## 19. Biomarker and Surrogate Endpoint

*François Noël, November 2020*
*(reviewed by Dr. Jaderson Lima, Aliança Pesquisa Clínica Brasil)*

Once again challenged by an event related to COVID-19, I begin this article with a question: was it appropriate to measure the reduction in viral RNA load in nasopharyngeal swabs on days 3 and 7 after the start of treatment as the primary endpoint of a clinical study to evaluate an antiviral treatment (hydroxychloroquine), as done in the article by Mitjà et al. (2020)? Or is this viral load merely a biomarker used for the indirect measurement of a clinical response to treatment? Would it not be more appropriate to use all-cause mortality within 28 days after randomization as the primary endpoint, as was done in the RECOVERY trial to evaluate the effect of dexamethasone (The RECOVERY Collaborative Group, 2020)?

In view of the numerous clinical studies published (or posted on websites, still without peer review) of questionable quality, it seems timely to define some terms specific to clinical research, within the context of clinical trials aimed at the approval of new medicines.

**Clinical endpoints** should be selected through measurements that take into account clinical relevance, feasibility of measurement, and cost. Examples of clinically relevant endpoints include death (mortality), hospital admissions, length of hospital stay, and quality of life (scales), which are variables commonly used in many clinical studies.

**Primary Endpoint:** This is the most important and relevant variable of the study (usually an efficacy variable, as well as safety and tolerability); it must be defined before the start of the study and be linked to the main objective of the research. For example, in a trial of a new anticancer drug, a primary endpoint could be the mean increase in survival time. It may be single or composite (a grouping of two or more endpoints or events). Composite endpoints are usually used to make randomized clinical trials more feasible, particularly when events or outcomes are rarer (low frequency), measurement costs are high, or long follow-up of the study cohort is required (Grady et al., 2001). Primary endpoints are generally based on the proportion of "successes" (i.e., cure or other measure of success) or on the time to or number of "failures", which may include death, disease development, or disease progression or recurrence.

**Secondary endpoints** are less important variables related to the primary objective or, alternatively, measures of effects related to secondary objectives that may provide relevant conclusions. For example, evaluation of a drug designed to prevent allergy-related deaths with concurrent measurement of improvement in quality of life.

**Biomarker and surrogate endpoint:** There is considerable confusion regarding the definitions and concepts involved in the use of biomarkers in research and clinical practice (Califf, 2018). As a general definition of a **biomarker**, one may adopt that proposed by the joint FDA-NIH task force aimed at achieving consensus definitions (FDA-NIH Biomarker Working Group, 2016): "***A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions***". An alternative definition, taking a more pragmatic view of the drug discovery and development process, was described by Lathia in 2002. According to this definition, "*a biomarker is a measurable property that reflects the mechanism of action of the molecule based on its pharmacology, pathophysiology of the disease or an interaction between the two*". A biomarker may or may not correlate perfectly with clinical efficacy or toxicity, but it may serve other purposes related to the research and development process of a drug (Lathia, 2002).

When a biomarker is recognized by a regulatory authority as sufficiently validated to be accepted as an indicator of efficacy, it is referred to as a validated surrogate endpoint (Blass, 2015). In general terms, a **surrogate endpoint** can be defined as "***a biomarker that is intended to substitute for a clinical endpoint"*** **and** ***"expected to predict clinical benefit (or harm or lack of benefit or harm), based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence***" (Atkinson et al., 2001). A validated surrogate endpoint (biomarker) can be used to support regulatory approval (marketing authorization) of a product or medical device without the need for additional studies to directly demonstrate clinical benefit (FDA-NIH Biomarker Working Group, 2016). It should be noted that only very few biomarkers meet this rigorous criterion, such as CD4+ T lymphocyte counts and measurement of viral RNA level and load for HIV disease progression.

Surrogate endpoints are often used because they are cheaper or easier to measure, but they are weaker than more robust indicators, such as survival time (a primary clinical endpoint).

It should also be noted that biomarkers are used to assess the safety of the drug or product under test and, in this context, are very effective tools in clinical trials, as they can provide early evidence that a drug candidate may present potential risk or adverse events (Blass, 2015). Moreover, different types of biomarkers have been classified according to their possible applications (Califf, 2018).

References

Atkinson, A. J.; Colburn, W. A.; DeGruttola, V. G.; DeMets, D. L.; Downing, G. J.; Hoth, D. F. et al. Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework. *Clin. Pharmacol. Ther.* 69(3):89-95, 2001.

Blass, B.E. - Chapter 10 - Translational Medicine and Biomarkers. Pp.415-446. *In:* Basic Principles of Drug Discovery and Development. ISBN 978-0-12-411508-8, 2015 Elsevier Inc., 2015.

Califf, R.M. Biomarker definitions and their applications. *Exp. Biol. Med.* 243: 213–221, 2018.

FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Silver Spring (MD): Food and Drug Administration (US); Bethesda (MD): National Institutes of Health (US), www.ncbi.nlm.nih.gov/books/NBK326791/ (2016, acesso em 08/09/2020).

Grady D., Cummings S.R., Hulley S.B. - Chapter 11 - Designing an Experiment: Clinical Trials II. Pp. 157-174. *In*: Designing clinical research: an epidemiological approach. 2nd ed. Stephen B. Hulley (Ed.) et al. ISBN 0-7817-2218-7, 2001. Lippincott Williams & Wilkins, PA, USA.

Lathia, C. D. Biomarkers and Surrogate Endpoints: How and when Might They Impact Drug Development? *Dis. Markers. 18:* 83–90, 2002.

Mitjà O., Corbacho-Monné M., Ubals M., Tebe C., Peñafiel J., Tobias A. et al., Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial. *Clin. Infect. Dis*. 2020 Jul 16

The RECOVERY Collaborative Group. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *N. Engl. J. Med.* 2020 Jul 17.