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The Reconstructed Cohort Design: A Method to Study Rare Neurodegenerative Diseases in Population-Based Settings

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Abstract
Rare neurodegenerative diseases are characterized by high heterogeneity and high clinical complexity, as well as low incidence and prevalence, thus making tracking small numbers of incident cases in the general population very challenging. Since it is not possible to use classical cohort studies to estimate the incidence of these rare diseases, we can "reconstruct" a theoretical cohort using case information from a well-defined geographic region collected through a surveillance system. The incidence rate is estimated as the ratio between the number of individuals at risk who were diagnosed with the disease of interest during the study period and the estimated overall amount of time individuals in the reference population spent at risk during the study period. If a series of assumptions are met, the approximate incidence proportion of a closed theoretical cohort without competing events and with the same follow-up duration can be calculated by multiplying the incidence rate with the length of the study time. This rationale relies on the presence of an effective referral system, which links all levels of the healthcare system together in the region, from general practitioners to specialized clinical centers. The reconstructed cohort design is a valid and cost-effective method to collect data on the incidence of rare neurodegenerative diseases and represents the theoretical framework for building up population-based registries.

Introduction

The study of rare diseases is particularly challenging because of the difficulties in tracking small numbers of cases in the general population. To this day, a uniform definition of rare disease does not exist. The European Medical Agency defines rare disease with <50 cases per 100,000, whereas in the United States, a disease is considered rare when it affects fewer than 200,000 Americans at any given time point. Across different countries and organizations, the most widely used definitions of rare disease are based on prevalences between 40 and 50 per 100,000 [1]. About 80% of these rare disorders are of genetic origin, and about 75% present neurological symptoms [2]. The key characteristics of rare neurodegenerative diseases are clinical complexity, heterogeneity, as well

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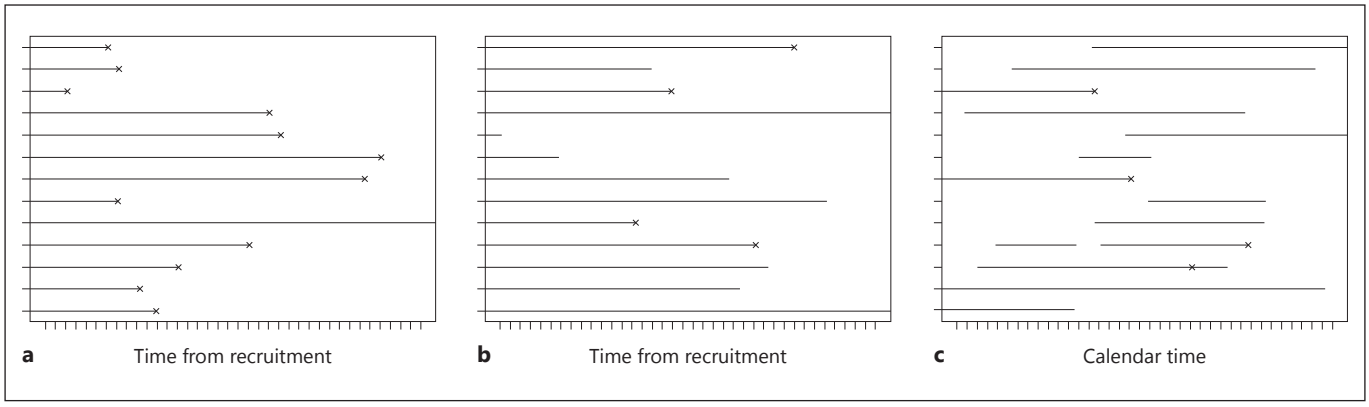

Fig. 1. Example of closed (**a**), closed-on-the-left (**b**), and open (**c**) populations with 13 hypothetical individuals. Horizontal lines represent the amount of time spent at risk of having the disease for each individual in the study, × symbol represents the occurrence of the disease of interest.

as low incidence and prevalence, which make studying these diseases difficult in both clinical and population-based settings. Additionally, tracking rare neurodegenerative disease cases to produce valid estimates of incidence is difficult due to the complexities of the referral system involved and the sparsity of centers able to provide accurate diagnoses.

A classic cohort design would not be feasible to study rare diseases due to the large amount of participants needed, the extensive follow-up time, and the constant intensive surveillance for disease occurrence during the follow-up visits. In the following sections, we will provide some insights on the theoretical framework behind the reconstructed cohort design, which represents a cost-effective alternative to classic cohort study design for estimating incidence of rare neurodegenerative diseases. We will additionally provide practical advice and useful considerations about the collection of cases, the definition of the population at risk, limitations, and future perspectives for this methodology.

Theoretical Framework

Quantifying the frequency of new disease diagnoses in a population, the incidence, and studying how this frequency changes over time in a given geographic region and among subgroups are of crucial importance in epidemiology [3]. It is even more important in rare neurodegenerative diseases, whose etiology is often unknown, as it could represent a first step in understanding possible genetic and environmental risk factors. In this paper, we make the assumption that there is no cure for such diseases, meaning that once an individual is diseased, they cannot re-enter the pool of individuals at risk. In clinical epidemiology, the main metric used for the incidence interpretation is the incidence proportion (or risk). This measure is the probability that an individual from a specified population at risk will develop a rare neurodegenerative disease of interest in a specific period of time. In order to estimate the incidence proportion, a closed population on the time from recruitment scale is usually required. This means that a cohort of individuals free from the disease of interest and potentially able to develop it has to be recruited and observed for the follow-up time t in order to collect information on the incidence of this disease. In a closed population, new individuals cannot join the cohort after the beginning of the follow-up, and recruited individuals cannot drop from the study without experiencing the disease (Fig. 1). The incidence proportion for the time span t will then be estimated as the ratio of the number of individuals diagnosed with the rare neurodegenerative disease of interest during the follow-up time and the number of individuals recruited at the baseline [3]. However, with the exception of very short follow-up studies, this scenario appears rather unrealistic. Population incidence studies are usually only "closed on the left" on the time from recruitment scale, as individuals are likely to be lost over the follow-up period or may experience competing events during that time (Fig. 1) [4]. The closed-on-the-left cohort design, often also referred to as "fixed cohort," is the most suitable and feasible study design to provide information on the incidence of a disease in a given reference population. In this setting, the metric used to quantify the incidence is the incidence rate,

which allows to account for loss to follow-up and the occurrence of competing events. The incidence rate is estimated as the ratio between the number of individuals who were diagnosed with the disease of interest during the follow-up time, divided by the total time participating individuals spent at risk in the study (overall amount of person-time) [3]. The incidence rate is not a probability and can range between zero and infinity. It is an instantaneous concept that can be thought of as the "average speed" at which the population at risk is shifting from the free-disease status to the disease status. However, the interpretation of the rate is less intuitive. The exponential formula describes the relationship between the incidence proportion and the incidence rate in a closed population ignoring competing risks [4].

Unfortunately, a closed-on-the-left classical cohort study design is just as difficult to implement as a closed cohort study design when we want to estimate the incidence of a rare neurodegenerative disease. Because of the rarity of these diseases, a closed-on-the-left cohort study as defined above would require hundreds of thousands of participants to only diagnose a few ill individuals. The effort such a study would require is tremendous in terms of funding and human resources. Moreover, the constant surveillance for disease occurrence during the follow-up visits would be complex and very expensive, as neurodegenerative diseases are usually very difficult to diagnose.

Since it is not possible to use a classic cohort study design, we can instead use information from a surveillance system on incident events during a calendar time period in a well-defined geographic region to estimate the incidence rate of a rare neurodegenerative disease by "reconstructing" a theoretical cohort of interest. This is the rationale behind the estimation of the incidence in population-based registry studies.

In the case of a population confined to a specific region observed over a calendar time period, such as the one covered by a population-based disease registry, we are dealing with a concept substantially different from the closed population described above. In such a case, the population is not considered as fixed in terms of size, but rather as an open or a dynamic population (Fig. 1) [5]. The population living in a geographic region can increase or decrease over time due to migration, birth, or death, because inhabitants "status" of residency dynamically changes over time. This stands in contrast to closed populations, such as birth cohorts or a cohort of individuals recruited for a clinical trial, in which individuals share an experienced "original event," therefore no new individuals can join the population [5]. The idea of a dynamic population, namely a flow of individuals living in a defined region in a specified time frame, is widely used in demography and explains the reason why rates are commonly used in this discipline [5]. As a matter of fact, the incidence rate is the only estimable and meaningful measure for assessing the frequency of new cases in an open population. In order to estimate the incidence rate of a rare neurodegenerative disease in an open population, such as the individuals living in a specific region, we need 2 quantities: the numerator and the denominator of the rate.

The numerator is the overall number of individuals living in the region who were diagnosed with the disease of interest during the study period. These are the incident cases collected in the population-based registry. The denominator is the overall amount of person-time spent at risk in the region during the study period by the individuals who were able to experience the disease of interest.

If the size of the open population of individuals living in the region is constant over the study period, the population is in a "steady state" [5]. This state implies that every individual who leaves the region, dies, or experiences the disease is constantly replaced by an individual who is born or moves into the region.

The steady state can be plausibly assumed in more situations than expected, especially for short time intervals [5].

Since we are dealing with a rare disease, which is characterized by a very low prevalence, we can easily assume that all the individuals in the region have been at risk of getting the disease, ignoring the presence of the few already existing cases.

If we assume a steady population without a change in terms of size during the study period, the overall amount of person-days in the denominator can be estimated by simply multiplying the number of living individuals in the region on one day and the number of days in the time period under study [5].

If the size of the population of the region increases or decreases during the study period, we cannot assume a steady state and a more realistic assumption can be made: a linear change over the study period. If the change in size of our open population is roughly linear, we can estimate the overall amount of person-days in the denominator by multiplying the number of individuals living in the region at the halfway point of the study period by the number of days under study [5]. For example, if we consider a study period of 1 year, the first factor can be the recorded number of individuals living

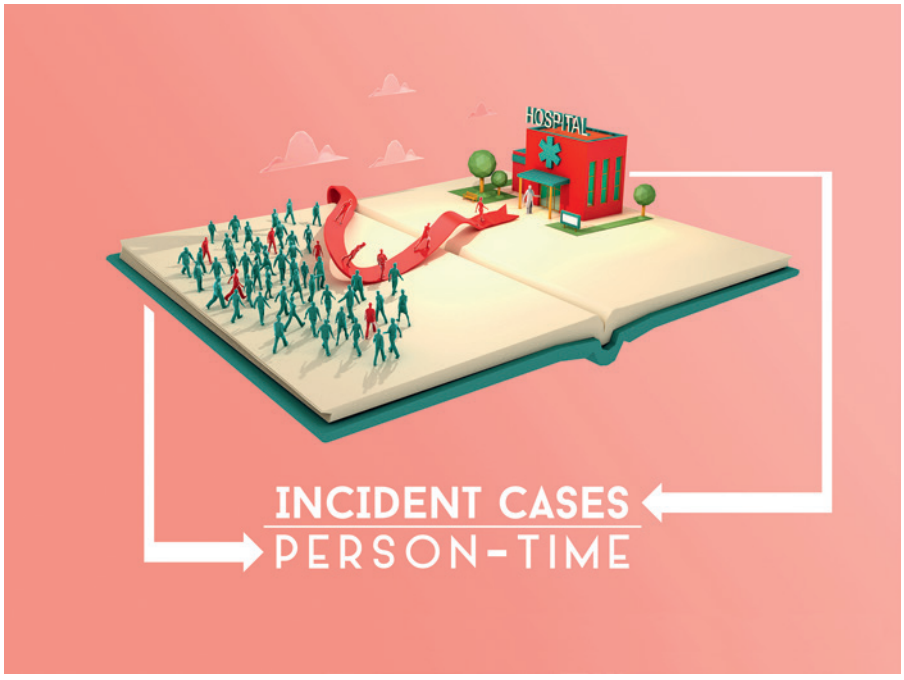

Fig. 2. Graphical illustration of the reconstructed cohort design rationale. A population-based disease registry, (here represented as an open book) is a capillary network of general practitioners, health care facilities and patients associations that covers a well-defined region. All the individuals from the general population (left side of the book) who are new cases of the disease of interest (in red) during the study period can access the health care network (here represented as a hospital), or are identified by the network, and will be registered as incident cases (moving towards the right side of the book). The incidence rate is then estimated as the ratio between the number of incident cases recorded by the registry and the overall amount of person-time spent at risk by the population in the region during the study period. The incidence rate can then be interpreted, under the fulfillment of certain assumptions, as an incidence proportion estimated in an "equivalent" population-based cohort study.

in the region as on June 30, or the average between the number of individuals living in the region on January 1 and the number of individuals living in the region on December 31.

Therefore, we can easily estimate the incidence rate of a rare neurodegenerative disease in a region using only the number of collected incident cases from a population-based disease registry in a calendar time period and information on the size of the reference population.

However, we want to go further and find an intuitive interpretation of this incidence rate.

We can assume that the incidence rate is constant over time and would be the same as if we had measured it in a closed population with the same characteristics of the participating individuals. This is a realistic scenario if we consider a short time period.

We can also assume that the product between the incidence rate and the length of the time period considered is a number close to zero. This is usually true if we are considering rare diseases and short time periods like 1 year.

We need to assume that the incidence rate is not affected by the presence of competing events, such as death. This means that the incidence rate would be the same with or without competing events. The idea that the incidence rate is not influenced by competing events is unrealistic, but is still very common in survival analysis literature [4].

If all these assumptions are met, we can approximate the incidence proportion of a theoretically closed cohort without competing events and with the same follow-up duration by multiplying the estimated incidence rate by the length of the time period under study [4]. Specifically, this would be the incidence proportion of a theoretical cohort without competing events that included all individuals living in the geographic region of interest at the beginning of the study, who were surveilled for the diagnosis of the rare neurodegenerative disease of interest over the whole study period.

This theoretically closed cohort is what we call the "reconstructed cohort" and is the foundation of interpreting the incidence rates estimated from population-based registries as probabilities.

Although this theoretical framework has been used for centuries in practice, we believe that some steps of the reasoning are not well understood and often misinterpreted. This mostly happens because the terms defining different types of cohorts and incidence metrics are often used interchangeably. We believe the concept of "reconstructed cohort design" to be suitable for rare neurodegenerative diseases, as it would make the process leading to the interpretation of an incidence rate estimated in an open population as an incidence proportion in a closed population explicit. We also provide a graphical illustration of the reconstructed cohort rationale to visualize the concept (Fig. 2).

Table 1. Advantages of registries in the reconstructed cohort design framework

Advantages
1. Complete case ascertainment
2. Full phenotypes description including real distribution of clinical subtypes
3. Inclusion of older cases
4. Biobank population-based
5. Sources of cases for pragmatic trials and analytic population-based studies
6. Cost-effective estimation of incidence measures

Uncertainty and Comparison of the Estimates in the Reconstructed Cohort Design

Despite the validity and the cost-effectiveness of the reconstructed cohort design, the estimation of incidence rates is always characterized by a high degree of relative uncertainty when only a few cases are observed. The confidence interval (CI) of an incident rate is obtained assuming that the number of recorded incident cases is a random variable with Poisson distribution, while the number of person-time at risk accumulated in the study is a non-random quantity [6].

The variance of the rate estimator, and therefore the width of the approximate incidence rate's CI, increases when the number of incident cases in the numerator increases and decreases when the number of person-time in the denominator increases [6]. This is why, in absolute terms, rare disease studies tend to provide more precise estimates of the incidence compared to studies of common diseases with the same amount of person-time. However, the degree of precision of the rate estimate is clearer on the relative scale [6]. The ratio between the width of the approximate incidence rate's CI and its point estimate is only inversely proportional to the square root of the number of cases. Hence, it is not surprising to find point estimates of the incidence rate in populations with a singular incident case that are almost 40 times the value of the lower bound, and 5 times less than the value of the upper bound of their exact 95% CIs. This may pose serious problems in the interpretation of incidence studies of rare diseases [6] such as neurodegenerative ones. The low precision of incidence estimates also negatively affects the descriptive cross-regional comparisons, which are a crucial step in discovering possible risk factors for rare neurodegenerative diseases. Such comparisons aim at identifying differences across regions in terms of incidence, which are not due to a different distribution of well-known risk factors. For this reason, they are usually conducted to compare age-sex standardized incidence rates instead of crude incidence rates.

It is a common misconception that the ratio of age-sex standardized incidence rates from 2 different populations is equivalent to the ratio of the crude incidence rates that would have been observed in 2 hypothetical populations with the same age-sex structure and underlying exposure conditions of the observed populations. When incidence is quantified using rates (person-time spent at risk at the denominator) rather than incidence proportions, except in very particular conditions, this does not hold true [4].

This is due to the fact that applying incidence rates to a different population is not the same as applying incidence proportions to that different population, because a change in the age-specific incidence rates impacts the relative distribution of the person-time spent at risk [4].

For example, applying a higher age-sex specific incidence rate from one population to the age-sex specific amount of person-time in a second population would increase the number of cases in this group. However, it would not have been possible to observe the amount of person-time recorded in the second population with this new incidence rate, because a higher incidence shortens the period spent at risk by persons who now have developed the disease [4]. A similar issue can arise for a difference in the occurrence of competing events between the 2 populations [4].

Despite this technical distinction sometimes being practically negligible, it further highlights the difference between the concepts of incidence rate and incidence proportion.

Numerator: Incident Cases

The incident cases collection in a population-based disease registry with a reconstructed cohort design relies on the identification of a network of diagnostic facilities to which subjects diagnosed or suspected with the disease of interest are referred for ascertainment. The number of facilities taken into account depends on the characteristics of the specific disease and the health system of the geographic region. Facilities will be fewer for less prevalent diseases. The general characteristics of the healthcare system involved are also important. An effective referral

system depends on proper activities linking all levels of the healthcare system, from general practitioners to specialized clinical centers. The ideal healthcare system will allow people to have the best possible care close to home. Nevertheless, is likely that within large areas only few multidisciplinary centers are able to diagnose and care for specific rare neurodegenerative disorders. The use of multiple sources to collect data is very important to keep track of all possible incident cases.

The heterogeneity of the clinical presentation is a key feature of rare neurodegenerative diseases. These diseases are usually characterized by the wide age of onset ranging from infanthood to mid-adulthood and older ages, a variable clinical course progression, and by neuronal loss in different regions of the central nervous system.

Usually, patients present with the classical clinical phenotypes, but they can also develop extreme phenotypes that are very different from the most common presentation. This heterogeneity is one of the reasons why rare neurodegenerative diseases are particularly challenging to be studied.

Population-based disease registries play a key role in the surveillance of rare diseases, because they are the only cost-effective and valid approach in which the identification of the phenotypic spectrum of diseases is relatively independent of the age and the severity of the clinical presentation. The inclusion of all cases in the numerator may determine a complete identification of the whole spectrum of phenotypes characterizing the disease of interest, including those that might otherwise be overlooked. Older individuals with a suspected diagnosis of interest are less likely to rely on specialized centers where unique care for neurodegenerative diseases is typically available. This is due to general practitioners tending to look less precisely for specific diagnoses in the elderly, thus making these patients less likely to be included in a registry [7, 8].

Over time, a sharp increase in the size of the numerator for the same geographical region, which is not explained by a change in the denominator size or population structure, can be due to a growing awareness of the disease or of specific phenotypes previously not searched for as a possible diagnosis. A good example is Niemann-Pick Disease type C with adult onset [9]. The presentation of Niemann-Pick Disease type C is highly variable and ranges from cases with an aggressive serious clinical course with perinatal onset to adolescent and adult cases with a slower disease progression. For many years, this disease was considered a pediatric disease. For example, no adult-onset cases were diagnosed in France until 1990 and only 1 out of 5 cases diagnosed in the period between 2000 and 2008 were adults [9]. In 2009, the only approved targeted therapy for neurological manifestation of Niemann-Pick Disease type C, miglustat [10], was introduced in Europe. The introduction of an effective therapy increased the importance of the diagnosis of Niemann-Pick Disease type C in clinical practice. As a consequence, in the period 2009–2015, adult-onset cases increased up to represent 50% of all the diagnosed cases in France [9].

Another possible explanation to consider for the rapid change in the number of collected cases within one geographical region in a short time period is the revision of diagnostic criteria that mandate which cases are to be taken into account. For example, the revised El Escorial criteria for amyotrophic lateral sclerosis diagnosis reclassified "possible" cases as "probable with laboratory support," meaning that such cases became eligible for registries, which only collect probable and definite cases [11, 12].

Finally, the presence of a registry infrastructure itself improves the quality and completeness of the inception of cases and data collection [13]. The best example for this is the Limousin Registry whose exhaustiveness has been estimated at 98.4% by capture-recapture analyses [14].

The Denominator: Population at Risk

In epidemiological studies, populations of interest are defined by eligibility criteria [15]. The main eligibility criterion for registries is a residency in a specific geographic region. The scope of the reference population's dimension should depend on the frequency of diagnosis of the rare neurodegenerative disease of interest. For diseases such as fronto-temporal lobar degeneration and amyotrophic lateral sclerosis, which generally present an incidence rate between 1.5 and 3.5 per 100,000 person-years [16], a region with at least 1 million residents is needed for a 1-year study, although regions with 3–5 million residents are preferable. As we described above, the number in the denominator is only estimated based on the statistics of the regional demographics at a certain point in time. In contrast, for closed-on-the-left cohort studies, it is actually possible to calculate the time participants spend at risk. However, in order to find incident cases in closed-on-the-left cohort studies, we would need to check the health status of millions of participants during the whole study period regularly. By using registries and the reconstructed cohort design, we avoid such a cumbersome process, substantially saving resources.

This is an important advantage in the assessment of rare diseases, because the process of sampling is generally challenging and can easily be a source of bias. In the reconstructed cohort design, all possible methodological problems from a researcher's perspective relate to the numerator and to the proper interpretation of the results based on the assumptions.

Limitations of the Registry Methodology

The structural basis of the reconstructed cohort design is the set-up of population-based disease registries. Though they have several advantages (Table 1), readers should also be aware of some limitations. Registries are complex and expensive infrastructures, despite being cheaper and simpler compared to classical cohort studies. The registry network is based on the willingness of local neurology and neurophysiology departments, and of public or private neurologists, to participate in them. The key element is the notification of every incident case of the rare neurodegenerative disease of interest to the registry over a sufficiently long time period. Registries with long durations, such as more than 2 decades, mainly contain collected incident cases from 1 or 2 main centers. Good examples for amyotrophic lateral sclerosis registries are the Piemonte Val d'Aosta Registry for ALS [17] in which almost all cases are collected in Turin and Novara areas, the Irish Registry with almost all the cases collected in Dublin [18], the Dutch Registry with almost all the cases collected in Utrecht [19], and the Limousin Registry in which all the cases are collected in Limoges [20]. The presence of major multidisciplinary centers, with numerous staff working in several clinical and research areas, facilitate the proper collection of multidimensional data and avoid part of the difficulties in managing complex networks. Registries for amyotrophic lateral sclerosis based on multiple sites for collection of data, such as SLALOM in Lombardy [21] or SLAP in Puglia [22], have a more challenging task in keeping these structures fully active and collaborative over time.

Today, another big challenge in building registries seems to be funding, since agencies do not allocate research money to registries due to them being considered infrastructures, rather than research projects with scientific questions, like most funding agencies require [23].

The majority of registries' financial resources are obtained for different purposes than research. A notable exception being the recent funding of the Scottish registry, due to the recognition of inestimable value for the amyotrophic lateral sclerosis community with regards to both care and research [24].

The always changing status of the patient's data protection regulations represents another common difficulty. Subjects involved in the registration process need to sign specifically designed informed consent forms prepared by the review boards in Europe and United States' institutions, which appear to become more and more stringent. The only possibility to deal with this new trend is to highlight the immense benefits of registries, which are unique resources to help in understanding the causes of diseases, plan better care, and eventually find new effective therapies.

Discussion

The reconstructed cohort design is the most appropriate study design to estimate the incidence of rare neurodegenerative diseases in a population setting in a cost-effective way, and furthermore provides the theoretical framework for adequate incidence data collection in registries. These registries offer the best infrastructure to organize a collection of information about individuals affected by specific diagnoses or conditions. In the last 2 decades, this approach attained new knowledge about the distribution of rare neurodegenerative diseases in different populations, and led to a better understanding of disease causation, including genetics and biological mechanisms. In the future, this type of study design could become the preferred method to collect data for clinical trials and to test new therapies. However, the difficulties of obtaining sustainable funding and the introduction of new data protection rules may favor different, less rigorous designs of registries to collect information about specific diagnoses and conditions at the population level.

For example, a significant change in the data collection for rare neurodegenerative diseases has been implemented after the "Bucket Challenge." A wide involvement of the patients and the public in the initiatives have prompted the idea of building up structures for the collection of data, based on the interaction between clinicians and patients, with a primary role of the patients. In this direction, nonprofit associations of volunteers have supported the construction of registries based completely on self-enrollment and self-reporting by the patients. The providers of these operations built a platform managing several databases as a source of information. Associations, scientists, clinicians, and patients take part in its management [25]. However, we need to be aware of the fact that,

despite their indisputable advantages and merits, patient-oriented registries will not guarantee the completeness and unbiased collection of data for rare neurodegenerative diseases.

The reconstructed cohort design is an optimal study design for estimating incidence and capturing the heterogeneity of rare neurodegenerative diseases across different geographic regions [26].

This design may, in a first step, fulfill the need of a properly representative sample with valid descriptive statistics, and in a second step, provide data to be used in studying biomedical causes of rare neurodegenerative diseases in analytic population-based studies [15].

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