16. Evidence-Based Medicine and RCTs (Randomized Controlled Clinical Trials)

François Noël, August 2020

"Science, science, science". Who does not remember the former Minister of Health calling for science to guide the treatment to be used in combating COVID-19? But what exactly does it mean to choose a treatment based on Science?

Evidence-Based Medicine was originally defined by the pioneer Dr. Sackett (1996) as "*the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients*". Note that Sackett immediately emphasized that individual clinical expertise was just as important as the best available clinical evidence, and that neither was sufficient on its own: "*The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research*".

What is currently considered the gold standard for assessing the efficacy and safety of a treatment? Without a doubt, at the top of the evidence hierarchy pyramid are **Randomized Controlled Clinical Trials (RCTs), conducted in double-blind conditions,** and even more so, systematic reviews of multiple RCTs (Akobeng, 2005).

WHAT ARE THE CHARACTERISTICS OF RANDOMIZED CONTROLLED CLINICAL TRIALS?

An RCT is a type of study in which participants are **randomly assigned** to receive one clinical intervention or another (Akobeng, 2005). In simplified terms, in a two-arm parallel study, one group of volunteers receives a treatment (a test drug, for example), while the other group (the control) receives a placebo or a standard treatment (a reference drug used as a comparator). The main purpose of random assignment is to prevent selection bias by distributing baseline patient characteristics randomly across the groups, so that any difference in outcome can be attributed solely to the treatment (Akobeng, 2005). In this way, it is more likely that the two groups of volunteers will be balanced with respect to factors that may affect the outcome, such as age, sex, disease activity and disease duration. In contrast, such biases (confounding factors) that influence results are very difficult to avoid in retrospective studies, as we have seen in the many hastily published retrospective studies on the use of drugs for COVID-19 treatment.

For a clinical trial to be properly controlled, it must also be conducted under masking (**blinding**) conditions. A study is said to be double-blind when both the patient and the clinical team are unaware of which treatment is being administered. If data analysts also ignore the blinding key, the study is said to be triple-blind**.** Blinding is extremely important, since expectations regarding the advantages of one treatment over

another can influence outcomes, particularly when subjective outcome measures are used, such as pain scales, leading to so-called assessment bias.

> ***Historical note:*** The first clinical trial that correctly used randomized control groups and fully blinded data analysis was conducted in 1948, when the usefulness of streptomycin as a treatment for *Mycobacterium tuberculosis* infection was assessed (Blass, 2015).

Despite the unquestionable importance of RCTs, it must be acknowledged that some therapeutic questions do not require randomized clinical trials (Sackett, 1996):
- either because there is clear efficacy of an intervention without which the risk of death is obvious, remembering that the use of parachutes has never been proven in an RCT, as humorously pointed out by Smith and Pell (2003);
- or because such questions cannot wait for rigorous and time-consuming clinical trials, as in pandemic situations.

Since nothing is perfect in the real world, it is worth paying attention to the warning made by Ioannidis (2005), the renowned researcher (H-index = 199) who dared to question the quality of the science being produced, in an article that received more than three million views and brought the issue of (lack of) reproducibility to the forefront in both basic and clinical research. In a more recent reflection, Ioannidis (2016) reported that even proponents of Evidence-Based Medicine now suspect that something has gone off track, since industry conducts a large share of the most influential randomized trials and these are performed for its own benefit. Perhaps somewhat exaggeratedly, Ioannidis (2016) argues that most of these studies tend to ask the wrong questions, use the wrong short-term surrogate outcomes, adopt incorrect criteria for judging treatment success, and draw incorrect inferences, even while meeting regulatory agency requirements (FDA). Thus, he concludes that "*Evidence-based medicine still remains an unmet goal, worthy to be attained*".

References

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