

# Prevalence and Predisposing Factors of Parkinson Disease: A Community-Based Study in Barangay Mangilag Sur, Candelaria, Quezon: A Research Protocol



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## ABSTRACT

Parkinson disease (PD) is a neurodegenerative disorder affecting the central nervous system caused by the death of dopaminergic cells in the ventral region of the pars compacta of the substantia nigra. The subsequent lack of dopamine causes movement-related disorders including tremors, rigidity, hypokinesia, and postural instability. The clinical diagnosis of PD is hinged on the triad of asymmetric bradykinesia, rest tremors, and rigidity, with an expert (usually

a neurologist) eliminating those cases having mimics of the symptomatology. Development of the disease is through certain environmental, hereditary, and genetic factors. In the Philippines, PD is a rarely seen disorder and establishing a prevalence study has been difficult for neurologists. Prevalence of the disease in the country has been estimated to be less than 1% based on a 2007 study conducted by the Philippine Neurologic Association but without ascertainment of cases. The researchers aim to determine the disease's prevalence in a locale and explore the possible predisposing factors on the development of the disease.

The research will be conducted through a two-phase descriptive design. Screening of the target population using a questionnaire will constitute the first phase, and the second phase will be through case ascertainment of positively screened participants by a neurologist. Point prevalence rate will be

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used for statistical treatment. The research protocol was approved by the UST Faculty of Medicine and Surgery – Department of Clinical Epidemiology, as it adheres to the Declaration of Helsinki in clinical studies or surveys.

**Keywords:** Parkinson Disease, Prevalence, Community Survey, Rural.

## INTRODUCTION

### Background of the Study

Parkinson disease (often abbreviated as PD and may also be called as idiopathic or primary parkinsonism) is a neurodegenerative disorder affecting the central nervous system (CNS) (1). It is caused by the death of dopamine-generating cells in the midbrain, specifically the ventral region of the pars compacta of the substantia nigra (2). The lack of dopamine in this region causes movement-related disorders (3), which are the primary signs for diagnosing PD. Although there are new neurodiagnostic tests, the diagnosis of PD is mainly done by clinical consultation with neurologists, who are considered to be the gold standard in diagnosing the disorder (4).

According to Jankovic (5), there are four (4) cardinal movement disorders associated with PD. These are tremors or shaking, rigidity, hypokinesia or slowness of movement, and postural instability. In addition, non-motor manifestations of PD, which occur in all stages of the disorder carry an impact on the quality of life of a person. For instance, the occurrence of a state of anxiety, depression, and fatigue in Filipinos diagnosed with PD have been well-documented in local PD cohort studies.

The causes of PD can be due to certain environmental factors and to a certain degree due to heredity and genetics of a person. Environmental factors that may cause the disease include, but are not limited to, exposure to pesticides and insecticides, injuries to the head, and the livelihood, lifestyle, and location of the patient, with those living in the rural areas being noted to have a higher exposure to such environmental factors (8). In genetics, PD is often considered as a non-hereditary disease, although in rare cases it may present itself as a genetic disease. A study by Hatano et al. (13) also pointed a mutation in the PINK1 gene in Filipinos that causes autosomal recessive PD.

In the Philippines, PD is a rarely seen disorder due to some of the symptoms being similar to certain health disorders. Furthermore, due to the geography of the Philippine islands, it is difficult for neurologists to ascertain reported cases of PD as some areas are inaccessible. A 2007 study conducted by the Philippine Neurological Association (PNA) (29) has reported that the nationwide prevalence of PD in the country is less than one percent (<1%), though this is the observed data without ascertainment of reported cases (15,16). At present, however, there are studies that have established the existence of an indigenous x-linked hereditary disorder which shows similar features to parkinsonism in the island of Panay. This is noted by the studies of Rosales (17), Fernandez and Rosales (18), and Lee, et al. (19) as the X-linked dystonia-parkinsonism (XDP) or “*lubag*” in the native/vernacular language. As of date, there is no existing community-based study regarding the prevalence of PD in the Philippines as well as case ascertainment of the reported cases. Case ascertainment is a crucial requirement for differentiating PD from XDP.

Thus, this study aims to conduct a community-based study on PD in order to determine the prevalence of PD in a selected rural and urban area accompanied by case ascertainment of the people in the community who have shown symptoms of PD. Furthermore, it is the long-term objective of the researchers of this study that the study will help in the creation of a protocol to diagnose if a person has PD.

### Science of the Study

As of today, there are no available community-based prevalence studies in the Philippines concerning PD. Only a nationwide survey has been done to observe the prevalence of the disorder in the country, but there is no case ascertainment made in certain study areas of the research to account for the actual statistics. This study will perform the community-based study accompanied with case ascertainment to improve the existing statistics of the prevalence of PD in the country. The data collected on the prevalence of PD will also open the pathway for the pharmaceutical industry to rationalize their entry in the Philippines and introduce established and new medications for PD. The derived data can also provide the platform for future participation in clinical trials (20). The study being a community-based survey will

also increase the potential of case-control studies in the future for homogeneous populations.

Furthermore, as the study site for this research is a specific community in contrast to a nationwide point-of-view, the selected study site may provide the necessary data on the predisposing risk factors and these factors' relation to the probability of a person developing PD after a period of time of his/her life. This study could provide a comparison of different predisposing risk factors which could include family-related, occupational or environmental contributory factors.

### Research Questions

What is the prevalence of PD in Barangay Mangilag Sur of Candelaria, Quezon?

What are the possible predisposing risk factors and these factors' relation to the probability of a person developing early onset PD?

### Objectives of the Study

The general objective of the study is to determine the prevalence and the predisposing factors of PD in a Philippine-based community. Specifically, to conduct a community-based survey to screen possible cases of PD in order to provide case-ascertained prevalence in the Philippines and the necessary data on predisposing risk factors and their association with the development of early-onset PD.

## REVIEW OF RELATED LITERATURE

### Parkinson Disease

PD, named after its discoverer Dr. James Parkinson, is a neurodegenerative disorder affecting the midbrain region of the brainstem. It is the second most common neurodegenerative disorder after Alzheimer's disease affecting 1% of the world population after the age of 65 years (21). The etiology of the disease remains unclear in most cases but current theories suggest a combination of age, genetic susceptibility, and environmental factors (11,22-24). The typical age of onset for the disorder is between 50-70 years old, though it may also develop in people who are less than 40 years old, the latter case being termed as Young Onset Parkinson Disease (YOPD) (29).

PD is often diagnosed after a clinical consultation with a neurologist, who is considered to be the

gold standard in diagnosing the disorder, although, this would only lead to the diagnosis of a probable or possible PD (4). To obtain a definitive diagnosis, Gelb (4) noted that neuropathologic examination must also be done. Histopathologic slides of the substantia nigra would show the loss of neurons and the presence of Lewy bodies in the remaining nerve cells confirming that a patient has PD (31). As PD also results from the loss of dopamine in the midbrain, a significant improvement of the symptoms after the intake of medications such as levodopa (which can improve dopamine production) can confirm an accurate diagnosis of PD.

### Parkinson Disease and the World

In some community-based studies done abroad, so that the researchers identify the target population, they either set an inclusion criteria (32) or recruit participants who are newly diagnosed with PD through case ascertainment (33). Patients are also identified through records available at specific (health) departments like the Department of Neurology in Akershus University Hospital, which is the only neurological department in Norway (32). PD is the second most common neurodegenerative disorder which is not only characterized by one's problem in movements but also non-motor symptoms (34). A community-based study done by Svensson, Beiske, Loge, and Sivertsen (32) focused on one of the non-motor symptoms.

Problems concerning disturbances in patients' sleep are typical in patients with PD. Studies involving this are well-documented. Another important clinical consequence for patients with PD as well as to their caregivers is the risk for dementia. A community-based cohort prospective study was undertaken in Rogaland, Norway involving 171 non-demented patients. The results of the study indicated that patients with PD have an almost six-fold increased risk of becoming demented compared to those without (37). Another risk for patients with PD is the occurrence of depression. In the community-based study conducted by Tandberg et al. (39) involving 245 patients with PD and two control groups of 100 (with diabetes) and 100 (healthy elderly individuals), 7.7% of the 245 patients with PD met the criteria for major depression, 5.1% were moderately to severely depressed and 45.5% had mild depressive symptoms based on the Montgomery and Ashberg

**Table 1.** PNA Questionnaire With its Sensitivities and Specificities Focusing on Parkinsonism (with permission, Philippine Journal of Neurology, 2007)

Illness	Questions (any history of...)	Sensitivity	Specificity
Parkinsonism	Several months of having HAND TREMORS while at rest	0.586 (0.469-0.694)	0.891 (0.870-0.910)
	Several months of SLOWNESS in movement or moving like a "ROBOT"	0.725 (0.610-0.816)	0.853 (0.829-0.874)
	Question 5 OR 6	0.771 (0.660-0.854)	0.801 (0.774-0.825)

Depression Rating. In addition, 24.1% of the patients with PD have a Beck Depression Inventory score of 18 or more which was higher compared to the two control groups. However, the results suggested that the prevalence of major depression in PD is actually lower compared to previously assumed.

**Parkinson Disease and the Philippines**

The clinical diagnosis of PD is made by the presence of the classical triad composed of bradykinesia or slowing, rest tremor, and rigidity, which stand to be the core features of the disease. Rest tremor or the presence of tremor when the affected limb is at rest, yet absent during voluntary activity is characteristic of PD. It may be a source of confusion during diagnosis owing to its absence in 30% of PD patients. Bradykinesia or slowing, on the other hand, may be tested by rapid, alternating movements to be done by the patient who may initially perform well, yet decline in speed and amplitude upon further repetition. Rigidity or increased muscle tone may be tested in the arm by gentle extension/flexion of the wrist and elbow, and supination/pronation of the forearm. It is also important to note that PD is asymmetric at onset, observable by the commencement of bradykinesia or tremor on one side. The contralateral side is affected with the progression of the disease eventually.

As for the treatment of PD, the PNA (29) states that "making a diagnosis of Parkinson disease is not a reason to start treatment." Rather, the onset of functional impairment is usually the marker for most specialists to begin pharmacological treatment. Absence of functional impairment would favor non-pharmacological approaches such as "education, support services, management of emotional needs of the patient and caregiver, exercise, nutrition and physical therapy." The presence of functional impairment, on the other hand, varies from individual to

individual and factors such as the involvement of the patient's dominant hand, his employment and employability, imbalance (possibly increasing the risk of falls and serious injury), as well as the impact of the symptoms on the patient's daily living must be taken into consideration. Pharmacologic therapy involves the use of dopaminergic agents (Levodopa being the "gold standard" and the "most effective antiparkinsonian drug"), anticholinergics, amantadine, and selegiline.

The research committee of the PNA consisted of Artemio Roxas Jr., MD, Mayvelyn Gose, MD, Jaqueline Dominguez, MD, Servando Liban, MD, Raymond Rosales, MD, and Madeleine Grace Sosa, MD (15,16). They determined the prevalence for stroke, parkinsonism, dementia, migraine, and epilepsy by creating and validating a questionnaire for this specific purpose. In their two-part paper, the researchers created and validated a 10-item PNA questionnaire where, for Parkinsonism, two concise and easy to deliver questions were produced (See Table 1).

In order to obtain national prevalence data on common neurological conditions, Artemio Roxas Jr., MD, Mayvelyn Gose, MD, Jaqueline Dominguez, MD, Servando Liban, MD, Raymond Rosales, MD, and Madeleine Grace Sosa, MD (15,16) conducted a cross-sectional study using a multistaged cluster sampling methodology by integrating the validated PNA questionnaire in the National Nutrition Health Survey (NNHeS). The survey was conducted on 4,753 adults aged 20 or more from 2,636 households, 17 regions, and 79 provinces of the Philippines. The basis for the prevalence of Parkinsonism was based on the participants' "Yes" response to both questions 5 (indicating tremors) and 6 (indicating slowness or bradykinesia, even possibly rigidity) in the validated PNA survey. A prevalence of 0.95% was acquired with increasing prevalence, increasing age, and a

**Table 2.** National Prevalence of Parkinsonism Based on the 2003 National Nutrition and Health Survey (with permission, Philippine Journal of Neurology, 2007)

Neurologic Illness	Basis for Prevalence	Prevalence	Male:Female Ratio	Peak Prevalence
Parkinsonism	Yes response to both Ques 5 (Tremors) and Ques 6 (Slowness)	0.95%	1:1.07	60 and above

notable female predominance with a male-to-female ratio of 1:1.07. There was a higher prevalence for hand tremors alone at 4.88% compared to the prevalence of slowness alone at 2.25%. Self-reporting for PD was also recorded in 0.03% of the participants. It was also discovered that there was a higher positive response to both questions in regions 6 and 7.

The researchers considered the prevalence obtained as high compared to neighboring Asian countries given methodological differences such as the focus on Parkinsonism and not PD itself as done in other countries. The prevalence rates of other Asian countries are as follows: India 0.148%, (40) China 0.057% (41) and 0.018% (42), Taiwan 0.127% (43) and 0.13% (44), Singapore 0.3% (14) and Japan 0.1% (45). Moreover, other factors such as "drug side effects, toxic exposures, genetic diseases, vascular diseases, metabolic diseases and infections, among others" may have contributed to the obtained prevalence of Parkinsonism given that such factors may cause the aforementioned disease.

### X-linked Dystonia Parkinsonism

X-linked dystonia parkinsonism (XDP), also referred to as 'lubag' in American literature, is an adult-onset, sex-linked, predominantly male, severe, progressive often debilitating movement disorder (17-19,46,47). This disorder has a high penetrance and a high frequency of generalization (46). XDP was first described in 1969 in Filipino males from the island of Panay (18,19).

In the 2003 National Nutrition and Health Survey, a significant increase in positive response to questions 5 and 6 (See Table 1) were noted in regions 6 and 7. These items in the questionnaire indicated the presence of tremors and slowness (15,16).

The February 2010 data on XDP showed a total of 505 registered XDP cases in the country. The current prevalence rate of XDP in the entire country is 0.31 per 100,000. For Panay Island, a significantly larger

rate is noted at 5.74 per 100,000. Within the island of Panay, the highest prevalence was observed in Capiz at 23.66 per 100,000. The total of 505 cases are from 253 families with a male-to-female ratio of 100:1 with 500 males and 5 females affected. Cases of XDP have been reported from other countries. Most cases though are among Filipinos with maternal ancestry traceable to Panay islands (19).

Depending on the exhibited signs by the patient, the pathophysiology of XDP could be divided into two phases: dystonic and parkinsonian phases. The dystonic phase usually starts at the third or fourth decade of life which spreads to generalization within 2 to 5 years. Beyond the tenth year of illness, either the two phases coexist or the dystonia is replaced by parkinsonism (46).

Understanding the pathophysiology of XDP and development of rational therapies will depend on observations from imaging, pathological, and genetic studies. The cranial magnetic resonance imaging (MRI) in XDP shows hyperintense putaminal rim during both dystonic and parkinsonian phases. The caudate head or putamen atrophies in the parkinsonian phase (17,47). Neuropathological findings confirm an atrophy of the caudate nucleus and putamen with mild to severe loss of neurons and gliosis (17,48). The neostriatum shows involvement of striosomes, but with matrix-sparing during the dystonic phase. During the parkinsonian phase, there is also an involvement of the matrix. In the dystonic phase, the loss of striosomal inhibitory projections lead to disinhibition of nigral dopaminergic neurons, likely resulting in a hyperkinetic state. In the parkinsonian phase, severe and critical reduction of matrix-based projection may result in extranigral parkinsonism (17,47,49). Genetic sequencing of the XDP critical region in Xq13.1 has revealed an SVA retrotransposon insertion in an intron of TAF1. This may reduce neuron-specific expression of the TAF1 isoform in the caudate nucleus and subsequently interfere with the transcription of many neuronal genes, including DRD2 (17,47-50).

## MATERIALS AND METHODOLOGY

### Research Design

The research design will be a descriptive study of the prevalence and predisposing risk factors of PD in a rural community. The target population for the study consists of all eligible residents of the chosen community aged 20 years or older in updated 2010 census lists from community registry offices.

The study will use a two-phase design to assess the prevalence of PD. In phase 1, participants will be screened in person using a symptom questionnaire. Those who screened positive will be extensively evaluated by a certified neurologist in phase 2.

To identify the predisposing factors of PD present in the community, the study will use a questionnaire which will include and enumerate various risk factors that contribute to the development of PD, in which the responses will be encoded and interpreted.

### Data Collection

#### Selection of study population

In order to identify where the study will be conducted, the researchers used systematic random sampling in order to select one rural community in a barangay setting.

The researchers used a third party, computer-generated randomizer in order to consecutively randomize similar types of lists, and thereafter, choose the first item on the produced lists. Of the first list, which comprised seven of the eight regions in Luzon (given the prevalence of XDP in Visayas and Mindanao; see *Part IV. Review of Literature*), excluding NCR due to urbanization, Region IV-A or CALABARZON was the first item on the randomly produced list. Consequently, of the second list, which comprised the five provinces of Region IV-A (Cavite, Laguna, Batangas, Rizal, Quezon), Quezon was the first item on the randomized list. Using the same method on the four districts of Quezon, District 2 was the district to be focused on. Of the five municipalities of the second district of Quezon (Candelaria, Dolores, San Antonio, Sariaya, Tiaong), excluding Lucena City due to its high urbanization, the same method resulted in the selection of Candelaria. Finally, of the 20 rural barangays of Candelaria (Buenavista East, Buenavista West, Bukal Norte, Bukal Sur, Kinatihan I, Kinatihan II, Malabanban Sur, Mangilag Norte, Mangilag Sur,

Masalukot I, Masalukot II, Masalukot III, Masalukot IV, Masin Norte, Mayabobo, San Andres, San Isidro, Santa Catalina Norte, Santa Catalina Sur, and Masalukot V) Barangay Mangilag Sur was chosen.

#### Ocular inspection

The first site visit of the researchers to the locale will provide them with necessary information regarding the area and community before proceeding with the research proper. During this period, the researchers will gather various information regarding the population and its demographics from the city/municipality/town hall. Preliminary data on health status will also be gathered based on community health records in the city/municipality/town health administration offices as well as the barangay health centers, depending on its availability. The initial site visit will also be the time for the researchers to finish all the necessary paper work and comply with all the requirements set by the city/municipality/town administration before proceeding.

#### Sample size computation

Sample size for the study is computed using the 2010 census of Barangay Mangilag Sur. Based on the demographics provided to the researchers by the barangay officials, Barangay Mangilag Sur consists of 1,406 households in total, with 6,706 individuals meeting the inclusion criteria for the study. The researchers will use the OpenEpi website ([openepi.com](http://openepi.com)) to compute for an acceptable number of households which can render the study as valid. The obtained number of individuals will be randomly selected throughout the entire barangay and will be part of the study. For the study, an obtained number of 364 individuals (CI = 95%) is the minimum number of individuals needed to make the study valid.

#### Survey and case ascertainment

After the completion and submission of all the necessary prerequisites and documents, the researchers will proceed to the research proper, which is a two-phase design to assess the prevalence of PD and the presence of risk factors of PD in the community. The resident population in this study will consist of individuals who are aged 20 years and above from every household within the selected community or locale.

Individuals are eligible for the study if they are permanent residents and/or residents of homes or nursing homes located in the community. Individuals will be excluded if they had died or no longer resided in the community. Meanwhile, a dedicated movement disorder training on how to clinically examine a patient will be undergone by the researchers under the guidance of a trained specialist.

In phase 1, the researchers will visit homes in the barangay randomly to administer the questionnaire which contains the screening items in a face-to-face interview. The administered questionnaire includes the respondent's age, sex, occupation, family medical and social history, economy, food and water source, pesticides, coffee consumption and tea consumption (light or heavy), cigarette smoking, alcohol drinking, ancestry, anxiety, depression, fatigue, sleep disorder, trauma, etc. These data will provide the researchers information regarding the respondents who are exposed to risk factors. This will be recorded and encoded to observe which risk factors potentially contribute to the cases of PD in the barangay.

The questionnaire includes the screening instrument for PD, which consists of two questions that had been validated by the Philippine Neurological Association (see *Appendix*). In addition, a third question on whether participants have been previously diagnosed with PD was included. In the event that the participant is unable to answer the questions as a result of speech or cognitive disturbances, the caregiver is permitted to answer on the participant's behalf (14). The screening tool will examine those who are already exhibiting or are starting to demonstrate certain symptoms related to PD. Participants who responded positively to any of the 3 questions will be considered to have screened positive and eligible for phase 2 evaluations. The potential cases will also undergo videotaping following an informed and written consent. A protocol for videotaping will be followed to the letter that may take a total of 3 minutes. The video will then be reviewed by the Parkinsonologist for screening.

Phase 2 of the study, or the case ascertainment phase, will be conducted once there is a "trigger" from the specified questions for PD. The researchers will return to the locale accompanied by an expert in the field of neurology, particularly in PD. The final

case ascertainment will then occur for the specialist to specifically do a consultation with the potential case. This would establish the point prevalence of the condition in the given locale.

### Statistical Treatment

Given that the study focuses on finding out the number of individuals from urban and rural communities who may have PD within their population, it is suitable to use prevalence ratio to analyze the data that will be gathered. Specifically, point prevalence rate was defined as the ratio of the number of subjects with evidence of disease on the screening day to the number of residents surveyed (51). The prevalence rates will be estimated as the number of cases in the community for subjects aged 20 years and over. To compare our results with previous studies, the age-standardized prevalence rates (will be standardized using the 2010 census), sex-specific prevalence rates, and 95% confidence intervals will be calculated.

### Pilot Study/Pretesting

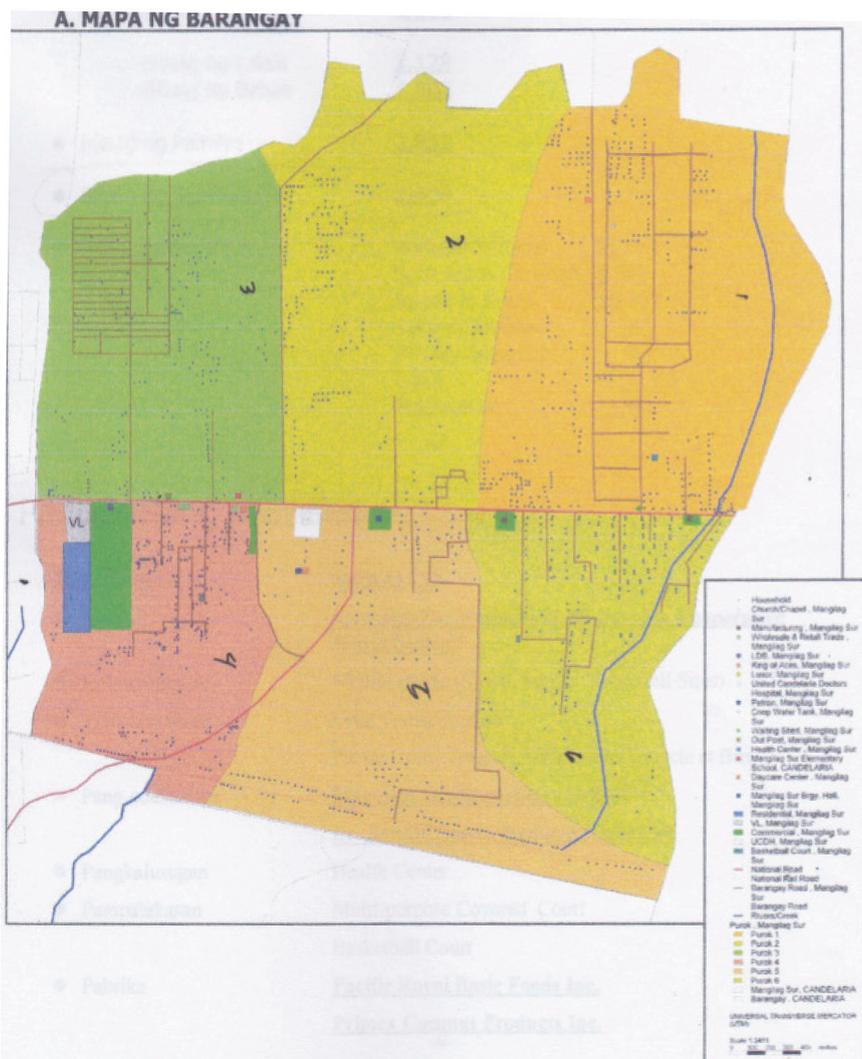
After conducting an initial ocular visit, the researchers will conduct a pilot study to determine if the questionnaire prepared will be simple for the residents to understand and answer, and more importantly, if it will be able to help the researchers fulfill the objectives of this study. The number of participating individuals for the pilot study will be arbitrarily selected by the researchers and will also be randomly selected from the sample size.

### Current Level of Research

As of today, the research proper, which was started in April 2016, is currently being performed. All necessary documentations and prerequisites prior to the research proper have been filed and duly accomplished by the researchers. The researchers are presently collecting the data from respondents in Barangay Mangilag Sur, Candelaria, Quezon Province, while simultaneously encoding previously collected data during the previous visits to the community. Statistical analysis will be done after the second phase of the research proper.



	April 2017	May 2017	June 2017	July 2017	Aug 2017	Sept 2017	Oct 2017	Nov 2017	Dec 2017	Jan 2018	Feb 2018	Mar 2018
Research topic selection												
Research proposal formulation and finalization												
Research proposal presentation, defense and panel approval												
Further reading for study; Ocular inspection of locale												
Presentation of proposal for IRB approval												
Training on Movement Disorders by specialist												
Field survey training by epidemiologist												
Surveying and case ascertainment												
Clinical Epidemiology 3 consultation												
Manuscript revision												
Data analysis and formulation of written output												
Thesis defense												



Sample Size for Frequency in a Population

Population size(for finite population correction factor or fpc)(N): 6706  
 Hypothesized % frequency of outcome factor in the population (p):50%+/-5  
 Confidence limits as % of 100(absolute +/- %)(d): 5%  
 Design effect (for cluster surveys-DEFF): 1

Sample Size(n) for Various Confidence Levels

Confidence Level(%)	Sample Size
95%	364
80%	161
90%	261
97%	441
99%	604
99.9%	933
99.99%	1236

Equation

$$\text{Sample size } n = [\text{DEFF} * Np(1-p)] / [(d^2 / Z^2_{1-\alpha/2} * (N-1) + p*(1-p))]$$

Results from OpenEpi, Version 3, open source calculator--SSPropor

Print from the browser with ctrl-P

or select text to copy and paste to other programs.

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