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Mota, Daniel Marques; Kuchenbecker, Ricardo de Souza
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Considerations on the use of scientific evidences in times of a pandemic: the case of COVID-19

Considerações sobre o uso de evidências científicas em tempos de pandemia: o caso da COVID-19

Daniel Marques Mota[I,*]

Ricardo de Souza Kuchenbecker[II]

ABSTRACT

Making better use of available evidence on drugs and non-pharmacological therapies in the context of the COVID-19 pandemic is critical for minimizing suffering and saving lives. This debate aimed to present considerations about the concept of evidence, the evidence hierarchy and the types of scientific evidence, seeking application in the context of the COVID-19 pandemic, with regard to the use of therapies for prevention and treatment of the disease. Initially, we made a brief introduction on the topic, highlighting the existence of doubts regarding the use of various drugs, as well as whether those available to combat other diseases can be safe and effective in the treatment of COVID-19. Then, we present some definitions about evidence, reinforcing that an exact definition depends on the context in which it will be used, and may even have a broad or restrictive connotation. Next, we mention that the evidence is classified in a hierarchical order, illustrated by means of a pyramid, according to the design of the study employed, one of the important markers to define the quality of the evidence. Emphasis is given to the evidence from the expert opinion, which is based on beliefs built on the basis of theory and non-systematic learning. Soon after, we resorted to basic concepts about three types of scientific evidence (direct, indirect and preliminary evidence) to explain the divergences between expert opinions. We conclude with comments and reflections on the need to define reasonably acceptable criteria for the use of evidence, for now available, in times of a pandemic, such as COVID-19.

KEYWORDS: COVID-19; Drug Effects; Evidence-Based Medicine; Pandemics; SARS-CoV-2

RESUMO

Fazer o melhor uso das evidências disponíveis sobre medicamentos e terapias não farmacológicas no contexto da pandemia da COVID-19 é fundamental para minimizar os sofrimentos e salvar vidas. Este debate objetivou apresentar considerações sobre o conceito de evidência, hierarquia das evidências e os tipos de evidências científicas, buscando aplicação no contexto da pandemia da COVID-19, no que tange ao uso de terapias para prevenção e tratamento da doença. Inicialmente, fizemos uma breve introdução sobre o tema, destacando a existência de dúvidas quanto ao uso de vários medicamentos, bem como se aqueles disponíveis para combater outras doenças podem ser seguros e eficazes no tratamento da COVID-19. Em seguida, apresentamos algumas definições sobre evidência, reforçando que uma definição exata depende do contexto em que será usada, podendo, inclusive, ter uma conotação abrangente ou restritiva. Na sequência, mencionamos que as evidências são classificadas em uma ordem hierárquica, ilustrada por meio de uma pirâmide, conforme o desenho do estudo empregado, um dos marcadores importantes para definir a qualidade da evidência. É dado destaque à evidência advinda da opinião de especialista, a qual está fundamentada em crenças construídas com base em teoria e aprendizagem não sistemática. Logo a seguir, recorremos a conceitos básicos sobre três tipos de evidências científicas (evidências diretas, indiretas e preliminares) para explicar as divergências entre opiniões de especialistas. Concluímos com comentários e reflexões sobre a necessidade de definir critérios razoavelmente aceitáveis para uso de evidências, por ora disponíveis, em tempos de pandemia, a exemplo da COVID-19.

PALAVRAS-CHAVE: COVID-19; Efeitos dos Fármacos; Medicina Baseada em Evidências; Pandemias; SARS-CoV-2

[I] Agência Nacional de Vigilância Sanitária (Anvisa), Brasília, DF, Brasil

[II] Programa de Pós-graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brasil

* **E-mail:** dmarques2003@yahoo.com.br

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INTRODUCTION

The use of drugs and other non-pharmacological therapies to prevent or treat diseases based on their best available scientific evidence obtained through systematic research is widely accepted, both as good clinical practice and for health guidelines and policies. However, there are severe and complex public health situations of unexpected occurrence and rapid geographic spread that, throughout their evolution, does not rely, effectively, on evidence produced from these researches[1,2,3].

Currently, with the COVID-19 pandemic, a disease without specific treatment and that is caused by the Severe Acute Respiratory Syndrome 2 coronavirus (SARS-CoV-2)[2,3,4], doubts have been raised regarding the use of several drugs, as well as whether those available to fight other diseases can be safe and effective in their treatment. n these conditions are the drugs that inhibit the angiotensin-converting enzyme and the angiotensin receptor blockers; nonsteroidal anti-inflammatory drugs, such as ibuprofen; antiparasitic drugs, such as hydroxychloroquine (associated or not with azithromycin), chloroquine, nitazoxanide, and ivermectin; antiretrovirals, such as lopinavir/ritonavir; nucleotide analogues, such as remdesivir, and convalescent plasma1,5,6,7. Nutritional therapies, such as the administration of vitamins A, D, and C and the use of zinc and selenium are also still considered to have no demonstrated effect in preventing and treating COVID-19[6].

The lack of robust scientific evidence on the use of drugs and non-pharmacological therapies in COVID-19 patients creates uncertainties in clinical and public health decision-making processes and potential serious consequences of the pandemic for the population, the health system, and the economy. For example: in terms of the clinical decision, the lack of evidence makes that a large number of patients receive medications in situations of compassionate use and off label use based on their antiviral or anti-inflammatory properties obtained from in vitro studies[8].

The purpose of this debate was to present considerations about the concept of evidence, the evidence hierarchy, and the types of scientific evidence, seeking application in the context of the COVID-19 pandemic, regarding the use of therapies for the prevention and treatment of the disease. It emphasizes the evidence produced by sources referred to in the context of the evidence pyramid, giving special attention to those characterized as an expert opinion.

What is evidence?

Evidence may be defined as information or facts that are obtained systematically (that is, obtained in replicable, observable, credible, and verifiable manner) for use in decision making or judgments[9]. Health Evidence Network from the World Health Organization defines evidence as the results of research and other knowledge that may be useful for decision making in public health and medical care[10]. It is possible, however, that the exact definition of evidence depends on the context in which it will be used and may even have a more comprehensive or restrictive conotation[10].

In a public health context, the evidence can take various forms, such as a laboratory test result to confirm a COVID-19 case or a death certificate that proves the patient's cause of death. Other forms of evidence come from scientific studies or the opinion of experts, which can vary both in the credibility of helping in clinical decision making and in the identification of factors capable of influencing the applicability of something that is proven to be safe and effective when it is used in specific geographical or institutional settings[10].

The notion of evidence with a more comprehensive connotation is known as colloquial, while that of a more restrictive character is called scientific. Outside the academic world, the colloquial definition of evidence prevails, which is more sensitive to the decision context. This means that saying evidence is "anything that establishes a fact or gives reason to believe in something"[10]. Public managers are more likely to use the colloquial definition of evidence in their decisions, even though the evidence-based decision-making movement has generated greater consideration for scientific forms of evidence[10].

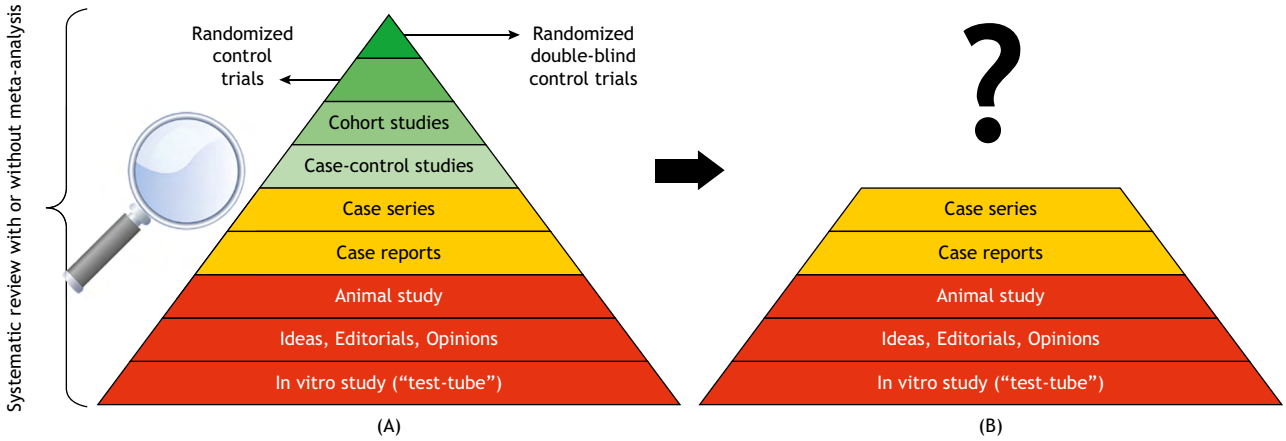
An example of the more restrictive definition of evidence is that proposed by Davis[11] and that can be applied in the context of uncertainties about the use of drugs in the clinical management of COVID-19. For the author's purpose, "evidence" means information on causal relationships between past interventions (causes) and their results (effects)[11]. These causal relationships are established by certain types of scientific studies highlighted in the evidence pyramid[12].

Evidence hierarchy

Scientists seek to use systematic and reproducible methods to produce quality evidence. These pieces of evidence are classified in a hierarchical order, illustrated by a pyramid, according to the design or alignment of the study, one of the important markers to define the quality of the evidence[12] (Figure).

The choice of study design to produce the best evidence depends on the research question to be answered[12], as well as on the feasibility of strategies used to answer it. At the top or near the bottom of the hierarchy are randomized controlled trials (RCTs), considered the best approach to answer questions on the efficacy and safety of disease treatment. In the medical literature, RCTs are referred to as the "gold standard" among the sources of evidence for establishing causal relationships[11].

In the context of a public health emergency, pragmatic clinical trials based on the effect of treatments are a useful alternative to RCTs that, when proving a concept, often use inclusion and exclusion criteria that limit the external validity (reproducibility) of their findings[14].



(A): represents a traditional evidence pyramid model applied to different diseases with proven treatments, in terms of safety and effectiveness in non-emergency situations in public health.

(B): represents a pyramid model of evidence in rare situations, such as COVID-19, mainly in its initial phase of the emergence of the first cases. It is important to mention that with the advances of science, throughout the evolution of the COVID-19 pandemic, new scientific evidence is expected to be produced from studies predicted at the top of model A.

Source: Adapted from Bigby[12] and Murad et al.[13].

Figure. The evidence pyramid in two public health contexts.

Pragmatic clinical trials correspond to one of the three categories of study designs that make up what is known as "real-world evidence"[15]. Food and Drug Administration (FDA) defines real-world evidence as clinical evidence on the use and the possible benefits or risks of a medical product derived from the analysis of "real-world data", which are data related to the patient's health status and/or the provision of health care routinely collected from various sources[16].

Advances in the use of "real-world evidence" are expected, since the 21st Century Cures Act - Cures Act, of December 31, 2016, by the United States Congress, which ordered the FDA to create a regulatory guideline to assess its potential use to approve new indications of drugs already approved and to meet post-approval requirements[17]. There are authors, however, who question the use of "real-world evidence" for approving new drugs to replace methodological rigor of an RCT[18].

It should be noted that the presence of certain methodological limitations of an RCT (or of another type of study), such as imprecision (wide confidence interval of the effect estimates) and inconsistency (presence of bias, such as hiding randomization and blinding the study), can affect the quality of the evidence generated[13].

The hierarchy in the quality (strength) of the evidence, an important principle of Evidence-Based Health Practices, attaches great value to systematic reviews with or without meta-analyses of several studies, mainly those that include RCTs[12]. In the model proposed in the Figure, systematic reviews, which usually are at the top of the pyramid as recommended by different authors[19], are used as a magnifying glass through which other types of studies must be observed, that is, evaluated and applied[13].

Opposed to the RCT, the opinion of a specialist, who forms the base of the pyramid, can potentially be valuable, especially in rare conditions, in which a specialist has more experience in a context of a series of cases or when other forms of scientific evidence are not available[12].

The order of the evidence hierarchy has been widely discussed, altered, and sometimes contested[12], resulting in several versions of the pyramid[19]. This evidence hierarchy should not be interpreted as a linear phenomenon, that is, as a scale that goes from "good" to "bad"[12]. The quality and relevance of the evidence must be contextualized and considered, mainly, in rare and serious situations, such as the COVID-19 pandemic. Thus, a large, well-conducted cohort study may be more reliable than a small RCT that has methodological limitations, such as those mentioned above. Likewise, a small, moderate-quality RCT that deals with the patient's exact problem (for example: palmoplantar psoriasis) is likely to be more useful than a large RCT, which addresses a different or broader problem (for example, psoriasis)[12].

The evidence hierarchy must consider the situational context represented either by the magnitude of the problems or by the quality of available evidence, which can be assessed using strategies such as the Grading of Recommendations, Assessment, Development and Evaluations - Grade. This tool analyzes aspects such as: methodological limitations of available studies, risk of bias, inconsistency, indirect evidence, imprecision, publication bias, the magnitude of the effect, dose-response gradient, and residual confusion[20].

Along the COVID-19 pandemic curve, the evidence at the base of the pyramid (part B of the Figure) is what has guided clinical decisions to prevent and treat the disease, with emphasis on the opinion of experts. Such sources of evidence are less

preferred because they imply a high degree of uncertainty and the need for a more careful assessment of benefits and risks in clinical practice[13].

Expert opinion

Since the emergence of the first cases of COVID-19 in the city of Wuhan (Hubei province), China, in December 2019[3], until now (April 20, 2020), the opinion of experts, such as authorities, scientists, and doctors on the use of drugs to prevent and treat the disease has prevailed given the lack of scientific evidence produced by systematic research. This opinion is based on the expert's beliefs and is formed by theory and non-systematic learning[11].

Theoretically based beliefs are generated by deducting assumptions, most often based on research on the positive impact of a drug therapy given the disease[11]. For example, a doctor uses existing drugs to treat the disease. He believes that the use of hydroxychloroquine associated with azithromycin may reduce the number of deaths in patients with moderate or severe COVID-19. The basis of this belief is an open, non-randomized clinical trial carried out with 42 hospitalized COVID-19 patients in France, pointing out that the addition of azithromycin to hydroxychloroquine resulted in a faster decrease in viral load in comparison with treatment with hydroxychloroquine only[21]. In this context, analyzes on the efficacy and safety of drugs concerning relevant outcomes, such as the reduction of complications associated with disease or mortality, are not possible.

Beliefs based on non-systematic learning are often a mixture of intuition and common sense based on personal experience, organizational culture, as well as information acquired in a non-systematic way on the experiences or beliefs of other professionals and are often combined with theory[11]. Considering the scenario portrayed previously, this same doctor, from conversations with other clinicians at the same institution who were successful in using hydroxychloroquine associated with azithromycin, started to prescribe this association for his patients. This is an example of a belief based on non-systematic learning[11].

No theory or non-systematic learning corresponds to conclusive evidence in itself and totally reliable to decide on safe and effective treatments[22], being necessary its confirmation through studies that are at the top of the pyramid. It is important to mention that the health system is full of treatments used based more on habits or very strong beliefs than on scientific evidence[22]. Treatments that often do not do any good that can sometimes cause damage[22].

The opinion of experts in their decisions in the context of an emergency in public health can be guided by Clinical Protocols and Therapeutic Guidelines (CPTG) These documents follow principles and methods of analysis of scientific evidence that consider criteria of efficacy, safety, effectiveness, and cost-effectiveness of health institutions[23]. CPTGs include, for example, the definition of the theme, characterization of the guiding questions, including uncertainties on best practices, potential to improve health outcomes, as well as considerations on reducing health inequities, among other aspects[23].

Even in the context of scarce evidence on the disease, the elaboration of CPTG can gather information necessary to reduce the variability of clinical procedures, the use of ineffective therapeutic measures, reducing the risk of occurrence of adverse reactions, and, therefore, of the health results obtained[24]. Another advantage of CPTGs is to minimize the influence of third parties on clinical decisions made by specialists[23].

It should be noted, however, that information contained on the CPTG must be adapted to each specific patient based on professional judgment, considering the patient's needs, the available resources, the appearance of new evidence, as well as any other unique circunstance[24]. This information should not be used to substitute or cancel the judgment of a qualified physician[25].

The use of therapies on COVID-19 patients based on scientific evidence

So far, a few of the potential therapies to prevent or treat COVID-19 are uncertain from the point of view of scientific evidence available, allowing to state that - until now - no treatment brings more benefits than risks to human health. This condition of uncertainty has produced differences of opinion among many specialists regarding the treatment of patients in severe, moderate, or mild stages of the disease.

In non-emergency public health situations, it would be advisable to wait for the emergence of scientific evidence that resulted in the development of the drug and, therefore, the entire regulatory measures necessary for its availability to the population. This journey, from the original idea to the launch of a finished product, is a complex process that can take from 12 to 15 years and cost more than US$ 1 billion[26].

However, given the COVID-19 pandemic, which has claimed thousands of lives around the world and challenged science, it is important to understand the arguments behind the diverging opinions of experts, turning to basic concepts about three types of scientific evidence[27] and its potential uses in clinical decisions to prevent and treat patients with COVID-19.

First, direct evidence is scientific information of enough quality to be incorporated into decision-making in humans, derived from studies that evaluated the therapy of interest directly in the disease in question, that is, COVID-19[27]. Until now, there are few studies completed in COVID-19 patients and those that exist are evidence with a low degree of certainty[7]. Furthermore, it is important to mention that a single study will rarely provide enough evidence[22] to definitely guide the treatment choices for COVID-19 patients. The alleged causal relationship between the drug and the

expected clinical outcomes is reinforced by the frequency of such observation from further clinical trials[28].

Second, the indirect evidence is quality scientific information from studies that did not directly assess the therapy of interest in COVID-19 but that came from similar diseases[27]. For example: the evidence from studies from the Middle East Respiratory Syndrome (MERS-CoV), a disease caused by a coronavirus, is considered more direct than that of influenza and, in turn, is less indirect than that of other respiratory diseases[27]. This type of evidence, that characterizes the drugs that are already available to the population for treating other diseases, is one of the first resources that researchers have been using to find COVID-19's cure. Examples of some of these drugs were mentioned in the first section of this debate.

Last, preliminary evidence is scientific information of pre-clinical studies carried out with the COVID-19 virus but that are not yet as relevant for clinical decision-making, such as experimental studies in animals and in vitro cell cultures[27]. Initial studies on people with COVID-19 who do not meet certain methodological characteristics[27], such as the random allocation of patients in two groups (intervention and control), ensuring that they are as similar as possible in all known and unknown factors[22], are also considered preliminary evidence. Initial studies in humans allow the identification of a statistical correlation but do not determine causation[29]. The objective of the preliminary studies is to generate hypotheses so that researchers can continue to advance in the identification of effective and safe therapies to prevent and treat patients with COVID-19[27].

The Chart presents the classification of scientific studies of drugs with possibilities of clinical benefits for COVID-19 patients, according to the types of evidence discussed previously.

The divergence of experts opinions on the use of several drugs and other non-pharmacological therapies in COVID-19 patients is due to the existence, so far, of only indirect and preliminary evidence with a very low level of certainty (that is, it is not possible to infer whether or not a particular drug is effective in the treatment of COVID-19), making it necessary that their interpretation and use in clinical decisions be made with great care[27]. As a general rule, these two types of scientific evidence do not allow strong recommendations on therapies[27] to be made for the treatment of COVID-19, so that, in such cases, the case-by-case assessment by the doctor may influence the management of the patient.

The uncertainties regarding indirect and preliminary evidence also fall on the "adequate" dose of drugs with potential uses in the treatment of COVID-19 patients. To illustrate, as the dose of a drug is increased, its benefits may no longer generate the desired outcome, being overcome by the emergence of adverse reactions that compromise the patient's health[22].

It is worth mentioning that the lack of evidence does not mean that therapy cannot be effective[34]. It just means that we do not know yet. However, it is reasonable to not conduct studies if there is not enough theoretical basis for a benefit to be expected. Therefore, the more irrational an intervention is, the easier it is to discard it without having to resort to scientific studies[34]. Again, the use of systematic evidence assessments such as Grade can be useful in contexts with a high degree of uncertainty[20].

Chart. Classification of scientific studies of drugs with possibilities of clinical benefits for COVID-19 patients, according to the types of evidence.

Drug	Therapeutic class*	Studies completed or under development mentioned in the literature	Type of evidence
Remdesivir	Nucleotide analogues**	Randomized clinical trials in development[a,b]	Direct[§]
		Reports of three cases using a protocol for the compassionate use of drugs[a]	Preliminary
		In vitro cell study against the Severe Acute Respiratory Syndrome 2 coronavirus (SARS-CoV-2)[a]	
Chloroquine	Antiprotozoal (P01BA01)	Clinical trials during an outbreak in China (data not available)[a]	Direct[§]
		In vitro cell study against SARS-CoV-2[a]	Preliminary
Hydroxychloroquine	Antiprotozoal (P01BA02)	Randomized clinical trials in development[b]	Direct[§]
		Open non-randomized clinical trial (associated or not with azithromycin)[c]	Preliminary
		In vitro cell study against SARS-CoV-2[a]	
Lopinavir/ Ritonavir	Antivirals for systemic use (J05AR10)	Open-label randomized controlled trial[a,b]	Preliminary
		Non-randomized retrospective cohort study[b]	
		Case reports and case series[a]	
Nitazoxanide	Antiprotozoal (P01AX11)	Double-Blind Placebo-Controlled Clinical Trial under development[d]	Direct[§]
		In vitro cell study against SARS-CoV-2[a,b]	Preliminary
		Three randomized controlled clinical trials performed with patients with influenza (data not available)[a]	Indirect
Ivermectin	Anthelmintic (P02CF01)	In vitro cell study against SARS-CoV-2[e]	Preliminary

Source: Elaborated by authors from studies published by: [a]McCreary et al.[1], [b]Sanders et al.[30], [c]Gautret et al.[21], [d]ReDO[31], and [e]Caly et al.[32].
* Therapeutical class, according to the Anatomical Therapeutic Chemical - ATC classification[33].
** There is no classification in ATC.
[§] The type of evidence may be altered, depending on the methodological limitations of the studies, in these cases, being classified as preliminary evidence.

CONCLUSIONS

In the impossibility of predicting exactly what will follow along the path of the COVID-19 pandemic, which has already caused 168,500 deaths around the world (04/20/2020 - 15h38m36s)[35], and given the lack of any treatment for the disease approved by regulatory agencies, clinical decisions to minimize suffering and save lives, so far, have been made based on the opinion of experts.

Under these conditions, in order to build a better clinical and public health decision scenario, it is necessary to consider at least the following aspects: i) gather whenever possible the largest number of evidence for decision making, preferably patients and their families should participate; ii) choose the therapeutic option that tends to be the most appropriate considering individual clinical circumstances and the values and preferences of patients and their families; iii) given that evidence is never enough to make clinical decisions, assess the relationship between benefits and risks, the associated burden, and costs involved in a decision, and, in doing so, also consider the (socioeconomic) situation of the patients[36]. Such care can contribute to the choice of more rational therapies, avoiding exhausting them for the treatment of diseases with proven efficacy.

In the absence of clear and reliable evidence about the risks and benefits of treatments, these uncertainties must be shared with patients[22], a condition that presupposes skills not always available among doctors. However, regardless of what happens, the doctor's final decision shared with the patient or family must be deeply respected, as it is expected that they have made use of the best resources and evidence that were within their reach to minimize suffering and save lives.

As decisions often need to be made in situations of public health emergencies, in which there is a lack of published scientific evidence, expert opinions are often employed[37]. Many of them based on beliefs built on theory and non-systematic learning, whose sources of information, in the context of the COVID-19 pandemic, have been indirect and preliminary evidence.

In this decision-making journey, it is important to consider some of the basic principles of Hippocratic Medicine, such as: i) favoring and not harming (*primo non nocere*, first, do no harm), which means choosing the lesser evil; ii) refrain from trying pointless procedures; and iii) the duty to dedicate priority loyalty to the patient[38]. It is also worth remembering that medical conduct should: "cure when possible, but comfort always"[38].

Therefore, to ensure a reasonably acceptable fit, the development of a checklist of the quality of evidence data from expert opinion[37] and guidelines indicating under what circumstances they can be used to support clinical decisions is essential, and further research in this direction should be a priority[37]. Even in scenarios of this nature, CPTGs, although based on scarce evidence and the need for reviews to be made almost daily to incorporate new scientific information, can reduce the variability of clinical procedures and the assessment of the results of the treatments employed. Perhaps, assessing the weight to be attributed to each type of evidence, for the time being available, allowing each of them to properly contribute to the final decision[37] needs to be included in this guiding document.

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Authors' Contributions

Mota DM - Conception, planning (study design), analysis, data interpretation, and writing of the work. Kuchenbecker RS - Analysis, data interpretation, and writing of the work. All authors approved the final version of the work.

Conflict of Interest

The opinion expressed in this article are solely the authors' and do not represent the views of their organizations.