



ASSOCIATION BETWEEN CERTAIN DEMOGRAPHIC INDEXES AND THE NUMBER OF CLINICAL TRIALS IN THE EUROPEAN ECONOMIC AREA

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SUMMARY

Purpose: The number of clinical trials conducted by the industry has increased significantly for the period 2014-2016. They have produced advances in disease prevention, treatment, and rehabilitation for many diseases. This was the main reason to carry a study on the association between certain demographic indexes and the number of clinical trials in the European economic area. Proving a correlation between those two variables could lead to additional research pursued by the industry during the feasibility phase of each study in order to have higher and quicker enrollment for the success of the clinical trial.

Materials/Methods: Three demographic factors were considered to have some importance on the clinical trial enrollment – the number of population, life expectancy at age 65 and Disability-Adjusted Life Years (DALY). The numbers were processed with Spearman's rho, and the result of the results shows a correlation to be present for the number of population and life expectancy at age 65.

Results: There is a correlation between the number of clinical trials opened for enrollment of patients and certain demographic indexes, which could lead to favorable conditions for trial conduct in the different countries of EEA.

Conclusions: Studying in advance if some demographic factors are significant for conduct of clinical studies is something new that could be used by the industry to avoid the wastefulness of a clinical project.

Keywords: clinical trials, number of population, life expectancy at age 65, Disability-Adjusted Life Years (DALY)

INTRODUCTION

The development of new medicines is a long, expensive and complex process. The precise definition of the time period and the monetary value for the development of a new medicine is hard, but according to scientific publications it takes 10-15 years, and the invested financial resources could grow to \$1,3 billion. The complexity of the investigational process is defined by the need for expertise and the interdisciplinary cooperation of scientists

and clinical investigators from different therapeutic spheres. Clinical trials can be complicated and confusing. Many patients refuse to participate in clinical trials, so the phase of planning the trial and selecting countries and sites is crucial. [1] Patient obstructions also cause large and unexpected expenses to pharmaceutical and biotech companies as they are forced to tread water. As the industry improves toward biologics and personalized medicine, these restrictions caused by consumers will become greater. [2]

Providing innovative therapy to patients and health-care services for free during the trial are the two main reasons for which patients are willing to participate. [3] Many factors play a role in the persistently low rates of trial participation, including financial barriers, logistical concerns, ethical aspects and the lack of resources for patients and clinicians to support clinical trial enrollment and retention. [4][5] The accurate planning of the progress and evolution of a clinical trial can be very rewarding. [6] Usually one of the main steps throughout the start of a new project in this field is feasibility, which is performed in order to be determined if a clinical trial will be successfully performed in a country or at an investigational site. Conducting feasibility study before the clinical trial could reduce the risk of spending resources on a trial that it is likely to 'fail'. [7] The purpose of the study is to verify whether there is an association between certain demographic factors and the number of clinical trials open for enrollment in the countries of the European Economic Area (EEA).

MATERIALS AND METHODS

Demographic data for the period from 2007 to 2016 is extracted from the structured database of the Eurostat portal (official statistical office of the European Union and its mission is to provide high-quality statistics for Europe). The information is compared to the generalized data of the number of ongoing clinical trials conducted in the countries of the EEA. Correlation link has been sought between certain demographic factors using Spearman rho (factor). This factor is used when the two variables are scaled, or one of the variables is scaled, and the other is quantitative. In this case, the quantitative value is transformed to scale. The Spearman's rank-order correlation is the

nonparametric version of the Pearson product-moment correlation. Spearman's correlation coefficient, (\tilde{r} , also signified by r_s) measures the strength and direction of the association between two ranked variables. [8]

R – correlation factor

p – the level of statistical importance (when $p < 0.05$ there is statistical importance, there is a relation between the investigated indicators).

N – the volume of the sample (in this case this is the number of countries, participating in the analysis, the number could be different because there is missing data for some countries)

RESULTS

Tracing the growth in the number of clinical trials conducted by the industry for the EEA countries during the period 2007-2016 shows that from 2008 to 2012 a significant increase was observed with a value in percentage for 2011/2012 being 141,29%. This number is twice the value of the average rate for the years 2007-2016 – 67,15%. Since 2014, there has been a decline in the numbers, with the rate for 2015/2016 of half of the average being 34,99%. The data for the number of ongoing clinical trials (open for enrollment) has been extracted from *www.clinicaltrials.gov* database. On the table below the growth rate of clinical trials can be followed through the period.

Table 1. The growth rate in the number of clinical trials conducted by the industry for the period 2007-2016 in %

Period	Growth rate of the number of clinical studies (%)
2007/2008	45,1
2008/2009	12,16
2009/2010	42,17
2010/2011	70,34
2011/2012	141,29
2012/2013	60
2013/2014	125,39
2014/2015	72,9
2015/2016	34,99
Average	67,15%

Table 2. The correlation between clinical trials open for enrollment and the number of population in the countries of the EEA for the period 2007-2016

Period Statistics	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
R	0,773	0,747	0,819	0,875	0,886	0,893	0,924	0,953	0,944	0,949
p	<0,001									
N	31	31	31	31	31	31	31	31	31	31

The research on the correlation between the number of opened for enrollment clinical trials and demography was performed with three major demographic factors – *Number of population, Life expectancy and Disability-Adjusted Life Years*. The reason for performing the study among the demographic factors is that the demographics have vast uses in society.

The correlation between the *number of population* and the number of clinical trials throughout the period of 2007 to 2016 was interesting to be determined due to the controversial dependency between this factor and many others such as economic growth, the stability of society, social norms, costs, health care standards, social norms, etc. The *life expectancy* is more than just a number. The level and variability of *life expectancy* have important implications for individual and accumulated human behavior because they affect fertility behavior, economic growth, human capital investment, intergenerational transfers, and incentives for pension benefit claims. [9]) *DALY* factor was chosen because it is highly used for measuring the benefits of healthcare. Enrollment in clinical trials and succession of a trial depends on the number of people willing to participate, which is in close relation to the satisfaction of people from the health care system. For the measurement of health benefits to having the greatest potential use in order to inform allocative efficiency arrangements, it needs to be based on a generic system so that gains/losses can be compared across the amplet possible range of therapeutic interference. [10] In this context, measures of health or health determination, and specially combined metrics that combine life expectancy and quality of life or disability have been extensively used. [11]

Number of population

In demographics, the world *population* is the total number of human beings currently living. *The term population* refers to the persons of the same group or species, who live in a particular geographical area, and have the competence of interbreeding. In sociology, *population* refers to a collection of humans.

The assumption made was that with the increase in the *number of population* in EEA, the number of clinical trials could grow. The result showed that the correlation factor is important, and there is a significant relationship between the two figures. When studying the indicator – the *number of population* - it can be considered that the population could influence the number of clinical trials open for enrollment and being conduct. The study period is 2007 - 2016. The beginning of the timeframe is the acceptance of Bulgaria in the European Union.

R - the calculated correlation factor between the number of clinical studies open for enrollment and population of countries in the EEA

p – factor showing statistical importance

N – 31 countries data used for number of clinical trials open for enrollment and number of population

Life expectancy at age 65

The definition of the index 'Life expectancy at age 65 years old' is the moderate number of years that a person at that age can be expected to live, estimating that age-specific mortality levels remain constant. However, the actual age-specific death rate of any particular birth cohort cannot be known in advance. If rates are falling, as it has been observed to be the case over the past decades in OECD countries (Organization for Economic Cooperation and Development), actual life spans will be higher than life expectancy calculated using current death rates. This indicator is measured in years.

The assumption was that with the increase of life expectancy at age 65, the number of people at age 65 or more grow, who are more vulnerable to chronic diseases and complications. With the increase in the number of people who suffer from chronic diseases, the possibility

of enrollment of patients in clinical trials grows. This leads to favorable conditions for the industry conducting clinical trials. The elderly population is the most extensive and the fastest-growing portion of the population worldwide. The elderly combine the lion's share of subjects for certain health conditions, like medical oncology conditions, heart disease, arthritis, and Parkinson's disease, among others in most parts of the world. Additionally, the elderly make up the majority of patients for many medicines treating chronic conditions. [12]

The results show that the correlation factor is significant for the years - 2007, 2008, 2009, 2011. The results confirmed that the relationship between life expectancy at age 65 and the number of clinical trials opened for enrollment for the period 2007-2015 is present for the years 2007 – 2009, 2011. The result is expected, considering the case of a higher value of the indicator of life expectancy at age 65 is normal that more people from the population are suffering from chronic diseases at this age and lots of them are interested in participating in clinical trials. The period of estimation is from the time point of acceptance of Bulgaria in the European Union, and it is related to all countries in the EEA.

Table 3. The correlation between clinical trials open for enrollment and life expectancy at age 65 in the countries of the EEA for the period 2007-2015

Period Statistics	2007	2008	2009	2010	2011	2012	2013	2014	2015
R	0,391	0,473	0,499	0,258	0,455	0,336	0,252	0,201	0,002
p	0,033	0,008	0,005	0,168	0,013	0,069	0,188	0,297	0,992
N	30	30	30	30	29	30	29	29	20

R - the calculated correlation factor between the number of clinical studies and the factor of life expectancy at age 65 of countries in the EEA

p – factor showing statistical importance

N – countries data used for number of clinical trials open for enrollment and factor of life expectancy at age 65 – varies through the years as no complete data was available for all countries in the EEA

Disability-Adjusted Life Years

The definition of *DALY* is the measure of overall disease burden, expressed as the number of years lost due to ill health, disability or early death. The term *DALY* was developed in the 1990s as a way of comparing the overall health and life expectancy between countries. The index is becoming increasingly common in the field of public health and health impact assessment. The disability-adjusted life years are a societal measure of the disease or disability in populations. [13] *DALYs* are calculated by combining measures of life expectancy as well as the ad-

justed quality of life during a burdensome disease or disability for the population. The *DALY* relies on an compliance that the most convenient measure of the effects of chronic illness is time, both time lost due to premature death and time spent disabled by the disease.

The disability-adjusted life year has emerged in the international health policy lexicon as a new measure of the 'burden of disease'. [14] The assumption was that with the increase of the *DALY*, the number of people with diseases and chronic diseases is rising, which leads to favorable conditions for conducting clinical trials. Treatments of chronic conditions are directed primarily to the relief of persistent symptoms rather than the cure of a rapidly evolving symptomatology. These very aspects make patients particularly suitable for clinical studies. [15]

The result shows that the correlation factor is not significant. When investigating *DALY*- it shows that the indicator has no impact on the number of clinical trials opened for enrollment. The period for the study is 2007-2014.

Table 4. The correlation between clinical trials open for enrollment and DALY in the countries of the EEA for the period 2007-2014

Period \ Statistics	2007	2008	2009	2010	2011	2012	2013	2014
R	-0,283	-0,339	-0,208	0,127	-0,119	-0,139	-0,232	-0,25
p	0,307	0,258	0,54	0,709	0,713	0,684	0,549	0,633
N	15	13	11	11	12	11	9	6

R - the calculated correlation factor between the number of clinical studies open for enrollment and factor of DALY in the EEA

p – factor showing statistical importance

N – countries data used for number of clinical trials open for enrollment and DALY – varies through the years as no complete data was available for all countries in the EEA

DISCUSSION

The researched demographic factors could be easily extracted from the database of the Eurostat portal, which makes them available for any kind of research that could be done in advance, before the conduct of a clinical study. This approach could facilitate the process of enrollment of patients in the clinical studies conducted by the industry, which could lead to shortening the timeframe from the point of creation of a new medicine to the time of registering it. Having innovative therapy available for patients is essential for their health and life status.

CONCLUSION

There is a correlation between the number of clinical trials opened for enrollment of patients and certain demographic indexes, which could lead to favorable conditions for trial conduct in the different countries of EEA. Correlation between the number of population and the number of clinical trials opened for enrollment and life expectancy at age 65, and the amount of opened clinical trials was proved by the study. This approach could be used by the industry for performing a more detailed feasibility step in order to guarantee the success of the clinical study in terms of enrollment of patients.

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