a board certified neurologist and epileptologist and clinical Professor of Neurology at MUSC. He specialized in the evaluation of persons with epilepsy at MUSC and in private practice. He previously served as Director of the EEG Laboratory and Director of the Seizure Unit at MUSC. As a well-recognized expert in epilepsy, Dr. Wannamaker has served as a member of the NINDS Epilepsy Advisory Committee and the NINDS Safety and Efficacy Monitoring Committee. Additionally, he served as a neurologist in the Epilepsy Branch of NINDS. He recently received the American Epilepsy Society’s “Service Award.” Dr. H. E. Booker as President of the American Epilepsy Society in 1982 asked Dr Wannamaker to develop a symposium on "Unexpected Unexplained Death in Persons with Epilepsy". He chaired and lectured at this symposium at the 1983 AES annual meeting. This was a joint international meeting in Washington, D.C. and the first ever professional and organized scientific meeting on sudden death in epilepsy (SUDEP). He has been at the forefront of SUDEP studies and is author of the chapter on Epilepsy and Sudden Death (Epilepsy and Sudden Death. Lathers CM, Schraeder PL (eds.), New York; Marcel Decker, 1990:26-37). Dr. Wannamamer was charged by the SC General Assembly to lead the study committee on Statewide Comprehensive Service Delivery System for PWE, which provided the foundational elements of the statewide system currently in the making.(101) Moreover, he has served as consultant to a multitude of pharmaceutical companies and as principal investigator of several anti-epileptic interventions. He has published extensively and participated in many seminal researches on epilepsy. He has been selected continuously from 1994-2006 as a “Best Doctor in America.” Dr. Wannamaker has served on the board of the Epilepsy Foundation and as President of the American Epilepsy Society. He was a longstanding board member of the Epilepsy Foundation of SC. As the project epileptologist, Dr. Wannamaker will direct the clinical evaluation effort by providing expert advice on case identification, ascertainment, clinical outcomes assessment and liaise with neurologists and the clinicians in the state.

3. GiGi Smith, RN, MSN, 0.20 FTE (Co-Investigator). Ms. Smith is a Certified Pediatric Nurse Practitioner in Pediatric Neurology and an Assistant Professor in the College of Nursing and Department of Neurology, Medical University of South Carolina. She has extensive experience in pediatric nursing and epilepsy. In addition, she serves as Co-Investigator of SCHOPE and SC Epilepsy Surveillance. She has been actively involved in the planning and production of scientific as well as community-oriented conferences on neuroscience and epilepsy, and has led epilepsy support groups in SC. Ms. Smith will have responsibility for assisting with reviewing medical chart abstraction summaries, interacting with clinicians, and to lead the evaluation of diagnosis accuracy of epilepsy comorbidities. She will also be involved in validating medical chart reviews, training of abstractors, development of manuals, and evaluation of data quality.

4. Janelle Wagner, PhD, 0.10 FTE (Co-Investigator), is a licensed clinical psychologist with expertise in pediatric psychology. She is an Assistant Professor in the College of Nursing and a faculty member of the Comprehensive Epilepsy Center at MUSC. Dr Wagner has been involved in the SCHOPE project as the lead researcher in the developing the survey tools for both adolescent and adult versions. She has particular interest in psychiatric comorbidities of epilepsy, particularly depression, and epilepsy self-management. Her particular focus in the proposed research is to evaluate the information available on psychiatric morbidities and participate in the development of these sections of the data abstraction tool. She has been funded for three separate projects by the Pediatric Partnership for Epilepsy Research.
(national Epilepsy Foundation (EF), American Epilepsy Society (AES), and Parents Against Childhood Epilepsy (PACE), the national EF, and Parents Against Childhood Epilepsy to assess psychological outcomes of pediatric epilepsy and the effectiveness of a brief cognitive-behavioral epilepsy self-management intervention for youth with epilepsy and their caregiver.

5. Jonathan Edwards, MD, 0.05 FTE, (Co-investigator). Dr. Edwards is the Director of Comprehensive Epilepsy center (CEC) at MUSC and Associate Professor of Neurology. He is a board-certified neurologist and epileptologist. Dr. Edward has extensive experience in epilepsy clinical services and research. His research focus is on the investigation of epileptogenic phenomenon and EEG assessment, including cognitive dysfunction and neurological disabilities. As the co-investigator and Director of CEC, Dr. Edwards will provide expertise in the relationships of the neuropathology of comorbid conditions and their relationships with epilepsy. He will also assist in optimizing the case ascertainment criteria for Phase II studies and interpretation of clinical data.

6. Gabriel Martz, MD, 0.10 FTE, (Co-investigator). Dr. Martz is an adult neurologist and epileptologist at CEC at MUSC and Assistant Professor of Neurology. He is board-certified in neurology and clinical neurophysiology and received broad clinical training in neurology, epilepsy, and clinical neurophysiology. Dr. Martz has strong research interest in epilepsy outcomes and epilepsy epidemiology including developing evidence-based clinical services. He is an active member of American Epilepsy Society Advocacy Committee. As the co-investigator, Dr. Martz will provide expertise in the relationships of the neuropathology of comorbid conditions and their relationships with epilepsy. He will also assist in optimizing the case ascertainment criteria for Phase II studies and interpretation of clinical data.

7. Chris Finney, MS, 0.30 FTE, (Co-investigator). Mr. Finney is a statistician in Health and Demographic Statistics Section, Office of Research and Statistics (ORS), South Carolina Budget and Control Board. He has specialty and interest in population health and management of healthcare utilization database including UB-04, home health, Medicaid, Medicare, the State Health Plan, and vital records data system. He works with individual researchers and planners to develop research designs necessary for special research projects utilizing data from any of the in-house claims-based systems. Mr. Finney will have responsibility to perform the linkage of the various datasets in ORS that will be used to identify epilepsy and seizure disorder patients throughout the various healthcare providers in the state. He will oversee the unduplication of records and will facilitate selection of records that need review. Mr. Finney will provide quality assurance and data integrity, confidentiality in accordance with ORS policy. He will play key role in identifying new cases that were not previously diagnosed with epilepsy.

8. Ja K. Gu, MS, 0.20 FTE, (Investigator). Mr. Gu is a biostatistician with training in mathematics and statistics at UNC and MS in biostatistics at USC. He has a part-time appointment in the Division of Biostatistics and Epidemiology at MUSC. He has extensive experience in SAS programming, SAS macro, SUDAAN, and various programming languages. He is a certified programmer from SAS Users Group International (SUGI) at various levels of training. He has been involved with various population health researches in SC along with Dr. Selassie, including SC HOPE and SCESESD. In this project, he will be involved in data management and analysis, programming, and data linkage for cost analysis.

9. Georgette Demian, MS, 0.10 FTE, (Investigator). Mr. Demian is an epidemiologist in SC DHEC, Bureau of Chronic Diseases and Health Promotion. She has MS in epidemiology from USC. She has extensive experience in data validation, sampling and editing abstracted data, developing abstraction tools, liaising with various hospitals and EDs. As an employee of the state health department, Ms. Demian has access to hospital medical files once consent is granted by participants. She has been involved with various population health researches in SC including SC TBI follow-up study, SCHOPE and SCESESD. In this project, she will be involved in coordinating the statewide effort to medical abstraction.

D. Research Design and Methods
D.1 Overview
The objectives of this statewide retrospective-cohort study include, 1) determine the magnitude and distribution of comorbid conditions of epilepsy and the factors accounting for the high prevalence in population subgroups; 2) determine the implications of epilepsy comorbidity on seizure conditions and mortality; 3) delineate the temporal sequence of events in the development of epilepsy and establish the association of common comorbid conditions with types of epilepsy among incident cases in the CEC of MUSC; and 4) determine the population attributable risk of hospitalizations and the direct medical care cost accounted by epilepsy comorbidities. All subjects will be identified from healthcare encounter data from January 1, 2009.
through December 31, 2013. Pertinent data on comorbidity, demographical, and direct medical care cost data will be acquired from administrative data sources. As shown in the schematic depiction of the study procedure (Figure 2), subjects will be sorted by source of care. Specifically patients evaluated and treated at the CEC, a Level IV Epilepsy Center at MUSC that serves as the referral site for all epilepsy patients in the state (double border box), will be differentiated from patients evaluated and treated in other medical facilities in the state during the same time interval. The purpose of sorting patients in this manner is to concentrate our resources and effort on acquisition and analysis of detailed clinical information, which is often available on CEC evaluated patients (EEG, fMRI, laboratory data, etc.). Further CEC is a high volume center with approximately 2,000 first time encounters per annum and serves as the referral site for new onset and refractory epilepsy patients in SC. CEC’s patient distribution by county of residence and demographic characteristics shows representativeness of the PWE to the surveillance data of the state. Both care groups will then be discriminated by the presence or absence of the comorbid conditions of interest. These first two steps of the study protocol represent Phase I of the study, demarcated by the area above the broken transverse line in Figure 2. This phase of the study will be used for the prevalence study, mostly addressing specific aims 1 and 2. Phase II is the part of the study where more information will be sought to fully evaluate the endogenous risk factors of comorbidity. Access to medical records is predicated on consent of subjects in compliance with HIPAA policy. Although access to medical records of subjects evaluated in CEC is viable without consent under the “covered entity” clause of the HIPAA policy, our proposal will seek consent of subjects to preserve patients’ rights and trust. From our past experience, there is little objection to accessing medical records when consent is sought from by the center.

In designing this study, we decided to include persons without epilepsy but treated for fracture of the extremities and persons with syncope/delirium with no epilepsy as the comparison group (controls) to determine if the patterns of comorbid conditions that we targeted are significantly different from PWE. The rationale for choice of two sets of controls is as follows. First, trauma controls with fracture of the extremities are highly comparable to the general population with regard to comorbidity patterns based on the comparison we made on selected comorbidities from SC BRFSS (Appendix E for BRFSS and ESD comparison). About 60% of the fracture patients acquired their injury from traffic crashes, 30% from falls, 7% from interpersonal violence, and the rest from other causes. It is therefore clear that these patients are similar to the general population with the exception of the fracture they sustained. Second, trauma related fractures are evenly distributed through out the state and have similar urban-rural patterns. Thus, the trauma controls with fracture of the extremities are a surrogate sample for the general population with the benefit of having complete clinical profile on their health status. Third, delirium and syncope are differential diagnoses of epilepsy with high residual comorbidity comparable with epilepsy. As shown in Appendix C of our pilot study, the overall prevalence rates of the comorbidities reported are 53.8%, 51.4%, and 41.6% for epilepsy, syncope/delirium, and trauma respectively. This suggests the comparability of the first two groups. It is therefore essential to identify a control group that is likely to have comparability in patterns of comorbidity with PWE to washout the bias if we limit the comparison group to the general population (healthier fracture controls) akin with the distortion noted in ‘healthy worker effect’. Fourth,
syncope/delirium and epilepsy might share similar levels of underlying psychopathology, especially in the area of general anxiety disorders. This high level of homogeneity allows teasing out the magnifying effect of the force of epilepsy associated with the selected outcomes, especially on mortality and hospitalization rates. This aspect of the study is seeking to answer the research question, “Do PWE with comorbid conditions have worse outcome when compared with syncope/delirium patients that have comparable burden of comorbidity?” We feel this is important consideration since syncope/delirium patients also have higher level chronic somatic comorbidities, particularly cardiovascular and diabetes, enabling us to see the extent to which risk of death or hospitalization is enhanced by epilepsy. In Phase II, there will be chart review from non-CEC medical facilities (depicted as regular chart review in Fig. 2) for the purpose of validating the accuracy of information and acquiring information for comparable analysis.

Figure 3 is a schematic representation of our Phase 2 study. It relies on identifying clinically established epilepsy with ongoing medication, and/or epilepsy patients on physician follow-up (case cohort). Persons diagnosed with syncope/delirium with no epilepsy diagnosis (comparison cohort I) and a representative sample of trauma patients with fracture of the extremities (comparison cohort II) will be used for detailed risk analysis and understanding of the underlying risk factors that contribute for differential rates of comorbid conditions in the discriminated groups. Chart review will seek more information (depicted as chart review plus in Fig. 2) on diagnostic and procedures and neuropsychological therapy. Given the resource intensiveness of extracting detailed information on trauma patients and the high incidence of fractures of the extremities, we will sample fracture cases to approximate to one-to-one ratio with epilepsy patients. Sample selection will account for demographic characteristics and will be based on stratum specific distributions. We will ensure that under-represented minorities are well represented, which necessitate oversampling of some demographic groups. Based on the pilot data shown in Appendix C, 5% of fracture trauma patients yield comparable number of observations to approximate the demographic distribution of epilepsy patients. Data collection for Phase II will end a year before the grant ending date to allow adequate time for data analysis and manuscript development.

D.2 Study population
D.2.a. Eligibility criteria—Persons eligible to participate in this study are SC residents age 1 through 85 with clinically established epilepsy, receiving ongoing medication or on regular physician follow-up. Persons diagnosed as seizure NOS (ICD-9-CM code of 780.39) will be considered as epilepsy if, a) clinical symptoms and signs listed in the narratives are suggestive of episodic, sudden, and usually unprovoked attacks of subjective experiential phenomena, altered awareness, involuntary movements, or convulsions, b) there is documentation to suggest that the seizures are noted previously, c) there is documentation of EEG abnormality, or d) there are recurring prescriptions of antiepileptic drugs. In SC, the diagnosis of seizure is assigned due to many reasons. Based on our evaluations, the key reasons are, a) inadequate patient history (sometimes deliberate to avoid label), b) as a provisional diagnosis until tests are completed at CEC, c) to avoid false positivity with the potential consequences of malpractice suit, and d) to protect the patient from higher insurance premiums and loss of job. As indicated earlier, 80-85% of the diagnoses of seizure in the SC satisfy the aforementioned case ascertainment criteria and are true epilepsy cases. Persons with epilepsy are excluded for the following reasons: a) not residents of the state, b) information on key variables is missing, c) if no seizure in the
preceding three years without medication even if on periodic observations after being waned from treatment. These exclusions are unlikely to compromise the expected sample size of the study. Eligible controls are delirium/syncope (ICD-9-CM 780.2, 293.0) and extremity fracture patients (ICD-9-CM 812.x, 813.x, 820.x, 821.x, 823.x) in the same age range and event occurrence from 2009 through 2013.

**D.2.b. Gender and Minorities**—We will secure representation of both genders and racial and ethnic minorities by using a random sampling protocol for control selection to minimize selection bias. Based on our epilepsy surveillance data, there is a slight preponderance of males, with a male to female ratio of 1.4:1 respectively. This slight male preponderance has been observed across several studies in the US and around the world. Likewise, there is slight preponderance of epilepsy/seizure among nonwhites. The proportion of Hispanics and other ethnic groups in the state is low, only 5.7%, and we expect comparable rates of epilepsy. We will ensure adequate representation of Hispanics by oversampling since state-based data indicate that the SES profile of ethnic minorities is even lower than African Americans. Our surveillance study on epilepsy/seizure showed that the rate at which the race/ethnic groups are captured is comparable across ED visits, hospital discharge, and outpatient encounters. 780.2, 293.0, 812.x, 813.x, 820.x, 821.x, 823.x

**D.2.c. Phase II study patient pool:** MUSC is the only Level IV comprehensive epilepsy center (CEC) in SC. Approximately 2,000 first-time patients are cared for by the MUSC CEC. Nine of the 11 epileptologists in the state are at MUSC CEC. Table 9 is the distribution of first-time epilepsy diagnosis at the center by year for both inpatient and outpatient clinics. Excluding patients with a provisional working diagnosis of epilepsy unspecified (345.9) and seizure NOS (780.39), the most common diagnosis is generalized convulsive epilepsy (345.1) followed by complex partial seizure (345.4). Because of being a referral center for the state, patients come from all 46 counties of the state and the payer mix is highly comparable with the state. Further, patients evaluated and treated in the center are distributed similarly to other epidemiological studies from tertiary sites, with 40% having medial temporal lobe epilepsy. The center was accredited in 2008 and since then patient volume has been steadily increasing at 30% per annum (Table 9). Subjects for Phase II study will be identified from the center since more detailed information is available to address the hypothesis to be examined.

**D.3. Case Ascertainment and Accrual**

**D.3.a. Recruitment and Informed Consent**—Eligible subjects will be identified from the three data sources—ED, hospital discharge, and outpatient encounters. Information from administrative data collection system provide ED visits and hospital discharge uniform billing (UB-92) abstracted data and outpatient encounter billing data (CMS-1450) on all patients. Since information put on these electronic billing forms are necessary for billing, data completeness is over 98%. Uniformly available data include, patient identifiers (i.e., medical record number, SSN, first and last names, address, and zipcode), demographics (date of birth, race, gender, place of residence), dates of admission/ED/Office visits, up to 15 diagnostic codes (1 primary, 14 secondary codes), discharge disposition, source of admission, principal payer, and hospital identification number and up to 20 procedure codes (CPT codes) and corresponding charges to the nearest dollar. Our surveillance verified the accuracy and completeness of these data as part of a routine evaluation protocol. The following procedures will be implemented to identify eligible participants.

1. Data will be restricted to ICD-9-CM codes of 345.0-345.9 (epilepsies) and 780.3 (seizure NOS) for case-cohort, 780.2, 293.0 (syncope/delirium), and 812.x, 813.x, 820.x, 821.x, 823.x (extremity fracture). The latter two clusters of diagnoses coded represent the comparison-cohorts.
2. Observations will be unduplicated by the unique ID (SSN, Lname, DOB, Race, gender) after the three sources are combined into a unified data set with an equal logical record length.
3. Data will be restricted to state residents.
4. Persons with 780.39 diagnosis will be excluded based on algorithm we developed (Appendix F)
5. Providers will be notified about the selection of subjects per the SC Data Oversight Council Policy.
6. Letters of invitation will be mailed by ORS to those selected to participate.
7. Informed consent forms will be mailed out to ONLY those who agreed to participate in the study.
8. Medical record abstraction will be conducted to ascertain the diagnosis and acquire other clinical data.
9. Those who did not satisfy the eligibility criteria will be notified about their exclusion from the study.
10. CEC patients included in the study might be contacted if additional information is needed.

D.3.b. Medical Abstraction—We will adopt the method we have used since 1998 for chart reviews. Accredited Health Information Technicians from DHEC Bureau of Chronic Disease, Division of Injury Prevention will be responsible for medical record reviews. In this approach, the unique identification numbers of the records selected for review by ORS will be mailed to the respective medical records offices organized by geographically clustered five abstraction regions. To comply with HIPAA guidelines, this will be done only after the person agreed to participate in the study. The abstraction coordinator (Ms. Demian) makes arrangement for the abstractors’ visit to review the records. Each abstractor is trained to enter the information needed on a laptop computer on an EPI Info data entry screen. The laptop computers will have the data dictionary that abstractors could check as needed. The design of the data entry screen will preclude entry of illegal and out-of-range values by using abstraction guides incorporated into the abstraction tool. To ensure data saving after each entry, the ‘auto save’ option of the program will be set in the default mode. Abstractors will be strictly instructed never to second-guess any statement or coding values recorded in the chart. They will be allowed to make comments if any discrepancy is noted.

D.4. Measures—The full range of variables in the ORS database and other healthcare resource files such as the multiple cause of death data files (MCDD) and free clinic encounter data, which can be linked through personal identifiers, are included in Appendix D. We will gather information on the following key domains.

D.4.1. Socioeconomic and demographic information—Variables in this category include age, gender, race, marital status, neighborhood and zip code, income, and occupation. These variables are provided in nominal or ordinal scale except age. A three-level SES will be created by combining census tract data and insurance type. Age will be categorized as <5, 5-14, 15-34, 45-64, 65-74, and 75-85 years for meaningful comparison interpretation. These intervals could be collapsed as deemed appropriate for the analysis.

D.4.2. Healthcare system information—Variables pertinent to healthcare include health insurance, availability of services, access to services, referral patterns, access to specialty care, and frequency of healthcare encounters per year. These variables will be categorized and utilized according to the definition provided the Institute of Medicine Report entitled ‘Unequal Treatment’.(111)

D.4.3. Intrinsic factors and mediators—This category includes variables gleaned from physician narratives, laboratory evaluations, clinical psychology consults, EEG and fMRI evaluations, epilepsy surgery if any, and baseline clinical indicators of seizure severity. Since we have listed seizure severity as mediator and outcome, the degree to which this will be calibrated depend on change in severity during the period of observation.

D.4.4. Primary exposures and outcomes—Data on main exposure will be based on ascertainment of the common comorbidities of interest included in Appendices A along with the ascertainment codes. Since some individuals have up to 7 of these comorbid conditions based on our pilot study, both count and type of the comorbid conditions will be included in the analysis as shown in the aforementioned Tables 2 and 7. The proposed outcome measures proposed in our study are direct and simple to formulate.

a) Seizure condition—will be measured as a function of increased frequency and duration of the attacks as compared to a referent point in time. Information can be gleaned from medical charts using questions we developed in consultation with various researchers in epilepsy and the CDC Technical Advisor. At a minimum seizure frequency will be categorized into five categories: 0-3/yr (Controlled), 4-11/yr (mild uncontrolled), ≥1/month (Moderate uncontrolled), ≥1/week (Severe uncontrolled), and ≥1/d (Very Severe uncontrolled).

b) Mortality—will be gleaned from linkage with MCDD and they will be subdivide as, i) Highly probable to be the result of epilepsy if underlying cause of death is stated as “cardiorespiratory arrest and place of death is at home and toxicological data are negative. This will certainly be defined as probable SUDEP; ii) Possible to be due to epilepsy if contributing cause of death lists 345.x or 780.3 and underlying cause is ‘drowning’ or ‘crash-related’ while operating a vehicle; and iii) All-other causes of death not directly related to epilepsy if underlying cause of death is none of the above. Dr.
Wannamaker has conducted a study on causes of death on a large cohort of epilepsy patients that he followed over the course of 35 years in his practice. This analysis will be informed and refined based on his experience.  

c) **Medical care cost**—will be determined based on direct cost, which will be approximated by billing charge. In SC, the ratio of charge to revenue is 1:0.83, i.e., for every dollar charged, the revenue collected is 83 cents (SC Hospital Association). We will factor the sum of charge incurred due to hospitalization, diagnostic testing, clinic visits by revenue ratio to derive direct cost for each patient under observation. Preliminary evaluation we conducted for medical care cost of epilepsy care is reported elsewhere. 

**D.4.5. Data Management**—The data management activities will be organized to enhance data use and establish methodological consistency for data collection, quality control, and analysis. The major elements under data management include, (1) determination of study eligibility, (2) monitoring subject accrual, (3) development of data code book, (4) development of a manual of operations, data inventory, and decision logs, and (5) sustaining data integrity, safety, and security. Data coming from the billing system (UB-04, CMS-1500), and medical record abstraction will be combined into a single data repository. This activity will also include building unified data models to meet the data analysis needs of the investigators. Mr. Gu will lead this effort. We have developed such a system for our on-going Traumatic Brain Injury Follow-up Registry and SC HOPE. We will use the existing data management system as the template for developing this study. 

**D.4.5. Privacy Protection**—Protection of participants’ medical information in epidemiologic research is of utmost importance and priority. To protect the privacy of participants, we will institute the following measures. First, all participants will be notified of their rights not to participate in the study if they do not wish to, and only when signed informed consent is granted will data collection take place. Second, all data containing medical information will be stripped off personal identifiers and will be replaced by coded serial numbers. Third, in rare occasions when information is provided in hard copies with personal identifiers, it will be shredded after data entry. Fourth, all personnel with access to identifiable data will be required to sign a confidentiality pledge that will result in legal suit and dismissal if violated. 

**D.5 Statistical Considerations and Analysis Plan**

**D.5.a. Sample Size** —We estimated the sample size needs for Phase II of the proposed study to test the hypotheses laid out under the specific aims. We used the literature and the findings from our preliminary studies to make reasonable estimates about the distributions of specific characteristics for the case cohort and two sets of comparison cohorts that will be identified from the same referent population. Distributional estimates for the groups are based on the pilot data as described in Table 7, Section C.4 and Appendix C. Using information from the pilot data presented, we selected three risk exposures of epilepsy comorbidity namely psychiatric, somatic, and cognitive disorders. We calculated sample size requirements with a fixed statistical power.
of 90% under three possible prevalence rates of comorbidity in the control groups and we assumed the prevalence rates in the fracture group will be reasonably comparable with syncope/delirium group. The tolerance level for Type I error rate was set at 5%. In determining the sample size needed, we made the following assumptions: (1) The prevalence rates of comorbidities in the comparison cohort will be about 30%, 40%, and 45% with the lowest rate for cognitive disabilities and the highest for psychiatric; (2) a safe and conservative low risk ratios that account for uncertainties, ranging from 1.2 to 1.4, which corresponds to low effect size despite the strong effect measure noted from our pilot data; and (3) the accrual of cases and controls will be relatively uniform over the course of the study. Table 10 is the summary of the sample size needed and Figure 4 is the plot of sample size across various levels of risk ratios derived from PS Version 3.0.14 software. As shown in the Table 10, the approximated effect measure (OR) is in the range of weak association (i.e.,<1.5). This is reassuring since we might want to look into rare comorbid conditions such as ADHD in children. It is therefore unlikely that there will be either inadequate sample size or inadequate statistical power threatening the endorsement of a true alternative hypothesis.

D.5.b. Treatment of missing data — All effort will be made to ensure completeness of data elements. Multiple data interfaces will be layered hierarchically, i.e., [lab/imaging ⊆ medical chart data ⊆ UB-04] and [MCDD ⊆ UB-04], to retrieve missing data. If data cannot be retrieved from existing sources, imputation techniques can be implemented using the techniques stated below. Imputation for missing values will be considered if, a) missing data account for more than 10% of the variable of interest and/or; b) missingness is not completely at random (MCAR) such that ignorability results in biased results, or c) subset analysis is required and the truncated sample size falls <200. If one or more of these conditions occur, the following procedures will be implemented as deemed appropriate to impute missing values for explanatory variables.

1) When missingness is at random (MAR), imputation with mean or median values observed in the data from the same subject at different points in time and from other subjects at the same point in time will be weighted to arrive at the final imputed values using SAS MI (multiple imputation) procedure.(112, 113) This technique provides least biased imputed values than single imputation techniques.(114)
2) For data with repeated measures, missing values will be imputed with the predicted values from regression models as found appropriate.
3) We will also explore the use of likelihood imputation approaches based on statistical pattern recognition with probabilistic approaches (i.e. Fisher’s linear discriminant analysis).

D.5.c. Exploratory analysis — For continuous data, we will explore univariate and multivariable distributions by employing both numerical and graphical methods. Graphical techniques include box plots, scatter plots, and ordinary least square (OLS) fitted lines. We will consider various data smoothers (e.g., kernel, spline) to generalize trend patterns. For dichotomous and categorical variables, association will be evaluated with chi square tests of homogeneity and independence. Categorical variables will be collapsed as deemed appropriate based on one-way frequency tables or visual approaches from bar charts and histograms.

D.5.d. Hypothesis testing and modeling. Several hypotheses will be tested. The following statistical techniques are templates to be employed to address the various hypotheses and are not exhaustive.

Specific Aim 1. To compare the magnitude and distribution of common comorbid conditions among PWE (Case group) relative to persons with fracture of the extremities and patients with delirium/syncope (Comparative Groups). There are three hypotheses that rely on deriving character-specific and overall prevalence ratios spanning the time frame of the study. To derive the prevalence ratios, we will assume both the population at risk, i.e., the base denominator corresponding to persons’ at risk of developing the comorbid conditions—epilepsy/seizure, Syncope/delirium, extremity fracture—and the prevalence pool, i.e., the numerator corresponding to persons with comorbid conditions for each denominator group are closed populations and fixed throughout the period of observation. Thus, the period prevalence estimate is an approximation of incidence (I) times duration (Δt). Incidence will then be calculated as the approximation of prevalence for each observation group in the following manner.

Let \( d_1, d_2, d_3 \) represent observed comorbid diseases (numerators) in the three cohort groups; and \( n_1, n_2, n_3 \) represent the number of persons in the three cohort groups (the denominator population)
Thus, the prevalence \( (I_1, I_2, I_3) \) will be, \( \frac{d_1}{n_1}, \frac{d_2}{n_2}, \frac{d_3}{n_3} \) respectively. The rate ratio (RR) comparing PWE to the syncope/delirium and extremity fracture cohort will be, \( \frac{I_1}{I_2}, \frac{I_1}{I_3} \) respectively. The 95% CI for the RRs will be calculated by setting limits on the ratio of observed events in the epilepsy group to the total number of the observed events with the comparison cohorts in the following manner, \( \hat{P} = \frac{d_1}{d_1 + d_2} \), and the general formula of the binomial proportion (\( \hat{p} \)), can be derived for the lower (\( P_L \)) and upper (\( P_U \)) limits of the confidence interval, which will be calculated as
\[
P_L = \hat{P} - 1.96 \times \sqrt{\frac{(1 - \hat{P}) \cdot \hat{P}}{d_1 + d_2}}; \quad P_U = \hat{P} + 1.96 \times \sqrt{\frac{(1 - \hat{P}) \cdot \hat{P}}{d_1 + d_2}};
\]
Converting to limits on the rate ratios, \( R_{R_L} = \left[ \frac{P_L}{1 - P_L} \right] \times \frac{n_2}{n_1} \); \( R_{R_U} = \left[ \frac{P_U}{1 - P_U} \right] \times \frac{n_2}{n_1} \), yields the upper and lower 95% confidence limits of the RRs. This evaluation will be repeated for each sub-hypothesis regarding race, urban-rural residence, and SES. Overlapping confidence limits of the rate ratios will be the hypothesis of no difference since they will be derived from the pooled variance.

**Specific Aim 2. To determine the implications of epilepsy comorbidity on mortality and seizure condition.** Three sub-hypotheses will be addressed under this specific aim. Mortality will be grouped as ‘all-cause mortality’ and SUDEP as mentioned under section D.4.4. Seizure conditions will be gauged by seizure frequency into five categories: 0-3/yr (Controlled), 4-11/yr (Uncontrolled), \( \geq 1/\text{month} \) (Moderately Severe), \( \geq 1/\text{week} \) (Severe), and \( \geq 1/\text{day} \) (Very Severe). To test HA:2a and HA:2b, analysis will rely on person-year (PY) data and estimation of incidence of mortality as a function cumulative incidence over the period of observation. The average rate of ‘all-cause mortality’ or SUDEP, referred in this instance as incidence density (ID), is the proportion of the total number of deaths (\( \Sigma D^+ \)) divided by person-year (PY), i.e., \( ID = \frac{\sum D^+}{PY} \). As indicated above, this estimation procedure also assumes a stable, dynamic population and will be conducted according to the following prototype table (Table 11), which will serve as the template for the two hypotheses listed under the specific aim. Risk of death corresponding to absence or presence of comorbidity and type of comorbidity will be compared using the estimation procedure proposed by Morgenstern et al. (115) as depicted in the prototype Table 11.

To test HA:2c, we will use simple comparison of proportions between the PWE with and without comorbidity. Using the general formula for the standard error of a two independent sample binomial proportion, the lower and upper limits of the 95% confidence intervals (CI) for seizure frequency-specific will be estimated according to the formula proposed by Fleiss. (116)

\[
\hat{\sigma}_{p_1-p_2} = \sqrt{\left( \frac{\overline{p}(1 - \overline{p})}{n_1} + \frac{\overline{p}(1 - \overline{p})}{n_2} \right)}; \quad z = \frac{p_1 - p_2}{\hat{\sigma}_{p_1-p_2}}
\]

\( D^+ \) and \( D^- \) are the presence or absence of the comorbid diseases.

<table>
<thead>
<tr>
<th>Seizure Frequency</th>
<th>( D^+ )</th>
<th>( D^- )</th>
<th>( N )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3/yr</td>
<td>( n_1 )</td>
<td>( n_2 )</td>
<td>( n_{12} )</td>
</tr>
<tr>
<td>4-11/yr</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>( \geq 1/\text{month} )</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>( \geq 1/\text{week} )</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>( \geq 1/\text{day} )</td>
<td>( n_9 )</td>
<td>( n_{10} )</td>
<td>( n_{910} )</td>
</tr>
</tbody>
</table>
Specific Aim 3. To determine the association of comorbidities with individual characteristics, AEDs, recency of onset, and treatment modality controlling for potential confounders. Three hypotheses will be addressed under this aim. The first hypothesis calls for estimating the relative risk of the presence of comorbidities as a function of SES, which will be defined as mentioned under section D.4.1. Analysis will adjust for potential confounders including demographic characteristics and duration of epilepsy diagnosis. We will use unconditional logistic regression model, which specifies that the odds of comorbidities, \( P(D) \), for the \( i \)th individual is expressed as:

\[
P(D) = \left[ 1 + e^{-(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p)} \right]^{-1}
\]

Where \( \beta_i \) = logistic coefficient for \( x_i \). Exponentiation of the logistic coefficient yields the relative odds of comorbid illness while controlling for all other variables in the model. Interaction terms evaluated in stratified analysis can be incorporated in the logistic analysis and their significance validated by Wald test. The Polytomous version of logistic regression is an extension of dichotomous logistic where risk characteristics are regressed to both epilepsy and syncope/delirium in reference to extremity fracture. This allows comparability of the odds ratios since they are derived from the same variance estimator.

The second hypothesis calls for the three mentioned categories of comorbid conditions (i.e., somatic, psychiatric, and cognitive comorbidities) to have increased risk of occurrence corresponding with number of AEDs PWE use controlling for confounders, which will include demographical and clinical characteristics. The principal analysis is based as shown on the prototype table for a dichotomous outcome and one major risk factor as an example and the aforementioned dichotomous logistic regression will be utilized. The third hypothesis calls for testing the remission of comorbid illnesses after refractory surgery. Specifically, persons with medial temporal lobe epilepsy (MTLE) who undergo epilepsy surgery have been noted to have improvement in the number of comorbidity they have. Although the literature is unclear on the directionality of change in comorbid conditions, we predict this relationship to be for the better. The analysis will follow the template and formula described under specific aim 2, comparing simple proportions of change in the counts of comorbid conditions before to after surgery. Since each patient will be his/her own control, confounding bias is less likely to affect the result.

Specific Aim 4. To determine the population attributable fraction of hospitalizations accounted by epilepsy comorbidities and the direct medical care cost. This aim has two hypotheses. The first hypothesis tests if comorbid conditions among PWE lead to higher rates of hospitalization than those without. Since hospitalization could result from the seizure type and severity independent of comorbid conditions, we will make stratum-specific evaluations of hospital admission rates. We will derive stratum-specific attributable risk of hospitalization as the absolute difference in risk of hospitalization between persons with and without comorbidities in the following manner.

\[
\text{Hospitalization}_{AR} = (\text{Risk}_{D^+}) - (\text{Risk}_{D^-}) ; \quad \text{Where} \quad (\text{Risk}_{D^+}) = \left( \frac{\text{Adm}^+}{D^+} \right) \text{Comorbid} ; \text{and} \quad (\text{Risk}_{D^-}) = \left( \frac{\text{Adm}^-}{D^-} \right) \text{Comorbid}
\]

Where \( D^+ \) Comorbidity present; \( D^- \) absent; \( \text{Adm}^+ = \text{hospital admissions} \)

The stratum-specific population attributable fraction (PAR\%) determines the residual hospitalization that is attributable to comorbidity among PWE in the same referent population. It will be estimated as follows.

\[
\text{PAR}\% = \frac{P_{ESD}(RR-1)}{1 + P_{ESD}(RR-1)} \times 100 ; \quad \text{Where} \quad P_{ESD} = \text{Incidence of Hospitalization in pop and} \quad RR = \frac{(\text{Risk}_{D^+})}{(\text{Risk}_{D^-})}
\]
Estimation of direct medical cost comparing PWE with and without comorbidity will be conducted. The cost values addressing this hypothesis will rely on revenue adjusted charges as indicated under section D.4.4., item c. This estimation will also account for severity of epilepsy by generating stratum-specific medical care cost by type of epilepsy. For example, the medical care cost of persons with Temporal Lobe Epilepsy with or without comorbidity will be estimated separately from persons with Juvenile Myoclonic Epilepsy with and without comorbidity. All costs will be adjusted to the 2014 dollar values using the consumer price index (CPI) for medical care cost.

D6. Project Management Plan and Oversight
The management plan is designed to enhance performance and timeliness of the activities. This plan will guide the process by which the project is managed and audited, the venues of communication within the management team and across collaborating partners, quality assurance, and strategic planning. A team of three investigators will assume the core administrative responsibility. Dr. Selassie will be in charge of the overall project activities. Dr. Wannamaker will be responsible for the technical oversight of the program and liaising with clinicians. Ms. Smith will be responsible for quality assessment of the medical chart evaluation and ensuring data extracted are complete. Budgetary oversight, IRB compliance, and other administrative activities will be under the charge of the project manager. Dr. Selassie monitors all program activities and sets general policies and supervises the project manager. The Project Manager will coordinate and support the activities of the Management Team. The Management team will comprise of MUSC research team—Drs. Selassie, Wannamaker, Smith—and Mr. Finney from the Office of Research and Statistics. The Management Team will meet on weekly basis for the first 6 months and bi-weekly thereafter. Off campus members (Mr. Finney) will join via conference call and will be responsible for policy decisions. Investigators’ committee which includes all investigators listed in section C.6. of this application will have quarterly meetings. Off campus members will join via conference call. The committee oversees the management component of the project and discusses the progress. It reviews periodic reports prepared by the Project Manager in consultation with Drs. Selassie, Wannamaker, and Ms. Smith on issues pertaining to budget, status report on timeline, and report from ORS. This committee will also review quarterly interim results. Potential problems and plans to resolve these problems will be discussed. The minutes from the committee meetings will be distributed at the subsequent meetings to ensure that committee’s input is effectively implemented. The project will invite three national experts from around the nation addressing epilepsy epidemiology (Columbia University, NY), econometrics (University Texas Health Science Center, TX), and epileptology in the underserved population (University of California at San Francisco, CA) to serve as Technical Advisory Group along with the CDC Technical Advisor(s). The advisory group will be invited to meet at the AES annual conference in the first, second, and fourth year and in Charleston, SC, in the third year. The purpose of assembling this group is to maximize data usefulness by sharing data and results, maximize the scientific impact of the study through joint publication. We believe the SC data system is unique enough to inform public policy by harnessing input from accomplished researchers and leaders in the field.

D7. Strengths and Limitations of the Proposed Research

Project Overview. This proposed research is designed to address gaps in comorbidity studies of epilepsy. Specifically, the proposed study seeks to enhance our understanding on comorbidities of epilepsy through the application of systematic epidemiological and clinical investigation of full range comorbid diseases that have been identified by experts.(102) Furthermore, the study seeks to investigate the risk factors that contribute to rate differences in population subgroups, the underlying associations between comorbidities and potential risk characteristics, and propose evidence-based explanations on the underlying pathogenesis of comorbidities. The goal of the project is to improve the lives of PWE by informing clinical practice and suggesting rational approaches of prevention and control in epilepsy comorbidities.

Limitations: While the proposed research is innovative and will certainly provide useful information on population-based estimates of the prevalence of comorbidity and the impact on morality, direct medical care cost, and rates of hospitalization, there are several challenges. First, information on identifying comorbidities relies on administrative data that are intended to maximize reimbursement. It is possible that omission and commission of comorbid illnesses might not be governed by medical relevance or relative meaning to PWE but revenue generation. Several studies have documented the coding irregularities in administrative data in the US.(118) Thus, there is a possibility of erring in the estimates derived from such data sources. Second, under-resourced and rural hospitals may not have the capacity to make accurate diagnosis, possibly distorting the
estimate. However, based on our pilot data analysis, the proportion of PWE evaluated in such hospitals account to less than 10% and the bias is less likely to affect the findings. Third, will likely be uncertainties about the occurrence of these comorbidities and their associations with epilepsy even if the observed frequencies are beyond chance given the challenges of identifying the genetic and molecular biomarkers of these conditions. However, the purpose of the study is not to establish causality but robust associations that could inform future clinical, molecular, and genetic evaluations. Fourth, we are assuming a stable cohort for estimating person-time and converting incidence density to risk. While this assumption is not far from the truth based on the state’s demographics and migration history, the estimate could be biased if PWE tend to cross the geopolitical jurisdiction to receive medical care in neighboring states. However, because of the lack of portability of Medicaid, Medicare, and some managed care plans; the bias resulting from this effect might be limited. In fact based on the payer distribution of the data, less than 20% of the cohort poses such a risk. Finally, there are potential biases that lurk behind the proposed study posing the threat of systematic error. The first is response bias. This form of bias is intrinsic to any method that fails to include all sample elements into the analysis (non-response). In this study non-response could set in if medical records are missing, or PWE refuse to participate. To try and determine the extent of this bias, we will compare the responsive and non-responsive sampled observations on key demographic and clinical characteristics. Further, even if there is non-response, de-identified analysis could be conducted relying on unduplicated publicly available data, which has all the diagnoses and demographics and payer status. The second potential bias is selection bias likely to result from distortion of the sample due to biases in capturing PWE from a reimbursement and revenue driven data collection system. The representativeness of the sample frame for the target population could be questionable if the frame fails to capture all PWE. To reduce this bias, we have attempted to identify PWE from multiple data sources over an extended period of time such that the odds of healthcare encounter increase by virtue of time. The third potential bias is misclassification bias due to inaccuracies in the coding of death data. MCDD relies on the automated classification of medical entities (ACME), a computerized approach that ranks cause of death using internal algorithm. While this may not be a problem by the most part, in SC the input data for ACME comes from coroners’ who may not have adequate knowledge on forensic pathology possibly distorting the observed associations. However, NCHS provides estimates of such errors by comparing jurisdictions that have medical examiner and coroner systems that may allow us to gauge the error margin.

Strengths: Despite the aforementioned limitations, our study has a number of important strengths. First, our study is designed to address a very significant public health problem facing PWE. Second, this proposal is responsive to the recommendation of Living Well Epilepsy II that emphasized the need for expanded research on comorbidities.(8) Third, epilepsy is gaining relevance with the rising incidence among the elderly and military personnel that sustain closed head trauma in combat and military duties are subject to epilepsy comorbidities. Fourth, to our knowledge this will be the first study on comorbidities to utilize a full range of comorbidities that have been recently identified by the workgroup that met to develop surveillance standards for epilepsy surveillance.(102) This study will also be the first statewide study of comorbidity in the US with large underserved and minority population that has one of the highest rates of epilepsy in the nation. Given the recent emphasis of Healthy People 2020 Objective on uncontrolled seizures (DH-6), the issues this proposed study addresses are both timely and relevant. Further, based on our literature search, we were unable to find a single population-based study that derived sub-group specific comorbidity rates among persons with epilepsy. A methodological strength of our study is the use of two sets of controls from the same referent population to ensure methodological robustness of the estimates. Finally, the investigative team is an added strength. We have assembled a multi-disciplinary group of investigators with expertise in epileptology, epidemiology, clinical psychology, nursing, statistics, health services, and public health. Our team has the conceptual knowledge and technical skill that are required to address the limitations described above in order to successfully complete the proposed research. Thus, the strengths of the proposed research significantly outweigh the potential limitations discussed earlier.
The research plan and the design of the study described under sections 6-8 of this application are responsive in addressing the Healthy People 2020 priority area of seizure control in epilepsy. Specifically, the findings of this study will provide the foundation for evidence-based clinical practice, disease prevention, and health promotion to help PWE lead healthy and productive lives. The research plan proposed in this application is also consistent with core functions of public health practice stated in the revised IOM report entitled, “The Future of the Public’s Health in the 21st Century.”(119) The evaluation plan stated in this section describes the specific activity monitoring processes incorporated to assess the overall performance of the project and in gauging the extent to which the research activities are aligned with CDC-NCCDPHP’s Epilepsy Program Office. The plan specifically addresses: a) the attainment of the program objectives according to the proposed timeline, b) the methods and sequences by which the objectives will be achieved, and c) the performance and productivity of the personnel involved to attain the research objectives. Furthermore, this evaluation addresses the following questions in light of the proposed study: 1) Are the specific aims achievable and research hypotheses testable with the amount of funding that will be available? 2) Is there adequate input and participation of the partners to get the needed result? 3) Is there timeliness in the activities and is there a properly designed management plan to achieve the specific aims within the grant period and justify appropriate use of public funds? To address these questions, we laid out the evaluation criteria shown in Table 11.

Quantitative Evaluations: This project will also incorporate an evaluation to assess, a) validity of the data sources regarding case ascertainment, b) measures of case accrual rates, c) measures of reliability and internal consistency of clinical data. The routine procedure to determine validity of the data sources is achieved by comparing the classification of the diagnosis codes in the administrative datasets against the clinical evidence collated from medical records, which will serve as the “gold standard.” Internal consistency will be assessed with Cronbach’s Alpha. Furthermore, we will use adjusted Kappa to test agreement between repeated readings of image and EEG data.

D.9. Study Timeline
As shown in Table 13, the proposed research will proceed over a period of 4 years, beginning with descriptive analyses prevalence estimates of comorbidities by demographic characteristics. Specific Aims 1 and 2 will begin right after the IRB approval and preceding activities are in progress or completed. Specific Aims 3 and 4 will begin and end during years 2 and 3 although residual activities may continue to be worked out. The progression of the analyses will be deliberate, with later analyses building on the findings of earlier ones. For each aim, we will produce at least one paper. As soon as we receive project notification, we will initiate organizing the data systems so that it is well-set by the time the project is ready to begin.
Table 13. Project Timeline for Major Activities

<table>
<thead>
<tr>
<th>Major Activities</th>
<th>Year I Quarters&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Year II Quarters</th>
<th>Year III Quarters</th>
<th>Year IV Quarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Committee formation</td>
<td></td>
<td></td>
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<td>Protocol Refinement</td>
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<td>IRB Approval</td>
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<tr>
<td>Pilot Test Instruments</td>
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<tr>
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<tr>
<td>Analysis for Specific Aim 3</td>
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<td>Analysis for Specific Aim 4</td>
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<td>Advisory Committee Meetings</td>
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<tr>
<td>Outcome Analyses</td>
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<td>Manuscript submissions</td>
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<td>Conference Presentation</td>
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<tr>
<td>Results Dissemination</td>
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</table>

<sup>1</sup> Meeting in Charleston  
<sup>2</sup> Quarter 1 = Sep 1-Nov 30, ……, Quarter 4 = Jun 1-July 31
E. HUMAN SUBJECTS

This proposed research entitled “Risk Factors of Epilepsy Outcomes: The Burden of Comorbidities in a Statewide Population with Epilepsy” will follow the Office for Human Research Protections requirements (Title 45 CFR Part 46) assuring compliance with human subject protection and confidentiality. All project activities will comply with the Health Insurance Portability and Accountability Act (HIPAA) 45 CFR 164.512(i)(2) regulations effective April 14, 2003. The study will not involve invasive procedures and will not directly target vulnerable populations or sub-groups. No procedures are experimental. Epilepsy and seizure disorders affect persons of all ages, all nations, and all races. At time of enrollment, all persons aged 1 to 85 years who meet the eligibility criteria of the study, regardless of age, race, ethnicity, gender, previous medical conditions and current health status will be invited to consent for their medical charts to be reviewed. Two sets of comparison cohorts of similar age range with syncope/delirium and fracture of the extremities with no epilepsy or seizure will be included. As a result, epilepsy patients who might have cognitive disabilities, pregnant females, and minorities identified through the Statewide Hospital Discharge, Emergency Department Visit, or outpatient clinic encounters as having epilepsy/seizure or syncope/delirium or extremity fracture (EF) and determined eligible will be invited to participate. In addition to aforementioned three data sources, data will be collected from medical record review and for deceased individuals from death certificates and multiple causes of death data set. The MUSC Institutional Review Board (IRB) and possibly the CDC IRB will have to approve this proposed study before chart reviews may begin. These IRBs have a history of taking precaution to ensure that the rights of children, as vulnerable research subjects, are protected. Additionally, the all medical centers where eligible subjects received medical care may require that their IRBs review the study protocol.

Subject recruitment will be through mailed correspondence sent to the residences of potential participants. Included in the correspondence will be 1) a letter describing the nature and purpose of the study; 2) an IRB-approved informed consent form detailing participation, risks and benefits, rights as a research participant, and the name and telephone number of the principal investigator; and 3) a business reply envelope in which the signed informed consent form is to be returned. If no response is received from potential participants after two weeks of the mailing, a second letter and/or telephone call will be made. Upon contact, the caller will explain the nature and purpose of the study and ask if they would like to be sent another mailing. Procedures designed to protect vulnerable populations require consent by a legal representative (parent or guardian) for participants who are younger than 18 years or cognitively limited. Upon obtaining the returned signed informed consent, the medical record abstraction office in SC DHEC will receive the names and chart location of participants.

Data collected under this protocol will be obtained without need to involve persons who provide direct health care to participants and should not affect such services or relationships. The study protocol includes extensive efforts to inform participants about the study to ensure that they know what they are being asked to do. For example, they will receive correspondence that describes detailed procedures well in advance of their charts to be reviewed. Furthermore, participants will be informed that they may refuse to participate in any aspect of the study.

Risks to participants appear minimal. The abstraction tool will be developed to only acquire information available in their medical records. However, it is conceivable that sometimes there may be a need to correspond with the participants or their legal representatives on conflicting information on their charts or to clarify questions that may not be adequately answered through chart reviews. We do not anticipate that there will be many instances where information is needed through correspondence. However, should such request routinely occur, a written protocol will be developed and an amendment will be requested.

Full confidentiality protection will be provided and extensive safeguards will be in place to protect the privacy of participants. All project personnel understand the importance of confidentiality and, in addition to the privacy requirements imposed by virtue of being employees of the Medical University, sign annual Confidentiality Agreements to that effect. Personnel found to be in violation of confidentiality will be subject to immediate repercussions.

To comply with a June 2005 Federal law, data collected for this study will be retained in secure files for a minimum of six years or until the participant reaches age 21 years, whichever is later.
### F. Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

**Study Title:** Risk Factors of Epilepsy Outcomes: Burden of Comorbidites in a Population with Epilepsy  
**Total Enrollment:** 33,439

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>732</td>
<td>944</td>
<td>1,676</td>
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</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>15,538</td>
<td>16,225</td>
<td>31,763</td>
<td></td>
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<tr>
<td>**Ethnic Category: Total of All Subjects ***</td>
<td>16,270</td>
<td>17,169</td>
<td>33,439‡</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Categories</th>
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</thead>
<tbody>
<tr>
<td>American Indian/Alaska Native</td>
<td>122</td>
<td>172</td>
<td>294</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>163</td>
<td>223</td>
<td>386</td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>65</td>
<td>86</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>3,416</td>
<td>5,150</td>
<td>8,566</td>
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</tr>
<tr>
<td>White</td>
<td>12,504</td>
<td>11,538</td>
<td>24,042</td>
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<tr>
<td>**Racial Categories: Total of All Subjects ***</td>
<td>16,270</td>
<td>17,169</td>
<td>33,439</td>
<td></td>
</tr>
</tbody>
</table>

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”
INCLUSION OF WOMEN AND MINORITIES

There is adequate representation of women and minorities in the study as reflected in the enrollment table. The distribution is proportional to the distribution in the general population. In this table, ethnic breakdown is not included in the racial category and we assumed all persons with Hispanic/Latino ethnicity as white because our data doesn’t show interaction of race with ethnicity. We also assumed 107 persons who did not want to identify their racial identity as white.

G. INCLUSION OF CHILDREN

Children 1 year of age and younger and young adults age 18 and older are included because of the design of the study. This research is intended to assess the burden of epilepsy comorbidities in the population.

H. VERTEBRATE ANIMALS

Not Applicable

I. CONSORTIUM/CONTRACTUAL ARRANGEMENTS

SC Department of Health and Environmental Control (refer to budget for additional details)

SC Budget and Control Board, Office of Research and Statistics (refer to budget for additional details)

J. LETTER OF COMMITMENT AND SUPPORT

Institutional Support, Director, Research and Sponsored Programs

Departmental Support: Jack Feussner, Chair, Department of Medicine

Departmental Support: Sunil Patel, Chair, Department of Neurosciences

Departmental Support: David Bachman, Chair, Division of Neurology

Comprehensive Epilepsy Center, Director, Jonathan Edwards

MUSC Epilepsy Comprehensive Center, Director, Jonathan Edwards

SC Dept of Health & Environmental Control, Deputy Commissioner, Lisa Waddell

SC State Budget & Control Board, Office of Research & Statistics: David Patterson

K. RESOURCE SHARING PLAN

Data Sharing Plan: As publicly funded research, we will encourage and promote the use of the final research data by all scientists and researchers to advance the science and maximize the impact of improving the lives of persons with epilepsy. We anticipate sharing the public-use data after three years from the end of the study. We will adhere to the federal guidelines, i.e., OMB Circular A-110, the CDC/ATSDR policy on Releasing and Sharing Data, and the NIH data release protocol if deemed necessary. To operationalize the data releasing and sharing process, we will adapt the protocol developed OMB should there be an urgent need to release the data. This protocol makes a distinction between data sharing and the release of data for public-use. Data sharing allows other researchers to participate in developing manuscripts with the investigators as the study progresses and as interim data become available. Under this plan, we plan to complete at least five manuscripts by including our CDC technical advisor(s) and technical advisors before the end of the four year funding. We will eventually
develop summary tables that could be used by anyone with an internet access to identify high-low risk groups of epilepsy and seizure disorder patients with comorbid diseases.
Reference List


Shafer PO. Burdens of epilepsy care -- need for advocacy and change. AES News 2002;(Summer):3-5.


(80) Hesdorffer DC, Lee P. Health, wealth, and culture as predominant factors in psychosocial morbidity 1. Epilepsy Behav 2009 Jun;15 Suppl 1:S36-S40.


(101) SC Study Committee on Epilepsy Services. Statewide Comprehensive Service Delivery System for Persons with Epilepsy. 2008.


(105) Ferguson PL, Smith GM, Wannamaker BB, Thurman DJ, Pickelsimer EE, Selassie AW. A population-based study of risk of epilepsy after hospitalization for traumatic brain injury


J Head Trauma Rehabil 2008 Nov;23(6):394-400.


