

## **Reported clinical trials in Republic of North Macedonia**

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### **Abstract**

Clinical trials are studies for medical research in which people are involved. All the new treatments need to be deeply and thoroughly tested before they can be approved for usage of the people. Firstly, laboratory tests are made by researchers, if the result of the new treatment give a promising result the new treatment is tested in the population. The Clinical Trials are divided in: Trials of new drugs, trials of new devices and trials of new procedures. There are different types of clinical trials: The main segregation can be the one in which according to the type of the clinical trials are divided as type of investigational clinical trials and type of observational clinical trials. Also, according to the type trials that can be mentioned are: Pilot studies and feasibility studies, Screening trials, Treatment trials, Prevention trials, Multi-arm trials, Case control studies, Cross selection studies, Cohort studies. And the other well-known differentiation of clinical trials is according to the phase in which a study can take place. According to this differentiation there are: Phase 1, Phase 2, Phase 3, Phase 4 clinical trials. However, there are trials that are in phase 0, which is a phase that aims to find out if the new treatment can reach to the targeted cells and will have some effect. Also, there are clinical trials who are in phase that is not defined by FDA. This are trials of behavioral interventions or trials in which devices are tested.

**Key words:** Clinical Trials, phases, types, clinical research

### **Introduction**

The aim of clinical trials is to provide information for some new treatment whether it is safe to use, is it better than a current approved treatment, if it affects the quality of life of the patient with a certain disease and if there are some side effects.

During a clinical trial the researchers get answers to the questions if the tested new treatment works and if there are some side effects that are worst compared to the

previously approved treatments. Also, the researchers are checking the impact of the new treatment on the life of the patients that are part of the trials and the quality of it.

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Interventional type of clinical trials aim is to get more information about intervention or treatment. In most of the trials in this groups the patients are randomly assigned to different groups so the end results can be compared in the end of the trial.

The Observational type of clinical trials aim to collect more information for a different treatment. Usually, this type of trials is organized once approval is received, and once the treatment can be used by patients. In this type, information about some new adverse events is collected that were not collected during the previous phases of a clinical trials. [1] [2]

Usually before a large clinical trial takes place a pilot and feasibility studies are organized. During this pilot and feasibility phases of a clinical trials information if the main study can be completed are collected, information about the potential patients, potential sites, and hospitals in which the clinical trial can take place are also collected.

Regarding the phases of clinical trials, it is well known that officially there are 4 groups of clinical trials, however there are 2 more groups that can be considered as a different phase of clinical trials.

- Phase I – is the first test in small group of healthy volunteers, in this phase, safe dose range and some side effects are evaluated. 15-50 volunteers are needed for this phase. In this phase the focus is on questions such as bioavailability and body compartment distribution of the drug and metabolites. It also provides preliminary assessment of drug activity. [3]
- Phase II – This phase is conducted once it is determined that phase one went well. This phase is designed to determine if the new treatment has promising efficacy so a further investigation can be made. In this phase up to 100 volunteers are part of the trial. Participants in phase II studies are usually carefully selected, with narrow inclusion criteria [3]
- Phase III – widely it can be considered as the most important phase before approval is granted. In this period there is a comparison between a new not approved treatment and a standard treatment. Usually, one of the groups that is part of this phase is getting the standard of care for some disease and there is

another group that is receiving the treatment that is under investigation. A special software randomly assigns a patient in a group. The number of patients in these phases is big. It can be between 300-3000 volunteers. Phase III trials of chronic conditions or diseases often have a short follow-up period for evaluation, relative to the period the intervention might be used in practice. In addition, they focus on efficacy or effectiveness, but knowledge of safety is also necessary to evaluate fully the proper role of an intervention in clinical practice. For instance, the FDA warned that morcellation to treat uterine fibroids by laparoscopic means, a procedure that had been used for years, could lead to spreading of unsuspected uterine sarcoma. [3]

- Phase IV – Is done after approval for the new treatment is received. Usually, the aim of this phase is more information to be collected.

There is also phase 0, in this phase the pharmacokinetics and pharmacodynamics are assessed.

And there are trials for which the phase cannot be determined by FDA. Usually, this are clinical trials in which new devices are tested and new behavioral interventions are tested.

A clinical trial lasts for a long period of time. Usually, phase 1 lasts up to several months. Phase 2 lasts from several months up to 2 years. The phase 3 of a clinical trial usually lasts the longest, it can take up to 4 years to the completion of this phase. And the phase 4 can also last for a long period of time but in this period only observation is made. There is not interventional part in this phase.

During all the phases in which patients are assigned, the patients have right to withdraw the trial at any moment. Everything is done on a voluntary basis, and everything must be done according to the Good Clinical Practice standards from the International Council for Harmonization of Technical Requirements for Human use.

The information that is available after a clinical trial is conducted not only shows the main goal of the trial, but it also can bring some new information regarding some disease, regarding treatment of a disease and the impact can be bigger than it was firstly planned.

Not every clinical trial has a positive result at the end the result of a certain clinical trial can show that the new treatment does not work properly as it was planned and that there are big side effects that are worse compared to some previously approved treatment or medication.

## **Materials and methods**

The research of this study includes review of reported and published information about the Clinical Trials available on the International Clinical Trials Registry Platform (ICTRP) which is available on the web page of the World Health Organization.

<https://www.who.int/>. The main mission of the WHO ICTRP is to ensure that a complete view of research is accessible to all those who are involved in health care decision making. This can improve the research and can strength the validity and value of the scientific evidence base.

The main filter that was used during the research was Country.

As country in which clinical trials were conducted was chosen Republic of North Macedonia.

After filtering the data to Republic of North Macedonia information about the number of reported clinical trials in Republic of North Macedonia, the years in which clinical trials were conducted are available, information about the phase of the study in which clinical trials are conducted is available. Information about health category and sub-category are available. Information about the targeted disease of a clinical trials is available, information about the age of the participants and information about number of participants is available.

A comparison was made to the number of organized clinical trials in Republic of Macedonia, with the number of organized clinical trials in other countries in which the number of organized clinical trials is close one to another.

To find out if most of the organized clinical trials are in proportion with the most common diseases, reports were checked from the Institute for Public Health of Republic of North Macedonia and the data was compared. [4]

After getting the results, they were sorted into diagrams for better visual display.

## **Result & discussion**

According to the statistical analysis from the Clinical Trials Registry Platform overall, in Republic of North Macedonia 348 clinical trials have been organized.

The first reported clinical trial in Republic of Macedonia has been organized in 1999. It was phase III study which has targeted population with malignant disease on the lungs.

From the reported data we can see that the number of clinical trials is getting higher slowly. From 2 in 1999, to 164 in 2014 and to 348 in present. The number of organized clinical trials is still low, but the good part is that slowly it is getting higher.

According to the data published by Institute for Public Health of Republic of North Macedonia, from 2008 to present the most common diseases in the country are:

1. Cardiovascular disease,
2. Respiratory Disease,

3. Malignant Neoplasms,
4. Gastrointestinal disease,
5. Genitourinary disease

According to the available data, published by the Public Health Institute the order of the above-mentioned disease is constant in years.

From the statistical analysis on Clinical Trials Registry Platform, it can be seen that most of the conducted clinical trials in Republic of North Macedonia are phase III studies. From 348 trials reported, 181 are in phase III. Second are clinical trials that do not have specific phase in which they are conducted, their number is 93, third are clinical trials in phase II, 52 clinical trials are in this phase. Fourth are clinical trials in phase IV, 16 of all the reported clinical trials are in this phase. Fifth are clinical trials in phase I, only 4 of all the reported clinical trials are in phase 1, and in phase 0 there is only 1 study.

This numbers are expected, since there are not a lot of Macedonian Pharmaceutical companies who can organize clinical trials in phase 0 or 1. That's why most of the studies are in phase 3, studies that have successfully passed the previous phases.

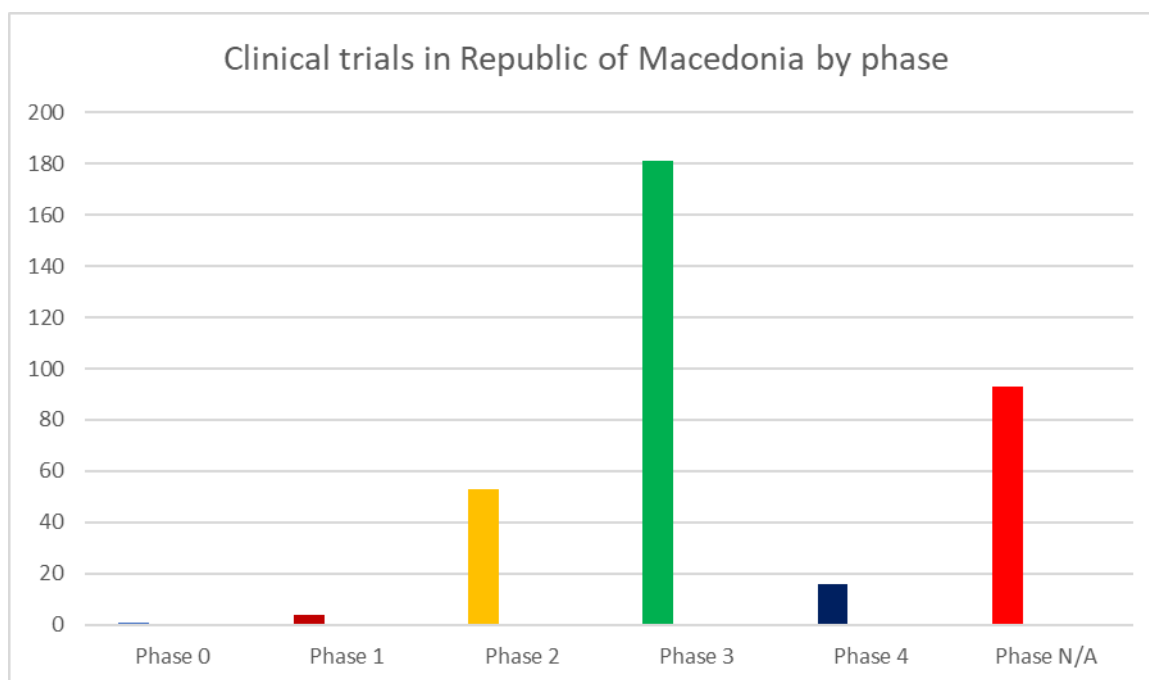


Chart 1. Phase of clinical trials in Republic of Macedonia

Separated by health sub-category in which clinical trials have been organized, it can be seen that most of the organized clinical trials are from the sub-category of endocrine, blood and immune disorders, there are 67 clinical trials in this group or 19.76% of all the organized clinical trials, on the second place are clinical trials related to malignant neoplasms, the number is 42 or 14.45% of all the organized clinical trials, on the third place are clinical trials related to neuropsychiatric conditions, the number is 42 or 12.39% of all the organized clinical trials, on fourth place are clinical trials related to cardiovascular diseases, the number is same as the trials related to neuropsychiatric disorders, 42 and 12.39% of all the organized clinical trials. Next are clinical trials related

to diabetes mellitus, the number is 41 or 12.09% of all the organized clinical trials, next are clinical trials related to Genitourinary diseases with number of 27 or 7.96% of all the organized clinical trials. There are also 27 clinical trials related to respiratory conditions or 7.96% of all the organized clinical trials. Related to musculoskeletal diseases there are 11 clinical trials or 3.24% of all the organized clinical trials. The rest of the clinical trials are less than 10 and their % is lower than 3% of all the organized clinical trials in Republic of Macedonia.

Separated by health sub-category it can be seen that the highest number of organized clinical trials are not in the diseases that are most common in Republic of North Macedonia. According to the data available for the morbidity in Republic of North Macedonia, the most common diseases are cardiovascular diseases, however the organized clinical trials related to cardiovascular diseases are on the fourth place. The clinical trials to the second most common diseases, the respiratory diseases are on the 7<sup>th</sup> place of the organized clinical trials. The third of the most common diseases, malignant diseases are on the 2<sup>nd</sup> place of the organized clinical trials.

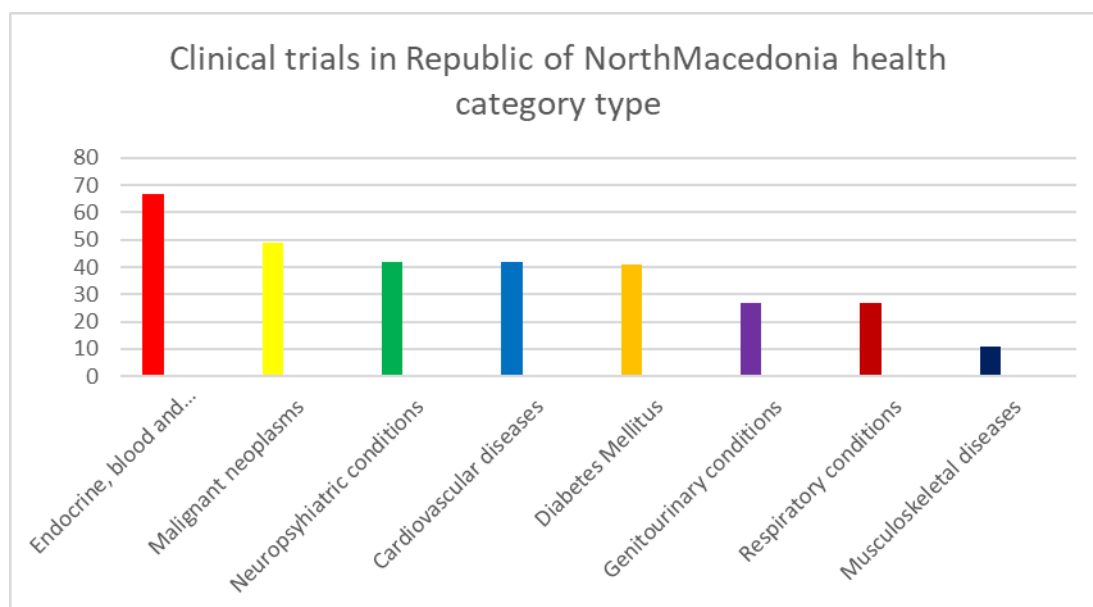


Chart 2. Clinical trials in Republic of Macedonia according to the health category

Regarding to the targeted disease in Republic of North Macedonia it can be seen that from the beginning there are 45 clinical trials related to Diseases of the immune system or 13.27% of all the reported clinical trials. There are 41 clinical trials related to Diabetes mellitus in percents 11.79%. Related to Multiple Sclerosis there are 22 clinical trials reported, in percents 6.49%. Related to Nephritis and nephrosis there are 21 clinical trials, in percents it is 6.19%. Related to ischemic heart diseases there are 18 clinical trials reported, in percents it is 5.31%. Related to disease of the blood or blood-forming organs there are 16 clinical trials reported, in percents 4.72%. Related to breast cancer there are 14 clinical trials reported, in percents 4.13%. Related to Rheumatoid arthritis and COVID-19 there are 10 clinical trials for each of the conditions or 2.95% per

condition. The rest of the disease which are target diseases for clinical trials are less than 10 or in percents less than 2.95%.

As mentioned in the health subcategory type the organized clinical trials does not correspond to the diseases with the highest morbidity in Republic of Macedonia.

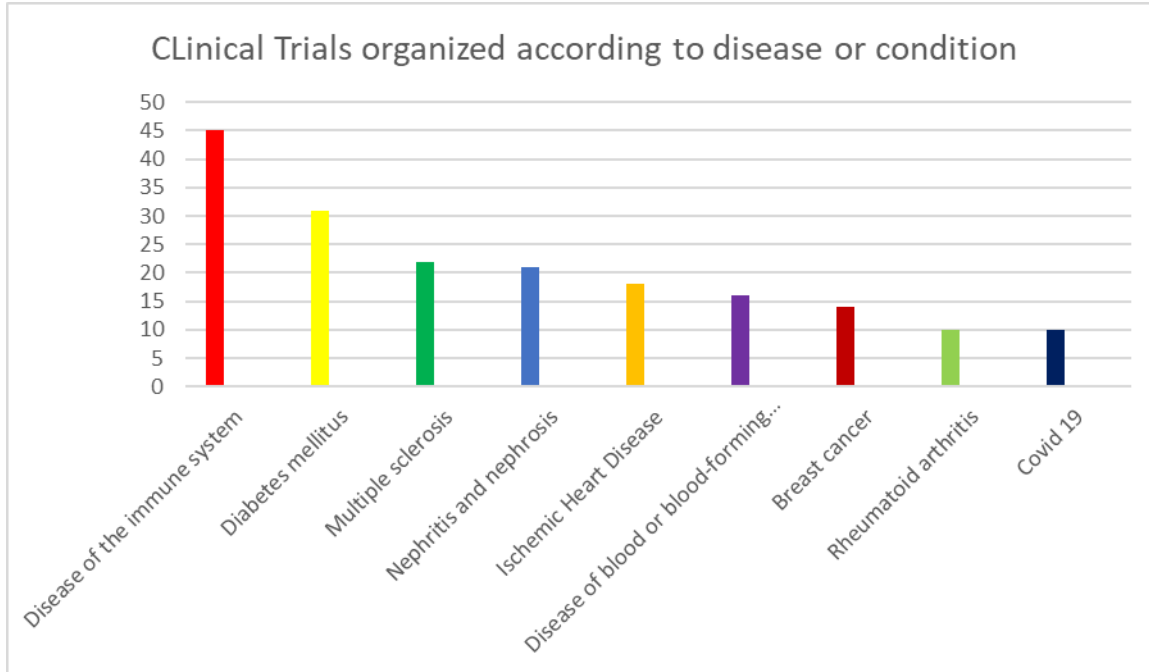


Chart 3. Targeted Disease or condition for clinical trials in Republic of North Macedonia

By the gender of the targeted population, it can be seen that in Republic of North Macedonia, on 278 of the reported clinical trials or in 80% of all the organized clinical trials, both male and female gender were the targeted population. In 15 or 4% of all the organized clinical trials only female patients were targeted and in 12 or 3% of all the organized clinical trials only male patients were targeted. For 43 of the clinical trials or 12% information is not available.

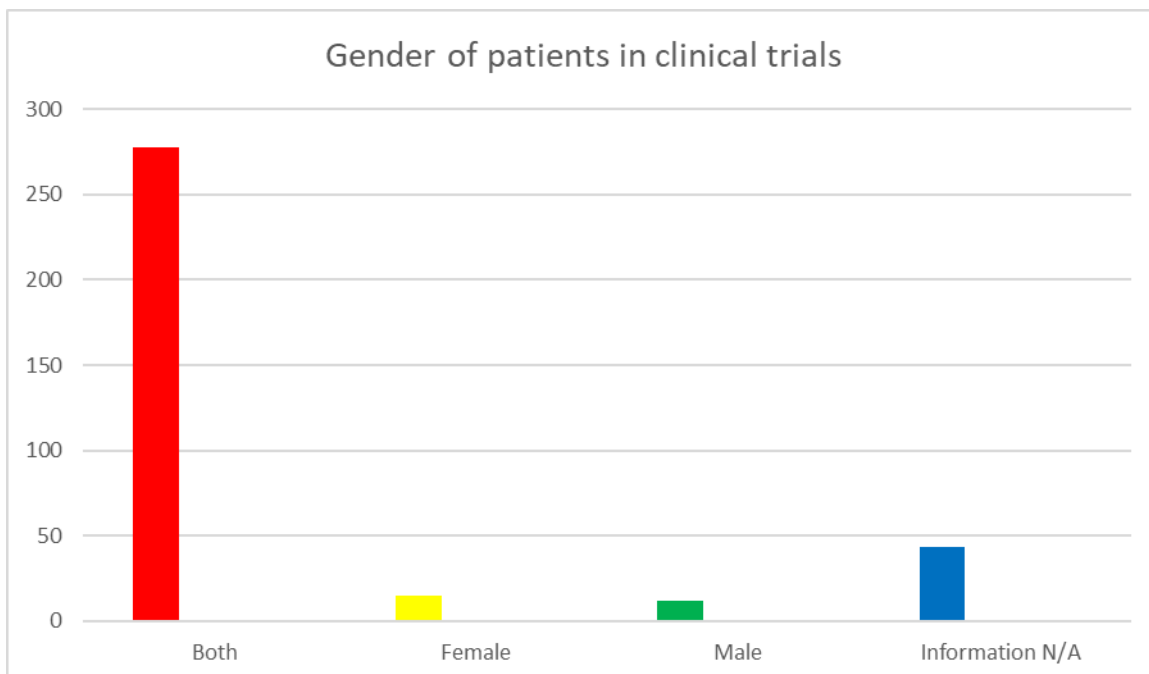




Chart 4. Gender of patients in clinical trials in Republic of Macedonia

These results are expected because according to the available data, the % of female and male population in Republic of North Macedonia is almost the same. 50.1% are males and 49.9% are females. [6]

According to the statistical analysis from the Clinical Trials Registry Platform, Republic of North Macedonia and the 348 of all the organized clinical trials are together in a group with, Ecuador with 353 organized clinical trials, Democratic People's Republic of Korea with 347 organized clinical trials and Zimbabwe with 312 organized clinical trials.

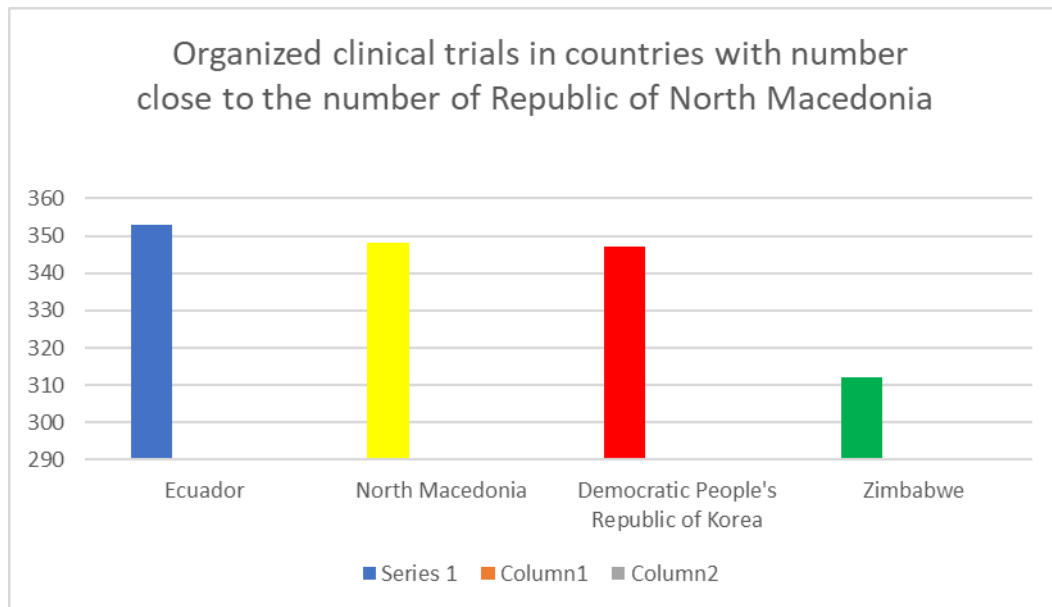


Chart 5. Organized clinical trials in countries with number close to the number of the organized in Republic of North Macedonia

According to this results Republic of North Macedonia is in a group together with Ecuador, Democratic People's Republic of Korea, and Zimbabwe. The first reported clinical trial from Ecuador is from 2000. The first reported clinical trial from Democratic People's Republic of Korea is from 2003 and the first reported clinical trial from Zimbabwe is from 2001. This result is putting Republic of North Macedonia in a bad group. Even though North Macedonia is still a developing country, the country is more developed than a lot of countries that have higher number of organized clinical trials.

## Conclusion

The study is based on statistical analysis available on the International Clinical Trials Registry Platform (ICTRP) which is available on the web page of the World Health Organization. <https://www.who.int/>. From those results and statistical analysis, it can be concluded that the number of Clinical Trials in Republic of North Macedonia from the beginning of organizing Clinical Trials until present, is low. In this period of almost 25 years only 348 clinical trials were organized.



Most of the clinical trials organized in Republic of North Macedonia are in phase 3, which is expected.

Most of the organized clinical trials in Republic of North Macedonia are not related to the diseases that has highest morbidity rate.

Most of the organized clinical trials in Republic of North Macedonia have target population of both females and males. The number of the clinical trials that have target population of only females or only males is significantly lower than the number of the clinical trials that are accepting both genders.

According to the number of organized clinical trials Republic of North Macedonia is together in a group with Ecuador, Democratic People's Republic of Korea and Zimbabwe.

From the numbers it can be noticed that Republic of North Macedonia and the authorities from the country should work harder and must improve the law regulations to attract interest from the big pharma companies and the CROs that can organize clinical trials. The fact that in Republic of North Macedonia there is organized one clinical trial more than Democratic People's Republic of Korea is overwhelming.

The authorities must work harder to improve the healthcare system and to show the clear picture of the country to potential companies that can invest in organizing clinical trials.

Organizing new potential clinical trials can be beneficial for both the country and the organizer of the studies.

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