Differences between randomized clinical trials and prospective registries. Although already well-known, it has become evident during the SARS-CoV-2 pandemic

Diferencias entre estudios randomizados y registros prospectivos. Aunque muy conocidas previamente, son fácilmente evidenciables en la pandemia SARS-CoV-2

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The different therapeutic results of pharmacological and/or interventional stress testing over certain clinical situations has been extensively described in the medical literature.

Randomized clinical trials can homogenize populations compared using the large patient selection bias they should meet before being included in the study. In most cases, 10% of the population initially studied meets the randomization criteria is eventually included in the study.

The differences reported between the populations of randomized clinical trials and prospective registries have been widely discussed by the scientific community. As a matter of fact, recently, it has been suggested to include large registries and randomized clinical trials as part of the requirements to elaborate clinical practice guidelines regarding treatment.

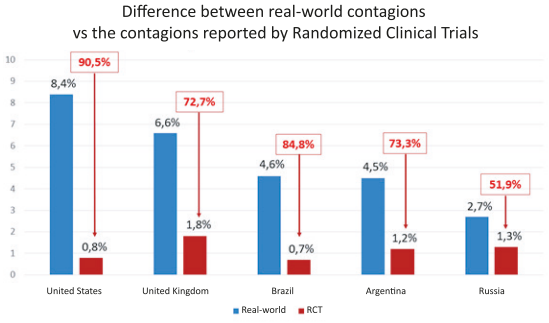

Figure 1. *Lower rate of contagions in the real-world vs the rate of contagions reported by randomized clinical trials [1-4].*

When analyzing the results of the 3 randomized clinical trials available (1-3) on different vaccines against SARS-CoV-2 and the global prevalence registry of this pandemic updated daily on the website www.worldometers.info/coronavirus (4) as of February 14, 2021, it may be interesting to try to understand these differences.

If we only take from this website (4) countries that participated in randomized clinical trials (1-3) such as the United States, Great Britain, Germany, Russia, Brazil, South Africa, and Argentina we will see differences between the number of patients infected in the real-world and the number of patients selected for the randomized trials considering the number of people who lived in each country by 2020.

As **Figure 1** shows (the real world), in each of these countries that participated in the clinical trials, the rate of infected patients per number of inhabitants was 8.5%, 6.6%, 2.7%, 2.9%, 4.6%, 2.5%, and 4.5%, respectively.

In the randomized clinical trials of the Pfizer, Sputnik V, and Astra Zeneca vaccines (1-3), the rate of people infected with SARS-CoV-2 in the placebo group was between 1% and 2.4%, suggestive of a significant reduction in the number of contagions just by being included in the randomized trial.

Regarding the number of contagions, the most significant reductions between registries and randomized trials was seen in the United States (8.4% vs 0.8%) followed by Great Britain (6.6% vs 1.8%), Brazil (4.6% vs 0.7%), and Argentina (4.5% vs 1.2%). All significant differences are shown on **Figure 1**.

In our country, if we analyze the differences between the coronavirus registry and the results of the randomized trial in the placebo group of the Pfizer vaccine, the reduction of contagion between the two is 73.4% just by selecting patients to be included in the study.

In the United States, this reduction is close to 90.5%, in Brazil, 85%, and in Russia, 52%.

In the case of Great Britain and the Astra Zeneca/Oxford vaccine, this reduction was 72.3%.

This analysis shows the huge mismatch between the so-called ***real world*** of the prospective registries and the selection of patients that is mandatory before conducting a randomized clinical trial.

However, this does not diminish the value of clinical trials that are actually essential to assess therapies, especially regarding the safety and efficacy profile of vaccines. We just wanted to draw the attention on the differences between both types of analysis in the internal medicine setting as well as inside our own specialty.

In light of this analysis, the benefit of vaccinating populations at risk of contracting COVID-19 would actually be exponentially more beneficial in absolute numbers.
In conclusion, building clinical therapeutic guidelines should include the results of the therapeutic measures implemented in the ***real world*** of our routine clinical practice, which, as we saw in our analysis, looks nothing like the clinical trial setting.

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