Prospective Systematic Data Collection in Early COVID-19 patients: A Protocol for Individualized Treatment and Outcomes Research

Author: **Flávio Dantas**

Corresponding author contact details: **Prof. Flávio Dantas. M.D., Sc.D.**

E-mail: dantasoliveiraflavio@gmail.com

Affiliation: **Department of Clinical Medicine, Federal University of Uberlândia, Brazil (retired professor)**

ORCID: https://orcid.org/0000-0002-2756-2412

Conflict of interest: **None**

ABSTRACT

Human infection caused by the SARS-CoV-2 virus, called COVID-19, is a new pandemic with devastating effects worldwide. Science seeks the rational and systematic explanation of phenomena. In pandemics, decisions on prevention and treatment of people should be consistently taken, supported by scientific knowledge and ethical principles to produce more good than harm. At first, prospective observational studies to systematically collect patient data, correlating protective or therapeutic interventions with outcomes to assess effectiveness and safety, should be prioritized as the most appropriate type of study. The proposed protocol in this article aims to provide doctors with information on the reduction of harm in early COVID-19 patients by applying individualized interventionist or expectant therapeutic strategies, respecting the autonomy and preferences of physicians and patients in clinical decision-making. The evaluation of the clinical status, besides laboratory confirmation of COVID-19, comprises an individualized symptom score for each patient, a global self-perception scale of the severity of the disease, a clinical progression scale developed by the WHO for clinical studies in COVID-19 and, at the first consultation, doctors´ overall impression on the clinical prognosis. The analysis of anonymized data should preferably use descriptive and inferential statistical resources. The case report form is available for free use in the protocol, along with examples of patient informed consent forms for the prescription of *off-label* medications and authorization to use the data. Their results may be useful to indicate interventions that are candidates for efficacy trials, in randomized controlled trials, with a higher chance of success. It respects the autonomy and preferences of doctors and patients to decide the best options for treatment in uncertain situations. It also allows the gathering of useful information for future more rigorous clinical trials, trying to link science, ethics, and personal clinical experience.

Keywords: COVID-19; Treatment outcome; Data collection; Pharmaceutical Preparations; Outcome Assessment, Health Care

INTRODUCTION

"Medicine is a *science* of uncertainty **and** an *art* of probability", according to a famous quote by William Osler, considered by many to be the father of modern medicine and bedside medical education. Medicine, as *science,* tries to discover useful generalizations to benefit other people, while as *art* is guided by personalized care and consideration of individual human needs.

The implications of this dissonance emerge in the assessment of pharmacological treatments in medicine. It is marked by a *tension* between the implementation of strategies based on *biomedical* (or specialized) models and *biopsychosocial* (or holistic) models[1]. The biomedical model emphasizes efficacy, statistical significance, internal validity and group analysis while the biopsychosocial model prioritizes effectiveness, clinical relevance, external validity and analysis of individual results[2] [3] . On the one hand, medical researchers want to know the *efficacy* of the drug, which refers to the extent to which a specific intervention, procedure, regime or health service produces a benefit under *ideal conditions*. On the other hand, *effectiveness* indicates the degree to which a specific intervention, procedure, regimen or health service produces what is expected for a certain population when used under *routine circumstances* [4]. In general, efficacy is determined through randomized controlled trials, with stricter inclusion and exclusion criteria. Effectiveness requires a wider variety of strategies, including observational studies (cohort, case-control) and even randomized studies comparing different medical treatments in real operational environments[5] .

Physicians need to make decisions that require as much certainty as possible in situations with unchangeable uncertainties. These uncertainties have immutable roots. The most important rests on the nature of Human Beings. Each person, **at the same time,** is *equal* to the others by law, *similar* to some others in various aspects, but is *unique* and utterly different from all other people. Besides, physicians as professionals have different skills, values and experiences that could lead to divergent decision-making for the same situation, due also to the rapid changes in knowledge and the technological environment that can impact their practice. COVID-19 is an excellent example of this change in standards as new information is incorporated over time, in an environment loaded with increasing politicization of technical decisions in the health area, which should be guided by scientific and ethical standards, without deviations of conduct.

Evidence-Based Medicine (EBM) considers the study design as a decisive factor to judge the scientific value of medical research. In the area of therapy, randomized clinical trials (RCTs) or systematic reviews of RCTs were considered the best designs until September 2000, when individualized randomized studies (n-of-1) were added at the top of the ranking of scientific evidence[6] in terms of validity. This change happened after a clear awareness of EBM leaders that RCTs, despite its strong internal validity, have insufficient external

2

validity, with low generalization capacity for most patients routinely treated. These patients do not fit the rigorous and highly selective criteria of inclusion and exclusion in RCTs, thus lacking applicability in many cases. A year earlier, a paper that analyzed 8,085 primary care research articles published by 85 medical journals over six months concluded that only 2.6% of the articles contained significant evidence that was related to patients usually seen in primary care. The authors were concerned about clinical outcomes that could modify the practice in primary care. They also showed that only 10 of the 85 researched journals published 50% of the papers[7]   Clinical applicability (or external validity) is an attribute considered more important by those who practice medicine and need to apply scientifically generated knowledge to each patient in particular.

RCTs are sometimes unnecessary, inappropriate, impossible or inadequate [8] . They may have hidden bias[9] or other systematic bias favouring products made by the companies funding the research[10] that could undermine the confidence in science. For COVID-19, it would not be reasonable and proportionate to require RCTs to support treatment decisions soon after the discovery of the disease. The indiscriminate acceptance of the RCT as a guideline for minimally acceptable conclusions in therapeutic efficacy has led public health managers, institutions responsible for boosting medical research and editors of medical journals, not rarely financially dependent on sources with interest in the results, to consider only this expensive category of study, denying the potential scientific value of well-conducted observational studies. In pandemics such as COVID-19, systematic documentation of a cohort of patients, combined with the correlation of relevant clinical outcomes, can be a less expensive, quick and more accessible way to obtain reliable data and to make better-informed decisions. Based on the accumulated clinical observation of numerous physicians in various places around the world, some promising therapeutic options could be later assessed, if necessary, in RCTs.

THE PROTOCOL PROPOSAL

Prospective data collection and evaluation of significant clinical outcomes, after interventions prescribed by numerous physicians in their daily routine, is a viable strategy to obtain a large amount of good quality information on the effects of different pharmacological and non-pharmacological interventions in suspected or confirmed COVID-19 patients. The proposal must be oriented to the benefit of patients and the improvement of health care from a collective perspective, open to different and competing interventions under the responsibility of physicians, and evaluated by simple and rigorous measurement instruments or clinimetric tools for the evaluation of clinical outcomes[11].

3

The main assumptions of the proposal are:

i.   Human Beings are at the same time similar to some others **and** different from all other Human Beings

ii. Medical practice is effective if it produces more benefits than harms

iii. Physicians have the right to decide on the best treatment for assisted patients and, in situations of high uncertainty, should never give up their legitimate and legal prerogative to take their decisions, for which they are always responsible. They must make decisions, after the informed consent of their patients, according to their values, knowledge and experience

iv. For some doctors, it is better something dubious than nothing (skeptical empiricism) and, for others, it is better nothing than something dubious (therapeutic nihilism): in both cases the responsibility for the patient is equal, and the patient deserves careful monitoring with documentation of the case results

v.   For patients, the guidance to do something under medical supervision, in general, is better than nothing, mainly if the recommendations are simple, safe, inexpensive and with reasonable clinical plausibility

vi. There is no better and exclusive scientific study design to be accepted as evidence in highly uncertain and urgent situations such as COVID-19. Observational and experimental studies can contribute, at their own pace and time, to better explain and help to make appropriate clinical decisions entirely in the best interest of patients.

Ethics

The protocol attempts to meet the ethical requirements necessary for research in the pandemic, as recommended by the World Health Organization (WHO) and the World Medical Association (WMA). For each patient, a consent form should be obtained with clarifications on interventions with the use of drugs without approved indications in COVID-19, with an additional authorization clause for the anonymized use of clinical information collected from individual care. Informed consent forms should also be obtained for cases of expectant conducts using only symptomatic medications, or even without any prescription medication, according to the physician's particular decision. It complies with WHO guidelines for the prescription of *off-label* drugs (without indication in the package leaflet) in patients with COVID-19, outside clinical trials, with the need to be well documented[12]. It conforms to paragraph 37 of the Helsinki Declaration. It recommends that "the physician may use an unproven intervention if in his judgment it offers hope of saving life, restoring health or relieving suffering", adding that such new information "*must be recorded and, where appropriate, made publicly available*[13]." Also, guideline 10 on health-related research involving

Humans, by the Council for International Organizations of Medical Sciences in collaboration with WHO, opens the possibility that the research ethics committee may approve a modification or waiver of informed consent to research. The waiver could be approved if the research would not be feasible or practicable to carry out without the waiver or modification, if the research has important social value and if the research poses no more than minimal risks to participants. The protocol is centered on respect for the autonomy of physicians and patients, with their preferences and values, taking advantage of all potentially useful and available therapeutic procedures that could have favorable effects in suspected or confirmed patients with the initial diagnosis of COVID-19.

Outcomes

Clinical outcomes come from the application of scales with objective descriptors on the disease and scores constructed from subjective perceptions of patients, in addition to medical observation. The main outcomes include (1) change in the total score of individualized COVID-19 symptoms presented by each patient; (2) Clinical progression assessed by the WHO scale[14] for clinical trials of COVID-19; (3) Global self-perception scale of disease severity; (4) Number and severity of adverse effects; (5) Proportion of hospitalized patients, particularly for those considered to be at high risk in the first visit; (6) Time to resolve symptoms and return to regular activities after the adoption of the interventional or expectant conduct by the physician and (7) Time to begin a favorable response of the organism, with reduction of discomfort, after the first medical consultation and adherence to therapeutic orientations.

Elements of the clinical protocol

Each clinical protocol should be structured, taking into account the following criteria: simplicity, feasibility and methodological quality. It should contain a minimum number of mandatory elements (inclusion criteria, general and clinical patient information, treatment and evaluation of outcomes) and others that could be aggregated according to local conditions and the possibility of implementation. It should improve clinical art, aligned with the conceptual framework proposed by Feinstein [15] of *Clinimetry.* Table 1 summarizes the previous elements, as well as provides an example of the suggested scales for evaluation of patients in the initial phase of COVID-19:

Area	Mandatory items	Example of assessment scales
Admission of patients	- Clinical and epidemiological information with laboratory-confirmed COVID-19 (RT-PCR) - Onset of symptoms	**INDIVIDUALIZED SYMPTOM SCORE FOR EARLY COVID-19 PATIENTS**

Current signs and symptoms: Identify, in the box next to each symptom, its intensity in the patient using **0** if it is absent, **1** if it is mild, **2** if it is moderate and **3** if it is severe, calculating the score at the end.

A (general)	Grade	**B** (local)	Grade	**C** (local and other)	Grade
☐ Fatigue		☐ Headache		☐ Nausea or Vomiting	
☐ Fever		☐Conjunctivitis		☐ Abdominal pain	
☐ Myalgia		☐ Rhynorrhoea		☐ Diarrhoea	
☐ Chill		☐ Sore throat		☐ Other (specify)	
☐ Ageusia		☐ Cough			
☐ Anosmia		☐ Dyspnoea			
TOTAL SCORE (A+B+C) =					

Recording of clinical information — Mandatory items: -Comorbidities -Degree of severity for each symptom - Use of other medicines for treating previous health problems

WHO CLINICAL PROGRESSION SCALE FOR COVID-19

Patient state	Descriptor
Uninfected	No viral RNA detected
Ambulatory mild disease	Asymptomatic, viral RNA detected
Ambulatory mild disease	Symptomatic, independent
Ambulatory mild disease	Symptomatic, needs assistance
Hospitalized moderate disease	No oxygen therapy
Hospitalized moderate disease	Oxygen by mask or nasal prongs
Hospitalized severe disease	Non-invasive ventilation or high-flow oxygen
Hospitalized severe disease	Intubation and mechanical ventilation, pO2/FiO2 _150 or SpO2/FiO2 _200
Hospitalized severe disease	Mechanical ventilation pO2/FIO2 <150 (SpO2/FiO2 <200) or vasopressors
Hospitalized severe disease	Mechanical ventilation pO2/FiO2 <150 and vasopressors, dialysis, or ECMO
Dead	Dead

Treatment — Mandatory items: -Description of all medicines in use as well as non-pharmacological interventions -Dosage regimen -The minimum time for patient follow-up

ECMO=extracorporeal membrane oxygenation. FiO2=fraction of inspired oxygen. NIV=non-invasive ventilation. pO2=partial pressure of oxygen. SpO2=oxygen saturation. ***If hospitalised for isolation only, record status as for ambulatory patient.

Evaluation of therapeutic outcomes — Mandatory items: -Measurement of clinical progression -Changes in Individualized symptom score -Description of adverse effects and complications

GLOBAL SELF-PERCEPTION SCALE ON SEVERITY FOR COVID-19

Globally, how ill does THE PATIENT feel (s)he is NOW?

	Extremely ill		A little ill
	Seriously ill		A little bit ill, almost cured
	Very ill		Disease-free, cured, back to normal
	Moderately ill		

Table 1. Essential elements of the protocol and examples of scales for evaluation of therapeutic results

Data analysis

The appraisal of outcomes from observational and non-randomized studies usually requires an exploratory data analysis perspective[16]. Data description strategies should be performed comprehensively, through graphs and charts, or applying influence analysis[17] or sensitivity analysis[18]. Data collection can indicate the most used pharmacological or non-pharmacological interventions, their associated use (or not), dosage regimen, adverse effects and clinical complications. From the exploratory point of view (generation of hypotheses), preliminary associations between the primary therapeutic outcomes for each set of medical interventions may be useful to suggest more effective treatment strategies, as well as to identify possible adverse effects of treatment. The systematic documentation could also help to detect the occurrence of possible side effects resulting from the concomitant use of other drugs with those prescribed for the treatment of COVID-19. Other information such as the existence of specific comorbidities, age, gender, time of onset of symptoms or presence of some severe symptoms in the initial phase may be later correlated with clinical outcomes for a possible proposition of clinical prognostic scales.

DISCUSSION

Science is a social, cumulative and complex activity that requests maximum transparency and strict honesty for its development. Respect for human beings is the only absolute principle of moral life, to be exercised daily by physicians in clinical practice and research. Excellent and useful medical science begins with careful observation of the facts by physicians. It continues with rigorous documentation, unprejudiced interpretation of data and impartial conclusions for better clinical decisions, followed by public diffusion.

Double standards in medical research are ethically unacceptable, from planning to publication. In this pandemic, one of the first RCTs published in the medical literature was a Brazilian RCT in critically ill COVID-19 patients attended in a public hospital. Patients received daily 2g of chloroquine diphosphate for ten days. At that time, this regimen was almost triple to the dose recommended by Chinese Health Authorities for moderate to severe pneumonia COVID-19 patients[19]. The authors halted the trial after 13 days due to a 39% lethality rate (more than double in the group using the recommended dose), shown later to be 49% in patients admitted to Brazilian Intensive Care Units in public hospitals[20]. An accompanying editorial in the Journal of the American Medical Association stated that "poorly conducted or poorly reported science is contrary to the public interest"[21]. There is no way to disagree with this statement, although a nuclear attribute common to medical science and art is **ETHICS,** notably the virtue of *prudence.* A proposed equation for Ars Medica (AM) reads **AM = E [EBM+(E_xBM)^2]**, where **E** is Ethics, and **E_xBM** refers to Experience-Based Medicine [22] . Without Ethics, there can be no good medicine or even medicine as a whole.

COVID-19 is a disease with a broad clinical presentation and uncertain prognosis in which there is currently no scientific proof of the efficacy of drug treatment or vaccine prophylaxis. Given the uncertainty caused by pandemic, the systematic and prospective collection of diagnostic and therapeutic data and information by physicians working in primary care, in observational studies or well-conducted cohorts, should be prioritized. The correlation of the findings of individualized treatments with disease progression, subjective appraisal of disease severity and evolution of suffering could help in recognizing disease patterns as well as more effective and safer interventions, which later may be the subject of RCTs.

To diagnose and treat infectious diseases, and in particular viral diseases, physicians often consider two general strategies: increase the body's defense power and inhibit the power of aggression of the virus as soon as possible, either by inactivation or by reducing its power of replication in the body. It seems that only the last strategy is being the object of attention in the current pandemic, with an active search for effective pharmacological interventions. With the common intention of doing more good than harm, some doctors and health authorities argue that, at an early stage of COVID-19, often no treatment is the best treatment, and patients should be isolated in their homes until more severe symptoms develop. In contrast, others argue about the importance of early empirical treatment and the careful observation of their results to prevent the 'cytokine storm' and the need for hospitalization in wards or intensive care units. Up to now, neither position has sufficient and robust empirical or experimental evidence for a reliable conclusion in favor of the beliefs or opinions strongly argued upon a disease that has its characteristics and is quite different from other pandemics.

A recent systematic review concluded that there are convincing effects of doctor-patient communication in clinical practice on objective and subjective health outcomes[23]. When physicians clearly explain the reasons for prescribing an off-label drug and obtain the consent of patients for its use and data documentation, they have an opportunity to explore patients' preferences and even to propose non-pharmacological interventions[24], as stated in the protocol. Even if the drugs prescribed as *off-label* in the initial phase of COVID-19 were shown later in RCTs as having no specific effects against SARS-CoV-2, the physician could argue that he did his best and got the informed consent of patients, including for documentation of their outcomes, and that by proceeding in this way added the contribution of positive effects of the context of the doctor-patient relationship, associated with better therapeutic effects.

On the other side, these *off-label* drugs could later prove to be effective in rigorous studies. Thus complaints may be proposed based on the increased risk of death or harm in courts or professional regulatory bodies due to the deliberate non-prescription after alarming safety results, as showed in the Brazilian study.

Complaints could also direct against health authorities or pharmaceutical professionals who deliberately obstructed or hindered the dispensing of later-proved beneficial drugs prescribed by doctors. In some instances, it could affect doctors who, grossly, have been negligent or treated the patient without consideration, or interrupted the care of suspected or diagnosed patients with COVID-19 asking for some antiviral drug at the beginning of the disease, without ensuring continuity of care by another physician. Medicine is not Mathematics; the rule used in the measurement of pain in visual analog scales does not have the desired millimetric accuracy because each patient lives his pain in a personalized and variable way over time. Patients are not numbers, and emotions should be taken into account to restore patients' health or alleviate their suffering.

Since its birth, EBM has three pillars, according to its founders. The clinical expertise of the physician and the values and preferences of patients are the other two pillars that must be cogently integrated into the best evidence of research[25]. In observational studies, there is an addition of nonspecific effects (so-called "placebo") that could lead to better therapeutic results by encouraging the use of all procedures that can help patients and respect their preferences. It includes proper medical communication and the use of empathy to decide on the best intervention, as well as making specific educational recommendations (e.g., smoking cessation) and non-pharmacological procedures (such as regular gargling and nasal washing). This type of medical attitude is rarely adopted in RCTs for drug tests. The main objective of RCT is to observe whether the drug alone could explain the results, with extensive use of procedures that reduce as much as possible the influence of other factors that could affect the results or cause confusion in the analysis of the results. In the case of gargling and nasal washing as a possible procedure to help in the initial fight against invasion by SARS-CoV-2, only five articles appeared in PubMed, despite being indicated by pediatricians and otorhinolaryngologists for the care of upper airway infections. It may be a vital procedure since the nasopharynx and oropharynx appear to be the main sites of the initial installation and replication of the virus. A recent study concluded that nasal washing and gargling, with home-made hypertonic saline solution, reduced by two and a half days the duration of the cold caused by the common coronavirus [26] [27] . This simple and inexpensive procedure, done early, could help reduce viral load in patients, thus reducing the severity of the disease and possibly its rate of transmissibility, and should be considered as another therapeutic option for COVID-19.

The proposed protocol has several utilities and can be easily modified or adapted by any physician or health manager interested in freely using it. It is especially suitable for publicly funded health systems, such as the Brazilian SUS or the National Health Service (NHS) in the United Kingdom. By prospectively collecting data in a cohort of patients with COVID-19, it complies with the WHO and WMA **documentation** requirements. It

may be useful for early assessment of the severity of COVID-19 by correlating patient age, vital signs (e.g., fever), more intense symptoms, comorbidities, and other health indicators with subsequent clinical outcomes, including hospitalization and death. It could also be useful to record the results in suspected or confirmed patients of COVID-19, under medical supervision, who do not wish to ingest drugs with supposed antiviral action and prefer to use symptomatic medications or only non-pharmacological interventions, such as gargling and nasal washing. Such outcomes could be, even in a rudimentary manner, compared with those of patients in which specific pharmacological interventions were performed for COVID-19 (such as the use of chloroquine diphosphate/hydroxychloroquine, azithromycin, zinc sulfate, ivermectin, nitazoxanide, homeopathic medicines, phytomedicines or preparations with medicinal plants, Traditional Chinese Medicine procedures or other regionally suggested alternative treatments in different countries), associated or not with non-pharmacological interventions. A more sophisticated prognostic scale, with weighted criteria, could be developed with the increasing inclusion of new patients in the database, helping to more accurately predict the risk of severe COVID-19 from the initial phase [28]. A full version of the proposal, with the case report form (CRF) and examples of informed consent terms (with or without authorization to use clinical data), is freely available in https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1102394. The electronic CRF in English (google form) can be accessed at https://forms.gle/B7CFd3Nm4oywk9T49 and in Portuguese at https://forms.gle/Wu9rRJBoh9ZZ22iQA and can be copied or modified.

It also has some drawbacks related to the compliance of doctors to fulfill the printed CRF or the electronic form, and in the admission and follow up of all sequentially included patients to reduce bias. It is time-consuming, particularly in a pandemic where time is a critical resource for doctors and health professionals. Although the filling is simple, it needs additional time from the doctor, particularly in a pandemic where time is a critical resource for physicians and health professionals. It cannot produce a conclusion of efficacy of a given procedure, only of effectiveness in a specific context of the set of procedures adopted by the doctor with the consent of the patient.

It may be that, despite the overall effectiveness of the set of interventions, one of them does not have any direct specific effect, which would require the planning of additional studies. According to Shapiro & Shapiro, "the history of medical treatments is characterized by the introduction of new placebos by successive generations of physicians, often accompanied by a vehement and vituperative denunciation of opposing physicians who prefer other placebos". Moreover, they conclude that "the strong beliefs of physicians, objectively unjustified, suggest that they have been as defensive about their treatments throughout medical history as they are today". Later the authors mention some studies that "demonstrate that physicians attribute the use of placebos to other physicians three times as often as they attribute it to themselves"[29].

Patients are pleased if they are assisted by competent physicians in which they can trust, with physicians being responsible for prescribing (or not) safe and potentially effective interventions to benefit patients. The prescription (or not) of drugs at the beginning of COVID-19 with the supposed antiviral effect is an inalienable medical decision that should be freely made, given the uncertainty and the need to do more good than harm, and without any discrimination.

There is a political and unhealthy debate among physicians and health scientists in Brazil, and in other countries, about the use of repurposed drugs for early treatment of COVID-19. There is still no substantial evidence, in the initial phase of viral replication, to support the early use of drugs with apparent antiviral effect or for the recommendation of the use of symptomatic drugs and to become isolated at home after the confirmation of the disease. Patients are influenced by the pharmaceutical industry and by doctors themselves to use some medication when they feel sick, and this habit continues in pandemics. When taking health decisions, the autonomy and preferences of patients and physicians must be respected.

There is an urgent and growing need to individually empower physicians, making them again the protagonists in independently building medical science-based in careful and honest experiential learning and rigorous clinical studies. Osler preached the union between homeopathic doctors and allopaths, in his farewell address to American doctors before moving to Oxford in 1905, stating that "long past the time when a difference of belief in the action of drugs—the most uncertain element in our art!— should be allowed to separate men with the same noble traditions, the same hopes, the same aims and ambitions"[30]. Perhaps this is the right time for the practice of tolerance, honesty, equanimity and prudence in the development of observational studies and in the collection of useful clinical data by physicians, supported by public health authorities and funding bodies, to take conscious and scientific clinical decisions, better informed and less harmful, that may benefit, even in the early stages of the disease, patients with COVID-19 and society as a whole.

References

[1] Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196(4286):129-136. doi:10.1126/science.847460

[2] Dantas F. Evaluation of therapeutic results of homeopathy: a proposal for the Brazilian reality. Rev Homeop. 2003; 68(1-2):47-62.

[3] Diamond GA, Denton TA. Alternative Perspectives on the Biased Foundations of Medical Technology Assessment. Ann Intern Med 1993:118:455-64.

[4] Last JM (ed). A dictionary of epidemiology. 3.ed. New York: Oxford University Press, 1995. p. 52.

[5] Simon G, Wagner E, Vonkorff M. Cost-effectiveness comparisons using "real world" randomized trials: the case of new antidepressant drugs. J Clin Epidemiol 1995; 48: 363-373.

[6] Guyatt GH et al. For the Evidence-Based Medicine Group. Users' Guides to the Medical Literature. XXV: Evidence-Based Medicine: Principles for Applying the Users' Guides to Patient Care. JAMA 2000; 284: 1290-6.

[7] Ebell MH, Barry HC, Slawson DC, Shaughnessy AF. Finding POEMs in the medical literature. J Fam Pract. 1999 ; 48(5):350-5

[8] Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ 1996; 312:1215-8.

[9] Gøtzsche PC. Methodology and overt and hidden bias in reports of 196 double-blind trials of nonsteroidal antiinflammatory drugs in rheumatoid arthritis [published correction appears in Controlled Clin Trials 1989 Sep;50(9):356]. Control Clin Trials. 1989;10(1):31-56. doi:10.1016/0197-

[10] Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ. 2003;326(7400):1167-1170. doi:10.1136/bmj.326.7400.1167

[11] Woolf SH, Baptist RN, Anderson GM, Logan AG, Wang And. Assessing the clinical effectiveness of preventive maneuvers: analytic principles and systematic methods in reviewing evidence and developing clinical practice recommendations: a report by the Canadian Task Force on the periodic health examination. J Clin Epid 1990; 43:891-905

[12] World Health Organization. Off-label use of medicines for COVID-19: Scientific brief. Available in: https://www.who.int/news-room/commentaries/detail/off-label-use-of-medicines-for-covid-19 . Accessed 09/04/2020.

[13] World Medical Association. Declaration of Helsinki of the World Medical Association: Ethical Principles for Medical Research involving Human Beings.

[14] WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research [published online ahead of print, 2020 Jun 12]. Lancet Infect Dis. 2020; S1473-3099(20)30483-7. two:10.1016/S1473-3099(20)30483-7

[15] Feinstein AR. Clinimetrics. New Haven: Yale University Press, 1987.

[16] Tukey JW. Exploratory data analysis. Reading, MA: Addison-Wesley 1977

[17] Rosenbaum PR. Discussing hidden bias in observational studies. Ann Intern Med 1991; 115: 901-5.

[18] Greenland S. Randomization, Statistics, and Causal Inference. Epidemiology 1990; 1:421-29.

[19] National Health Commission of the People´s Republic of China. Notice on adjusting the usage and dosage of chloroquine phosphate in the treatment of new coronavirus pneumonia. Released in 28/02/2020. Available in http://www.nhc.gov.cn/xcs/zhengcwj/202002/0293d017621941f6b2a4890035243730.shtml. Accessed in 23/08/2020.

[20] AMIB. UTIs Brasileiras: Registro Nacional de Terapias Intensivas. Available in http://www.utisbrasileiras.com.br/sari-covid-19/benchmarking-covid-19/ . Accessed in 23/08/2020.

[21] Fihn SD, Perencevich E, Bradley SM. Caution Needed on the Use of Chloroquine and Hydroxychloroquine for Coronavirus Disease 2019. Editorial. JAMA Netw Open. 2020;3(4): e209035. doi:10.1001/jamanetworkopen.2020.9035. Published online April 24, 2020. Available in https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2765500

[22] Porto CC, Dantas F. AC=E [MBE + (MBV)^2] : A mathematical equation for the clinical art of healing. Journal of the Brazilian Society of Medical Clinic 2003; 1(2):33-34.

[23] Riedl D, Schüßler G. The Influence of Doctor-Patient Communication on Health Outcomes: A Systematic Review. Z Psychosom Med Psychother. 2017;63(2):131-150. doi:10.13109/zptm.2017.63.2.131

[24] Schenker Y, Fernandez A, Lo B. Placebo prescriptions are missed opportunities for doctor-patient communication. At J Bioeth. 2009;9(12):48-50. two:10.1080/15265160903234144

[25] Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-Based Medicine: How to practice and teach EBM. 2 ed. Edinburgh: Churchill Livingstone, 2000.

[26] Ramalingam S, Graham C, Where J Morrice L Sheikh A. Hypertonic Saline Nasal Irrigation and Gargling Should Be Considered as a Treatment Option for COVID-19. J Glob Health 2020 Jun;10(1):010332. two: 10.7189/jogh.10.010332

[27] Ramalingam S, Graham C, Where J Morrice L Sheikh A. A pilot, open labelled, randomised controlled trial of hypertonic saline nasal irrigation and gargling for the common cold. Scientific Reports 2019; 9:1015. https://doi.org/10.1038/s41598-018-37703-3

[28] Zhou Y, He Y, Yang H, Yu H, Wang T, Chen Z et al. Development and validation a nomogram for predicting the risk of severe COVID-19: A multi-center study in Sichuan, China. PLoS One. 2020;15(5): e0233328. Published 2020 May 18. doi:10.1371/journal.pone.0233328

[29] Shapiro AK, Shapiro E. The powerful placebo: from ancient priest to modern physician. Baltimore: John Hopkins University Press, 1997. p.59

[30] Osler W. Aequanimitas, 3rd ed. New York: Blakiston, 1953.